Ketamine

Critical Review Report

Expert Committee on Drug Dependence
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Ketamine
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## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUMMARY</td>
<td>8</td>
</tr>
<tr>
<td>1. Substance Identification</td>
<td>10</td>
</tr>
<tr>
<td>A. International Non-proprietary Name (INN)</td>
<td>10</td>
</tr>
<tr>
<td>B. Chemical Abstract Service (CAS) Registry Number</td>
<td>10</td>
</tr>
<tr>
<td>C. Other chemical names</td>
<td>10</td>
</tr>
<tr>
<td>D. Trade Names</td>
<td>10</td>
</tr>
<tr>
<td>E. Street Names</td>
<td>10</td>
</tr>
<tr>
<td>F. Physical properties</td>
<td>10</td>
</tr>
<tr>
<td>G. WHO Review History</td>
<td>11</td>
</tr>
<tr>
<td>2. Chemistry</td>
<td>11</td>
</tr>
<tr>
<td>A. Chemical Name:</td>
<td>11</td>
</tr>
<tr>
<td>B. Chemical Structure</td>
<td>11</td>
</tr>
<tr>
<td>C. Stereoisomers</td>
<td>11</td>
</tr>
<tr>
<td>D. Synthesis</td>
<td>12</td>
</tr>
<tr>
<td>E. Chemical description</td>
<td>12</td>
</tr>
<tr>
<td>F. Chemical properties</td>
<td>12</td>
</tr>
<tr>
<td>G. Chemical identification</td>
<td>12</td>
</tr>
<tr>
<td>3. Convertibility into controlled substances</td>
<td>12</td>
</tr>
<tr>
<td>4. General pharmacology</td>
<td>12</td>
</tr>
<tr>
<td>4.1. Pharmacodynamics</td>
<td>12</td>
</tr>
<tr>
<td>4.2. Routes of administration and dosage</td>
<td>15</td>
</tr>
<tr>
<td>4.3. Pharmacokinetics</td>
<td>15</td>
</tr>
<tr>
<td>5. Toxicology</td>
<td>16</td>
</tr>
<tr>
<td>6. Adverse reactions in humans</td>
<td>20</td>
</tr>
<tr>
<td>7. Dependence potential</td>
<td>23</td>
</tr>
<tr>
<td>8. Abuse potential</td>
<td>31</td>
</tr>
</tbody>
</table>
9. Therapeutic applications and extent of therapeutic use ........................................ 32
10. Listing on the WHO Model List of Essential Medicines .................................... 33
11. Marketing authorizations (as a medicine) .......................................................... 33
12. Industrial use ........................................................................................................... 33
13. Non-medical use, abuse and dependence .............................................................. 33
14. Nature and magnitude of public health problems related to misuse, abuse and dependence .................................................................................................................. 34
15. Licit production, consumption and international trade .......................................... 35
16. Illicit manufacture and traffic and related information ......................................... 35
17. Current international controls and their impact ..................................................... 35
18. Current and past national controls ........................................................................ 36
19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance ........................................................................................................ 36

References .................................................................................................................... 37

Annex 1: WHO Questionnaire For Review Of Psychoactive Substances For The 35th ECDD – Evaluation Of Ketamine ....................................................................................... 47
Ketamine - Brand Names ........................................................................................... 49


Executive Summary ...................................................................................................... 51

1. General introduction ................................................................................................. 52
2. Pharmacology of ketamine ....................................................................................... 52
3. Clinical effects of ketamine ....................................................................................... 53
4. Medical use of ketamine in industrialised countries ................................................. 55
5. Ketamine in veterinary practice ................................................................. 56
6. Ketamine use in developing countries .................................................... 57
7. Alternatives to ketamine in the developing countries .......................... 59
8. Investigations in some African countries ........................................... 60
   8.1 Ethiopia ............................................................................................... 60
   8.2 Nigeria ................................................................................................... 63
   8.3 Tanzania ............................................................................................... 68
9. Conclusion .................................................................................................. 74
Annex 3: Use Of Ketamine In Benin ............................................................ 75
1. Introduction ............................................................................................... 75
   1.1 Background information on ketamine .................................................. 75
   1.2 Information on Benin ............................................................................ 76
   1.3 Geographical situation of Benin and of the towns of Cotonou and Abomey .... 76
2. Our study .................................................................................................... 78
3. Comments ................................................................................................... 81
4. Conclusion .................................................................................................. 84
5. Recommendations ...................................................................................... 84
6. Bibliography ............................................................................................... 85
7. List of abbreviations ................................................................................... 86
Annex 4: Abuse Of Ketamine In The United States ...................................... 87
Annex 5: Abuse Of Ketamine In China, Macao SAR And Hong Kong SAR .......... 89
Summary

Ketamine is chemically (+)-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone (CAS No. 6740-88-1 for base, 1867-66-9 for hydrochloride (previous: 81771-21-3; 96448-41-8; 42551-62-2)). It is an arylycycloalkylamine structurally related to cyclidines, like eticyclidine, phencyclidine, rolycyclidine and tenocyclidine. This NMDA-receptor-antagonist is used as an anaesthetic in both human and veterinary medicine for short diagnostic and surgical procedures that do not require skeletal muscle relaxation. Its use in veterinary medicine must also be considered while considering control.

Ketamine is marketed under many trade names. Preparations containing the S-enantiomer only are increasingly being marketed. It can produce a depression of the central nervous system, resulting in hallucinations, disturbances in thinking, perceptions and also in motor function. However, adverse events in patients are quite different from those found in recreational users.

Ketamine has been misused as a hallucinogen for almost 30 years. The effects are similar to those of phencyclidine, but with a much shorter duration. Dependence has been demonstrated in various animal models. There is some human data also supporting this. Ketamine misuse is reported from a number of countries in Asia, Europe and North America. Misuse by medical personnel has also been reported. However, available data do not show this constitutes a major public health and social problem in most parts of the world, with a few possible exceptions.

It has already been placed under national control in several countries. During its 34th meeting, the WHO Expert Committee on Drug Dependence discussed the critical review report on ketamine and came to the following recommendation: “The Committee reviewed the information contained in the critical review document and concluded that this information was not sufficient to warrant scheduling. However, in the course of the meeting, the Committee was informed that the United Nations Commission for Narcotic Drugs at its 49th session, held in March 2006, had adopted a draft resolution for transmission to ECOSOC, on the listing of ketamine as a controlled substance. The Committee requested the Secretariat to produce an updated version of the critical review and present it to the next meeting of the Expert Committee on Drug Dependence”.

Earlier, during its meeting in September 2002 the WHO Expert Committee on Drug Dependence did a pre-review on ketamine (WHO, 2003). Based on the available information a recommendation was given for a critical review of this substance. In about the same period both in the Netherlands (CAM, 2002) as well in the European Union (EMCDDA, 2002) separate risk assessment procedures for ketamine were performed, concluding that there was no need to tighten the current systems for control of this substance, i.e. as a pharmaceutical product.

The information used in the three aforementioned procedures (meanwhile published) has been the starting point for this critical review report. A review of pharmacological and toxicological data prepared by Dutch experts (Van Aerts and Van der Laan) has been used (with their permission) for the relevant parts of this report. In addition to these data, an online literature search has been performed in the following databases: Pubmed, Toxline, Psycinfo and Embase.
The critical review report of 2005 forms the backbone of the updated review and has been extended with the latest information on the substance, ketamine and its use and misuse and takes into consideration available literature until 2011. Based on all the available information no significant changes have been noted when comparing the earlier report and the updated version. However, China reports an increased misuse.

The substance is difficult to synthesize, so illegal production is rare, but happens in some parts of the world. Preparations are mainly used in hospitals and veterinary clinics. Diversion has been reported from some countries. It is not expected that diversion will take place on a large scale. Summarizing all available information and relevant current data on medical use and misuse, international control is not really necessary at present and it may affect availability for medical use. However, it is important for the international community to work in harmony to strike a balance between legitimate use of ketamine for medical purposes and prevention of trafficking in and abuse of ketamine. It is also important to keep a close watch on developments and trends.
1. **Substance Identification**

   **A. International Non-proprietary Name (INN)**
   Ketamine; ketamine hydrochloride.

   **B. Chemical Abstract Service (CAS) Registry Number**
   - 6740-88-1 (free base)
   - 1867-66-9 (current: hydrochloride salt)
   - 81771-21-3; 96448-41-8; 42551-62-2 (previous: hydrochloride salt)

   **C. Other chemical names**
   - 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride;
   - 2-(o-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride;
   - 2-(methylamino)-2-(2-chlorophenyl)cyclohexanone hydrochloride;
   - 2-(methylamino)-2-(o-chlorophenyl)cyclohexanone hydrochloride;
   - cyclohexanone, 2-(2-chlorophenyl)-2-(methylamino) hydrochloride;
   - cyclohexanone, 2-(o-chlorophenyl)-2-(methylamino) hydrochloride.

   **D. Trade Names**
   Some of the trade names used include:
   - Anaket®, Anasket®, Anesketin®, Brevinase® Brevinaze®, Calypsol®,
   - Calypsovet®, Chlorketam®, Ereska®, Imalgene®, Inducmina®, Kalipsol®,
   - Katalar®, Keta®, Keta-Hameln®, Ketaject®, Ketalar®, Ketalin®, Ketalor®,
   - Ketamav®, Ketamax®, Ketamil®, Ketamin®-ratiopharm, Ketaminol Vet®,
   - Ketanarkon®, Ketanest®, Ketanest-S®, Ketaset®, Ketasil®, Ketava®,
   - Ketaved®, Ketavet®, Ketmine HCl®, Ketolar®, Ktmin®, Narkamon®,
   - Narketan®, Pan-Ketamine®, Ralatek®, S-Ketamin®, Tekam®, Velonarcon®
   - Vetaket®, Vetalar®, Vetus Ketha-Thesia®.

   See additional brand names reported by countries in Annex 1, report of the WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD

   **E. Street Names**
   A number of street names for ketamine can be found in the literature, like:
   - “1980 acid”, “Purple”, “Special K”, “Special LA coke”, “Super acid”,
   - “Super C”, “Super K”, “Tac et Tic”, “Vitamin K” (EMCDDA, 2002; Nabben
   - and Korf, 2000; Pagliaro and Pagliaro, 2004).

   Some names clearly refer to the veterinary origin of the product.

   One should be aware of the fact that street names are not always exclusive for
   just one substance. Flatliners is also used for 4-MTA and Liquid E for GHB.

   **F. Physical properties**
   White to almost white, crystalline powder.
G. **WHO Review History**
During its 34th meeting, the WHO Expert Committee on Drug Dependence discussed the critical review report on ketamine and concluded that this information was not sufficient to warrant scheduling. However, in the course of the meeting, the Committee was informed that the United Nations Commission for Narcotic Drugs at its 49th session, held in March 2006, had adopted a draft resolution for transmission to ECOSOC, on the listing of ketamine as a controlled substance. The Committee requested the Secretariat to produce an updated version of the critical review and present it to the next meeting of the Expert Committee on Drug Dependence.

2. **Chemistry**

A. **Chemical Name:**
   IUPAC Name: 2-(2-Chlorophenyl)-2-(methylamino)-cyclohexan-1-one
   CA Index Name:

B. **Chemical Structure**
   Free base:
   
   ![Chemical Structure Diagram]
   
   Molecular formula: C_{13}H_{16}ClNO (free base)  
   C_{13}H_{17}Cl_{2}NO (hydrochloride salt)
   
   Molecular weight: 237.73 g/mol (free base)  
   274.18 g/mol (hydrochloride salt)
   
   Melting point: 92-93°C (free base)  
   262-263°C (hydrochloride salt)

C. **Stereoisomers**
Ketamine contains a chiral centre at the C-2 carbon of the cyclohexanone ring, so that two enantiomers exist: S-(+) ketamine and R-(−) ketamine. The S-enantiomer being the pharmacologically more active stereoisomer. Increasingly, the S-(+) enantiomer is being used in the commercially available preparations.
D. **Synthesis**

Ketamine is manufactured by the pharmaceutical industry. The preparation is described by Stevens, Belgian patent 634208 (1963), which corresponds to the U.S. patent 3254124 (1966 to Parke-Davis). The synthesis of the optical isomers is described by Hudyma et al., German patent 2062620 (1971 to Bristol-Myers) (Budavari et al., 1989).

As the substance is difficult to synthesize, Ketamine is obtained almost exclusively by diversion of commercial sources. There are however, recent reports suggesting illegal synthesis from precursors such as hydroxylimine.

E. **Chemical description**

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) is an arylocycloalkylamine structurally related to phencyclidine (PCP).

F. **Chemical properties**

Ketamine hydrochloride is a water-soluble, white crystalline powder and has a pKa of 7.5 (Budavari et al., 1989). Its free base, ketamine, has lipid solubility 10 times that of thiopentone. The commercially available pharmaceutical form is an aqueous solution for injection of the racemic mixture of the hydrochloride salt.

G. **Chemical identification**

Ketamine is metabolized to at least two compounds. The parent compound and both major metabolites are further transformed by hydroxylation and conjugation prior to elimination. About 90% of a dose is excreted in urine in 72 hours, with about 2% of the dose unchanged. There are different methods described in the literature to analyze KT in the urine. One of them is an analytical method using solid-phase extraction and positive ion chemical ionisation-gas chromatography-mass spectrometry (Kim E.M. et al., 2008).

3. **Convertibility into controlled substances**

Ketamine is not converted into controlled substances.

4. **General pharmacology**

The pharmacology of ketamine will be described in two parts. The first one will deal with the effects of the substance on various neurotransmitter systems related to both its clinical use and its use as a recreational agent. The second part will deal with the effects on various organ systems often wanted in clinical or veterinary practice or occurring during non-medical use and sometimes leading to adverse reactions.

4.1. **Pharmacodynamics**

Ketamine is a dissociative anaesthetic (Domino et al., 1966). Originally, the dissociation component refers to a functional and electrophysiological dissociation of thalamoneocortical and limbic systems (Reich and Silvay, 1989; Haas and Harper,
More recently, the nature of the subanaesthetic ketamine experience has led to the use of the term 'dissociative' in a more psychological sense referring to a feeling of dissociation of the mind from the body (Jansen, 1990; 2000a).

Ketamine binds to the so-called PCP-binding site of the N-methyl-D-aspartate (NMDA)-receptor complex, located within the ion channel, thereby blocking the transmembranous ion flux. This makes ketamine a non-competitive NMDA-receptor antagonist. NMDA-receptors are calcium-gated channel receptors. The endogenous agonists of this receptor are the excitatory amino acids glutamic acid, aspartic acid, and glycine. Activation of the receptor results in opening of the ion channel and the depolarisation of the neurone. The NMDA-receptor is involved in sensory input at the spinal, thalamic, limbic and cortical levels. Ketamine would be expected to block (or interfere with) sensory input to higher centres of the CNS, with the emotional response to these stimuli, and with the process of learning and memory (Bergman, 1999). Awakening from ketamine anaesthesia takes place at plasma concentrations of 0.64-1.12 µg/ml (Reich and Silvay, 1989). Psychotropic effects have been described in the presence of plasma concentrations ranging from 50 to 300 ng/ml and with regional brain concentrations higher than 500 ng/ml (Bowdle et al., 1998; Oranje et al., 2000; Hartvig et al., 1995).

Several studies indicate that opioid receptors are also involved in the pharmacological effects of ketamine (Freo, 2002), and that the analgesic effect of ketamine may largely be attributed to the activation of these central and spinal receptors (Crisp et al., 1991).

The plasma levels at which analgesia is achieved are 0.15 µg/ml following intramuscular administration and 0.04 µg/ml after oral administration. This difference may be explained by a higher norketamine concentration due to first-pass metabolism. This main metabolite apparently contributes to the antinociceptive effect of ketamine (Shimoyama et al., 1999).

Furthermore, new developments show strong interactions between the opioid and the NMDA system in the brain of animals. In contrast to earlier findings, new results point to NMDA receptors and not sigma-receptors as having a role in the morphine withdrawal response (Brent et al., 1993). Gonzalez et al. (1997) have shown that competitive and non-competitive NMDA receptor antagonists prevent morphine tolerance and decrease the development of physical dependence on this opiate in mice. The study of Ji et al. (2004) indicates that ketamine has the ability to suppress morphine withdrawal syndrome in experimental settings without motor interference. The nucleus accumbens (NAc) is mentioned as the site of action.

Some effects of ketamine may be due to its actions on catecholamine systems, notably an enhancement of dopamine activity (White and Ryan, 1996; Vollenweider et al., 2000; Smith et al., 1998). A series of experiments by Hancock and Stamford (1999) on the effects of ketamine on uptake and efflux of dopamine in the rat NAc led the authors to conclude that ketamine increases NAc dopamine efflux not by the blocking of dopamine uptake, autoreceptors or NMDA receptors, but by mobilisation of the dopamine storage pool to releasable sites. In the rat, it has been shown that repeated ketamine administration diminished the initial five-fold increase in dopamine release in the prefrontal cortex, whereas the increase in extracellular 5-hydroxyindole acetic acid (a serotonin metabolite) levels is enhanced. This suggests that the balance between
dopamine and serotonin neurotransmission in the prefrontal cortex is altered after repeated exposure to ketamine (Lindefors et al., 1997). The dopaminergic effects may be of relevance for the euphorogenic, dependence-producing and psychotomimetic properties of ketamine.

Other neuropharmacological actions are an agonistic effect on α- and β-adrenergic receptors, an antagonistic effect at muscarinic receptors of the CNS, and an agonistic effect at the σ-receptor (Bergman, 1999).

The principal metabolite, norketamine, is pharmacologically active. Its binding affinity to the NMDA-receptor and anaesthetic properties are approximately one third of the parent compound contributing significantly to the analgesic effect of ketamine (Shimoyama et al., 1999).

The commercially available ketamine is a racemic mixture of two enantiomers. The S-enantiomer is shown to be the more potent one with an approximately 3-4 fold anaesthetic potency compared to the R-enantiomer. This correlates with the higher binding affinity for the PCP-site of the NMDA-receptor. The psychotomimetic properties of ketamine are mainly caused by the S-enantiomer, although subanaesthetic doses of R-ketamine may induce a state of relaxation (Vollenweider et al., 1997; Engelhardt, 1997).

**Effects on the cardiovascular system**
Ketamine differs from most anaesthetic agents in that it appears to stimulate the cardiovascular system, producing changes in heart rate, cardiac output, and blood pressure (Haas and Harper, 1992). Possibly, re-uptake inhibition of circulating catecholamines may contribute to this phenomenon. On the other hand, cardiodepressant effects have been noted in critically ill patients. This may be due to chronic catecholamine depletion preventing any sympatomimetic effects of ketamine and unmasking a negative inotropic effect, which is usually overshadowed by sympathetic stimulation (White and Ryan, 1996; Reich and Silvay, 1989). The cardiovascular effects of ketamine usually do not pose a problem, but its use is contraindicated in patients with significant ischaemic heart disease and should be avoided in patients with a history of high blood pressure or cerebrovascular accidents (Haas and Harper, 1992). In recreational ketamine users, presenting to an emergency department, tachycardia was the most common finding upon physical examination (Weiner et al., 2000).

**Effects on the respiratory system**
Ketamine is a mild respiratory depressant. It causes a shift of the CO₂ dose–response curve to the right, in a dose-related manner, but does not change the slope of the curve. Respiratory drive to CO₂ may be depressed as much as 15 to 22%. This effect is similar to that of opioids, but dissimilar from most sedative hypnotics and anaesthetics, suggesting that opioid receptors may play a role in the respiratory depressant effect. In clinical studies, the effects were observed only at high doses. Some case reports describe respiratory depression after rapid intravenous injection, but also after routine paediatric use of ketamine administered intramuscularly (Reich and Silvay, 1989; White and Ryan, 1996). At recreational doses, respiratory depression is not likely to occur, but cannot wholly be excluded.
Ketamine has a bronchodilatory effect and pharyngeal and laryngeal reflexes are maintained (Reich and Silvay, 1989).

**Other pharmacological effects**
Ketamine increases muscle tone (Reich and Silvay, 1989).
Blood glucose and plasma cortisol and prolactin are increased after ketamine administration (Reich and Silvay, 1989; Krystal *et al.*, 1994).
Ketamine may decrease intraocular pressure (Reich and Silvay, 1989).

4.2. Routes of administration and dosage

Clinically, the medicine is usually administered by intramuscular or intravenous injection. For analgesia, the intrathecal route is used as well. Also, the oral and the rectal routes have been described (Reich and Silvay, 1989).

A dose equivalent to 2 mg of ketamine per kg body-weight given intravenously over 60 seconds usually produces surgical anaesthesia within 30 seconds lasting for 5-10 minutes (dose may range from 1 to 4.5 mg/kg); an intramuscular dose equivalent to 10 mg per kg body-weight (range 6.5-13 mg/kg) usually produces surgical anaesthesia within 3 to 4 minutes lasting for 12 to 25 minutes (Reynolds *et al*., 1989).
Analgesia is obtained by administration of 0.2-0.75 mg/kg intravenously (Reich and Silvay, 1989).

Subanaesthetic doses inducing psychotropic effects range from 0.1 to 1.0 mg/kg i.v. In clinical studies, this dose may be divided into a bolus of 0.1-0.2 mg/kg and a maintenance infusion of 0.0025-0.02 mg/kg/min. (Krystal *et al*., 1994; Engelhardt, 1997; Malhotra *et al*., 1996; Vollenweider *et al*., 1997; Oranje *et al*., 2000).
Intramuscular administration of ketamine in a dose range from 25 to 200 mg has been reported to produce psychotropic effects in humans (Hansen *et al*., 1988).
Malinovsky *et al.* (1996) found that bioavailability of nasally administered ketamine in children was approximately 50%, whereas bioavailability of intramuscularly administered ketamine is approximately 93% (Grant *et al*., 1981).

4.3. Pharmacokinetics

The reported volume of distribution varies from 1.5 to 3.2 l/kg. The clearance is in the range of 12-28 ml/(kg.min). The volume of distribution and clearance for $S$-ketamine are 9 and 14% greater than those for $R$-ketamine, respectively (Engelhardt, 1997).

**Absorption**
Ketamine is rapidly absorbed when administered through the intramuscular (Tmax 5-15 min), nasal (Tmax 20 min) or oral route (as a solution) (Tmax 30 min). Bioavailability is low when ketamine is given orally (17%) or rectally (25%). Extensive first-pass metabolism in liver and intestine is largely responsible for this effect. Bioavailability after nasal administration is approximately 50% (Malinovsky *et al*., 1996). This may partly be caused by significant swallowing of the fairly large intranasal deposit.

**Distribution**
Ketamine has a high lipid solubility and low plasma protein binding (12%), which facilitates rapid transfer across the blood–brain barrier. Initially, it is distributed to highly perfused tissues, including the brain, to achieve levels 4-5 times those in plasma...
(distribution half-life after i.v. 24 sec.). CNS effects subside following redistribution to less well-perfused tissues (re-distribution half-life, 2.7 min.).

**Biotransformation**
Biotransformation primarily takes place in the liver. The most important pathway is \(N\)-demethylation to norketamine. When administered orally or rectally, initial plasma norketamine concentrations are higher than those of ketamine, but the plasma area under the curve (AUC) for norketamine is similar for all routes of administration. Norketamine has one-third the anaesthetic potency of ketamine and has analgesic properties. Norketamine may be metabolised through multiple pathways, but the largest part is hydroxylated and subsequently conjugated.

**Elimination**
The predominant route of elimination is by liver metabolism. The high extraction rate (0.9) makes ketamine clearance susceptible to factors affecting blood flow. The conjugated hydroxy metabolites are mainly excreted renally. Terminal elimination half-lives range from 100-200 minutes.

**Pharmacokinetic interactions**
Ketamine, and its primary metabolite, norketamine, are metabolised by enzymes from the cytochrome P450 (CYP) family. In a recent study, it has been shown that ketamine induces the expression of multiple forms of P-450 in rat liver microsomes and increases CCl4-induced liver toxicity and cocaine-mediated acute toxicity (Chan et al., 2005). As the combination of cocaine and ketamine is used and known in the party scene (as CK or Calvin Klein), these findings should lead to further investigations into the possible risks for users of this combination.

5. **Toxicology**

The clinical safety profile of ketamine is largely based on extensive clinical experience. The preclinical data may therefore be of less importance. However, in contrast to recreational use, long-term clinical use of ketamine is rare. Therefore, some preclinical data may be of greater importance for the recreational substance user than for clinical practice.

**Animal**

**Single-dose toxicity**
Single dose acute toxicity shows an LD\(_{50}\) between 140 (intraperitoneally in the neonatal rat) and 616 mg/kg bw orally in the mouse (EMEA, 1997). In adult mice and rats, LD\(_{50}\) values were 224±4 mg/kg and 229±5 mg/kg, respectively (route not indicated) (Budavari et al., 1989).

In squirrel monkeys (Greenstein, 1975), doses above 25 mg/kg i.v. caused anaesthesia. At the highest concentration tested (350 mg/kg) 4 out of 5 monkeys died. In humans, the lowest recommended i.v. dose to induce anaesthesia is 1 mg/kg. Applying the same ratio of minimal anaesthetic dose to highest non-lethal dose to humans implies that doses above 11.3 mg/kg i.v. may be lethal in humans. For a person of 60 kg this is equivalent to i.v. doses above 680 mg. This estimate is based on an experiment with a
low number of animals and interindividual and interspecies differences may exist. Yet, considering data from case reports of fatal ketamine intoxications in humans, this estimate seems to be a realistic one.

Several studies investigated the local tolerance of ketamine when administered intrathecally (e.g. Errando et al., 1999; Malinovsky et al., 1993). Ketamine, when injected without preservative did not cause neurotoxicity in the spinal cord of swine or rabbits.

Repeated-dose toxicity
In rats daily intravenous doses of 2.5, 5 or 10 mg/kg bw for 6 weeks provoked a slight but not significant decrease of food intake and moderate weight gain depression (EMEA, 1997).
In a toxicological repeated toxicity study in dogs, 3 groups of 4 animals were given daily intramuscular doses of 4, 20 or 40 mg/kg bw during 6 weeks. At all dose levels there was some degree of weight loss and anorexia. Some blood parameters were also elevated and dose-related. Histological changes in the liver were minor (EMEA, 1997).

Reproduction function
Rats were injected during the pre-mating period (10 mg/kg bw i.v. on Days 9, 10 and 11 prior to mating). No effect on litter size was observed (EMEA, 1997).

Embryo-fetal and perinatal toxicity
Summarizing the available literature, at doses ten times those used in humans for anaesthesia, histopathological changes in rat foetuses have been observed. These effects are dependent on the period of exposure. Based on these preclinical data, in the absence of sufficient toxicokinetic data in animals, and considering that rodents have a higher metabolic rate and doses administered were in the subanaesthetic range in these animals, it cannot be excluded that ketamine in (sub)anaesthetic doses may adversely affect pregnancy outcome in humans (Bandazhevskii and Shimanovich, 1991; El-Karim and Benny, 1976; Kochhar et al., 1986; Hammer and Herkenham, 1983). Other studies in rats and rabbits point in the same direction but have limited value, since the duration and level of exposure in these studies do not meet current standards of toxicity testing (EMEA, 1997).

A study in female dogs, injected with 25 mg/kg bw intramuscularly six times during one trimester of pregnancy did not show apparent adverse effects on the bitch or the pups (EMEA, 1997).

No data on human pregnancies exposed to ketamine exist (Friedman, 1988). There is some clinical evidence during use of ketamine during parturition, where it has been shown that ketamine may depress fetal functions when 2 mg/kg (i.v.) is administered to the mother.

Two studies will be discussed in more detail below as they deserve more attention because of possible serious consequences for users of party-drugs, especially in combination with other such substances.

Abdel-Rahman and Ismael (2000) studied the teratogenic potency of ketamine hydrochloride in CF-1 mice with and without cocaine. It was shown that ketamine (50
mg/kg/day) potentiated the teratogenic effects of cocaine (20 mg/kg/day), but was not teratogenic on its own. Considering the higher metabolic rate of mice, the authors stated that the doses applied were comparable to those used by dependent humans and should be toxic to first-time users. As also shown in the study by Chan et al. (2005) the combination of cocaine and ketamine is a deleterious one.

Olney and co-workers (2000) suggested that ketamine has the potential to delete large numbers of neurones from the developing brain by a mechanism involving interference in the action of neurotransmitters [glutamate and gamma-aminobutyric acid (GABA) at N-methyl-d-aspartate (NMDA)] and GABAₐ receptors during the synaptogenesis period, also known as the brain growth-spurt period. Transient interference (lasting less than or equal to 4 hr) in the activity of these transmitters during the synaptogenesis period (the last trimester of pregnancy and the first several years after birth in humans) causes millions of developing neurones to commit suicide (die by apoptosis).

**Mutagenic and carcinogenic potential**

Taking all the information together, the published data from genotoxicity testing of racemic ketamine are insufficient and do not allow for a reasonable assessment of the genotoxic potential of ketamine. Whereas negative findings were obtained in poorly conducted (compared to current standards) bacterial tests, a positive result was reported from a sister chromatid exchange (SCE) test in vitro. However, the effects observed in the SCE study were only weak (i.e. less than a doubling of control values) and thus the relevance of this finding is questionable. Moreover, unpublished data (submitted to the German Federal Institute for Drugs and Medical Devices as part of an application for a marketing authorization) from genotoxicity testing with the S-(+)-enantiomer of ketamine in a standard battery of validated in vitro and in vivo tests did not reveal any evidence of a genotoxic potential. Provided that the genotoxicity findings with the S-(+)-enantiomer of ketamine can be extrapolated to the racemate, it can be concluded that ketamine is highly unlikely to possess any relevant genotoxic properties (Adhvaryu et al., 1986; Waskell, 1978).

**Carcinogenic potential**

No data on the carcinogenic potential of ketamine are available.

**Immunotoxicity**

As previously mentioned the combination of cocaine with ketamine is currently popular among young substance misusers. Rofael et al. (2003) did a series of investigations in rats in order to elucidate the possible mechanism of action. From the experiments, it can be concluded that cocaine has immunotoxic properties possible by neuro-endocrinal mechanisms. These effects may at least in part be counteracted by ketamine. The immunotoxic effects of cocaine may especially be detrimental in vulnerable groups, like people with HIV or hepatitis-infections.

**Neurotoxicity**

One issue that has been investigated in animals, but has received little attention in the clinical literature and that may be of importance for especially the recreational user of ketamine, is the neurotoxicity as observed in rats (Olney et al., 1989; 1991). When administered subcutaneously, ketamine (40 mg/kg) caused vacuolisation in posterior cingulate and retrosplenial cerebrocortical neurones in the rat. Lower doses (≤20 mg/kg) did not cause such pathological changes. These highly localised neurotoxic
effects have been shown for other NMDA-antagonists as well (Olney et al., 1989; 1991; Auer, 1994; O’Callaghan, 1994).

After intrathecal administration to rabbits, postmortem investigation of the spinal cord and nerve roots revealed histopathological lesions suggestive of toxic damage in 11 rabbits, from a group of 12 receiving S- (+)-ketamine. In 5 control animals, no histological changes were observed. Nevertheless there was no significant difference in neurological status between the two groups after 7 days of intrathecal treatment (Vranken et al., 2006).

Also in rhesus monkeys, neuronal cell death has been reported, but this was very much dependent on the stage of development of the animal and the duration of administration. Electron microscopy indicated that ketamine-induced neuronal cell death is most likely to be both apoptotic and necrotic in nature (Slikker et al., 2007).

The mechanism for this neurotoxic response is proposed to be based on a NMDA-antagonist-mediated hypofunction of the NMDA-receptor, resulting in a combination of enhancement of excitatory neuronal pathways and inhibition of inhibitory neuronal pathways that lead to and from specific groups of neurones in the cingulate and retrosplenial cerebral cortices. Consistent with this hypothesis, it has been shown that several classes of drugs effectively inhibit the neurotoxic effects of the NMDA antagonists, including a) muscarinic receptor antagonists, b) (GABA)A-receptor agonists (such as benzodiazepines), c) σ-receptor antagonists, d) non-NMDA (kainic acid) receptor antagonists, e) α2-adrenergic receptor agonists, f) some typical antipsychotic agents (for instance haloperidol) and g) atypical antipsychotic agents (clozapine, olanzapine) (Bergman, 1999). It may be anticipated that substances with opposite pharmacological actions to those classes of drugs mentioned here may enhance the neurotoxicity of ketamine. In this context, from the recreational drug repertoire should be mentioned: Amanita muscaria mushrooms (muscarinic agonist), alcohol (NMDA- and (partial) GABA)A-antagonist, yohimbine (α2-adrenergic receptor antagonist), and other dissociative drugs like PCP and tiletamine.

Two recent publications give additional insights into the possible mechanisms of the neurotoxicity of ketamine. Wang et al. (2005) show that upregulation of the NMDA receptor subunit NR1 following ketamine administration is, at least, partially responsible for the observed apoptosis. And Liao et al. (2004) describe the induction of the expression of HSP70 by ketamine and also that ketamine injures the neurons of rat hippocampus, and the higher the dose given, the more serious the injury is. Furthermore, ketamine induces a higher level of HSP70 expression in adult rats than in infant rats. A more pronounced neurotoxic effect in adult rats is also mentioned as a result of the investigations of Beals et al. (2004) - an effect ketamine shares with nitrous oxide, another NMDA-antagonist also used in the party scene.

There may be several reasons why these findings in rats have not led to the abandonment of the clinical use of ketamine. First, ketamine is generally accepted as a safe anaesthetic without long-term adverse effects (Shorn and Whitwam, 1980; Reich and Silvay, 1989). Therefore, the preclinical data are considered of limited clinical relevance. Secondly, benzodiazepines are usually co-administered with ketamine to reduce the occurrence of emergence phenomena (for a description, see below Human,
Clinical experience). Benzodiazepines have been shown in rats to protect against the ketamine-induced neurotoxicity.

Contrarily, there may be reasons why the findings on the neurotoxicity of ketamine in the rat may be of concern to recreational users of ketamine. First, substance users will not take ketamine in combination with protective agents like benzodiazepines. Moreover, compounds increasing the neurotoxic potency of ketamine might be co-administered. Secondly, recreational use implies repeated exposure, whereas clinical use is mostly incidental. Long-term adverse effects in long-term users of ketamine have been reported, however are scarce. These included persisting impairment of attention and recall and a subtle visual anomaly (Jansen, 1990). A review on internet reports from heavy users of ‘dissociatives’ (i.e. dextromethorphan, ketamine and PCP) is summarised. Effects mentioned after frequent use were “jolts” or “shocks” when moving the eyes, sharply impaired visual tracking, impaired recognition of metaphor, impaired language skills and memory problems. These adverse effects (that fade with time) are related by the author to malfunction of or damage to the cingulate and retrosplenial cortices. To date, there is insufficient evidence to ascertain such a relationship in humans.

6. **Adverse reactions in humans**

**Human**

*Clinical experience*

Ketamine is considered to be an anaesthetic with a good safety profile (Reich and Silvay, 1989). Its major drawback, limiting its clinical use, is the occurrence of emergence reactions. Emergence phenomena in patients awakening from a ketamine narcosis have been described following early clinical experience, and include hallucinations, vivid dreams, floating sensations and delirium. These symptoms were found to be reduced by concurrent use of benzodiazepines, putting the patient in a low stimulus environment and by providing information on the possible emergence reactions preoperatively. These emergence phenomena appear to occur more frequently in adults (30-50%) than in children (5-15%) (White and Ryan, 1996; Bergman, 1999). No adverse outcomes were noted in nine healthy children treated in the emergency department who inadvertently received 5 to 100 times the intended dose of ketamine. Toxicity manifested as prolonged sedation in all nine and brief respiratory depression in four of the children. The margin of safety in ketamine overdose may be wide (Green et al., 1999).

*Respiratory depression*

In two cases, a severe respiratory depression has been described after co-administration of ketamine. In one case, it appeared after premedication with secobarbital in a seven-year-old patient given a subanaesthetic dose of ketamine (approximately 3.3 mg/kg i.m.) (Kopman, 1972). In the other case, ethanol was involved with a fatal ending (Moore et al., 1997).

*Sympathicomimetic effects*

Serious side effects like hypertension and lung edema have been reported (Murphy, 1993). Such adverse effects appear to be rare and may be related to the combination of ketamine with other substances of abuse.
This may be due to the sympathicomimetic properties of ketamine. Inhibition of central catecholamine re-uptake and increased levels of circulating catecholamines are believed to cause the cardiovascular stimulant effects.

On the other hand, cardiodepressant effects have been noted in critically ill patients. This may be due to chronic catecholamine depletion and so preventing any sympathicomimetic effects of ketamine and unmasking a negative inotropic effect, which is usually overshadowed by sympathetic stimulation (White and Ryan, 1996; Reich and Silvay, 1989).

**Non-medical experience**

*Fatal intoxications*

In the EMCDDA report, a short overview is given of 13 reported deaths in which recreational use of ketamine was involved. The following conclusions can be drawn from the data as presented in the report:

- Only in 3 out of 13 cases of fatal intoxications was ketamine solely identified. It was administered by injection. Two reports describe mixed drug fatalities. In the other cases ketamine had either a minor role or there was a lack of data for a proper evaluation.

- In contrast to what is known from non-medical use where usually lower dosages are used, the ketamine blood concentrations in the described cases were in the anaesthetic range or above. Where clues about the quantity administered were available, such indicators suggested amounts of approximately 1 g administered i.v. or i.m. in the absence of other substances. Based on a body weight of 60 kg, such a dose is 4-17 times the recommended i.v. dose for anaesthesia or 1.3-2.5 times the recommended i.m. dose for anaesthesia. The i.v. data are in line with preclinical findings. In squirrel monkeys death occurred when ketamine was administered (i.v.) at a dosage more than ten times the dose producing anaesthesia (Greenstein, 1975). The relatively small margin of safety for the acute toxicity applying the i.m. route cannot be explained without any further investigation. From a clinical point of view it is at least not expected.

In the subgroup of multiple substance users, the ketamine concentrations found are lower than those found in the few cases involving ketamine only. This indicates that drug interactions may play a significant role in contributing to these deaths. In this respect, substances with CNS/respiratory depressant effects, like ethanol, opioids, barbiturates, and benzodiazepines, or substances with cardiotimulant effects, like cocaine and amfetamines, are indicated as drugs that may increase ketamine toxicity.

Benzodiazepines can have favourable effects in clinical practice as co-administration prevents the occurrence of emergence phenomena (as described above). But when used simultaneously in a recreational setting without proper monitoring of vital functions, they may enhance the respiratory and CNS-depressant effects of ketamine.

In an article by Gill and Stajic (2000), all ketamine-positive deaths (87) over a two-year period (1997 to 1999) examined at the New York City Office of Chief Medical Examiner were reviewed. There were 15 non-hospital deaths with 12 due to acute multidrug intoxications. In no instance was a fatal intoxication caused exclusively by
ketamine. Opiates, amphetamines and cocaine were the most frequent co-intoxicants. Ethanol was found in only one death.

In 2004 two other cases were published in which the use of ketamine was fatal (Lalonde and Wallage 2004). One case strongly points to ketamine as the sole factor responsible for the fatal ending. In the other case the presence of asthma as co-morbidity factor cannot be excluded.

In a letter to the editor, Schifano et al. (2008) present an overview of all the ketamine-associated deaths in the UK over the period 1993-2006. Twenty three cases are presented but in only four cases ketamine has been identified postmortem as the sole substance present. Blood levels have not been measured and a direct contribution of ketamine to the deaths could not be established.

The WHO Uppsala Monitoring Centre (UMC) reported, out of 1277 reports from adverse effects from world wide PMS-data, over a 2-year period, 25 cases of death, (2.0 %) and 1 case of sudden death (0.08%) (unpublished, communication to WHO, 2005).

Non-fatal intoxications
From the available data on non-fatal intoxications after the use of ketamine by recreational users, the following conclusions can be drawn (Siegel, 1978; Dalgarno and Shewan, 1996; Weiner et al., 2000):

The main effects are neurobehavioural:
- anxiety (especially in first-time users),
- agitation (Arditti, 2000),
- changes of perception (e.g. loss of notion of danger, visual disturbances),
- disorientation and impairment of motor function, such as ataxia (Arditti, 2000) and dystonic reaction (Felser and Orban, 1982).

In such a condition, the misusers will have severely impaired self-control, which poses a risk for injury for him or her self or others (e.g. when participating in traffic).

Common side-effects reported by users were:
- slurred speech,
- dizziness,
- blurred vision,
- palpitations,
- chest pain,
- vomiting, and
- insomnia.

The predominant symptom found on physical examination in users that went to an emergency department was tachycardia (Weiner et al., 2000). Rhabdomyolysis was noted in several cases (Weiner et al., 2000). Other physical side-effects appear to be rare.

Some other effects less often reported were:
neuropathy of Guillain-Barré type and some physical effects such as general stiffness, increase of body temperature (38 °C), hepatic crises, myalgia and mydriasis.

Recently, lower urinary tract symptoms have been described as a new adverse effect of ketamine misuse (Chu et al., 2008, Colebunders and Van Erps, 2008, Shahani et al., 2007). The cases presented show cystitis and bladder dysfunction, urinary frequency, urgency, dysuria, urge incontinence and occasionally painful haematuria. Secondary renal damage can occur in severe cases.

Two remarks should be made on these findings:
As NMDA-receptors are present in the urinary tract, effects can be expected and have been reported in animals. These effects do not translate into significant reporting of adverse effects to the WHO Uppsala Monitoring Centre. Only a limited number has been found in their database.

Furthermore, most cases (almost 60) arise from Hong Kong. It cannot be ruled out that either a genetic component contributes to this effect or that besides ketamine, one or more other factors are present which have contributed to these symptoms. Combination of ketamine with other substances of abuse has been described in the literature.

7. Dependence potential
Behavioural studies in animals

Self-administration
Animal models of dependence are used to test the induction of substance-taking behaviour which might be similar to the recreational use of ketamine. To date there are no animal models that incorporate all the elements of dependence. The observation that animals readily self-administer drugs has led to the argument of face-validity, and psychologically this is based on the reinforcing properties of a compound. This animal model has also a high predictive validity, although there are some limitations (Willner, 1997; Koob et al., 1998).

Early assessments of the reinforcing properties of ketamine reported that rhesus monkeys shown to self-administer intravenously metamfetamine or cocaine also self-administered ketamine (3.2-1600 microg/kg/inj) under limited access conditions at an intense schedule of reinforcement. An inverted U-shaped dose–response curve was observed. A variation of the fixed ratio so that the animals have to put more effort to obtain their reward, produced an orderly increase in the response rate with a factor of 3 (Moreton et al., 1977). Increasing the fixed ratio on PCP administration, however, eliminated the responding on PCP (Marquis and Moreton, 1987) suggesting a higher intrinsic power of reinforcement for ketamine, which might be more related to the depressant action of the substance than to the psychotomimetic action. In baboons, however, self-administration was obtained at a FR160 schedule (Lukas et al., 1984) both for ketamine and PCP, suggesting that the observed difference between ketamine and PCP might be specific to rhesus monkeys. No obvious behavioural changes
occurred during exposure to doses of 10-32 microg/kg. A ten-fold higher dose of PCP was associated with sedation and ataxia. Food intake was unaffected by the lower doses.

From data in various species, it appears that substance intake tends to increase slightly with increases in unit dose in each species. However, the increase is of a lesser degree that generally occurs with the self-administration of CNS depressants such as pentobarbital and morphine (Marquis and Moreton, 1987).

**Drug discrimination**

Animals are able to give an indication as to how a drug makes them “feel” with the drug-discrimination paradigm, in a behavioural method offering animals a choice and reinforcing them by pelleted food if their choice is correct depending on the treatment (drug or saline or another drug). This drug-discrimination approach is a powerful method to differentiate between subjective feelings (called the stimulus) of drugs, e.g. opioids from psychomotor stimulants. It is well-established that the drug–response data in this respect can be handled as pharmacological data showing selectivity and sensitivity.

It is well-recognized that drug-discrimination paradigms can be used also for non-dependence-producing drugs. However, when carefully designed, such studies might be certainly of value in the assessment of common subjective states produced by drugs (Schuster and Johanson, 1988).

Drug-discrimination data from a series of stereoisomers of compounds generalising to PCP or ketamine indicate that compounds exhibiting reinforcing properties comparable to PCP share similar stimulus properties of this pharmacological class (Shannon, 1981; Young et al., 1981).

**Tolerance and withdrawal**

A number of studies have demonstrated tolerance to the effects of ketamine (White and Ryan, 1996). This type of acute tolerance is related to changes at the site of action rather than any increase in rate of metabolism, as it was shown to be induced after one injection, without changing the plasma concentration.

Continuous IV infusion of PCP and ketamine at maximum tolerated dosages in rats was used to demonstrate whether dependence could be induced by these compounds. The animals were trained to lever press for their daily food rations under an FR30 schedule of reinforcement. Withdrawal of PCP as well as ketamine markedly reduced response rates, providing evidence of dependence. Readministering the compounds, the rates increased rapidly to control rates, providing evidence of reversal of withdrawal. Cross-tolerance and withdrawal from ketamine to PCP was described.

Observable withdrawal signs have been reported for rhesus monkeys with unlimited access to ketamine self-administration.

Rats, chronically exposed to ketamine, exhibited subcortical withdrawal seizures without gross behavioural manifestations for up to 5 days after self-administration was discontinued (White and Ryan, 1996)
**Behavioural studies in man**

**Acute effects**

Studies investigating the pathophysiology of schizophrenia, using ketamine as a model substance, and studies investigating the psychotrophic effects of ketamine in their own right, have provided a good characterisation of the psychotomimetic action of ketamine (e.g. Krystal *et al.*, 1994; Vollenweider *et al.*, 1997; 2000; Malhotra *et al.*, 1996; Adler *et al.*, 1999; Oranje *et al.*, 2000; Hartvig *et al.*, 1995; Bowdle *et al.*, 1998). It appears that ketamine in subanaesthetic doses induces a state of mind that both neurophysiologically and behaviourally resembles that of a schizophrenic psychosis, but that may be experienced by the experimental or recreational substance user as an altered, ‘psychedelic’, state of mind that allows him to travel beyond the boundaries of ordinary existence.

**Effects on cognitive functioning (neuropsychological assessment)**

Ketamine acutely affects cognitive performance, including attention, working memory and semantic memory.

Hartvig *et al.* (1995) showed in a double-blind randomised crossover study with five healthy volunteers that short-term memory could be impaired dose-dependently by administration of 0.1 and 0.2 mg/kg (i.v.), as assessed by a word recall test. Ketamine binding in the brain correlated well with the regional distribution of NMDA-receptors. Ketamine hydrochloride (0.1 or 0.5 mg/kg i.v. during 40 minutes) did not produce a significant effect on the mini-mental state examination (a brief bedside evaluation of cognition) in healthy subjects (n=18), however tests of vigilance, verbal fluency, and the Wisconsin Card sorting test showed a dose-dependent impairment (Krystal *et al.*, 1994). Delayed word recall was reduced, but immediate and post-distraction recall were spared.

Malhotra *et al.* (1996) assessed the effects of ketamine (total dose 0.77 mg/kg i.v. during 1 hour) on attention, free recall of categorically related words and recognition memory of categorically related words. All three cognitive functions showed significant decrements. Memory impairments were not accounted for by the changes in the subjects' attention and did not correlate to psychosis ratings. In further studies, Adler *et al.* (1998) found that ketamine induced thought disorder significantly, correlated with decrements in working memory, but did not correlate with ketamine-induced impairments in semantic memory.

Narendran *et al.* (2005) demonstrated that chronic ketamine users exhibit a regionally selective up-regulation of D1 receptor availability in the dorsolateral prefrontal cortex, an effect also seen after chronic dopamine depletion in animal studies. These data suggest that the repeated use of ketamine for recreational purposes affects prefrontal dopaminergic transmission, a system critically involved in working memory and executive function.

**Effects on emotional status, behavioural patterns and personality (psychological instruments, rating scales)**

Ketamine profoundly affects perception of body, time, surroundings and reality. A study in ten psychiatrically healthy volunteers was performed by Bowdle *et al.* (1998). The subjects were administered an escalating dose of ketamine by i.v. infusion.
with plasma target concentration of 50, 100, 150 and 200 ng/ml. Each step was maintained for twenty minutes and the subjects were asked to rate various aspects of their consciousness on a visual rating scale (VAS). A good correlation between the plasma ketamine concentrations and the VAS ratings was obtained.

The following VAS scores were increased by ketamine, compared with a saline control:

- **Body**: Body or body parts seemed to change their position or shape.
- **Surroundings**: Surroundings seemed to change size, depth or shape.
- **Time**: The passing of time was altered.
- **Reality**: There were feelings of unreality.
- **Thoughts**: There was difficulty controlling their thoughts.
- **Colours**: The intensity of colours changed.
- **Sound**: The intensity of sound changed.
- **Voices**: Unreal voices or sounds were heard.
- **Meaning**: Subjects had the idea that events, objects, or other people had particular meaning that was specific for them.
- **High**: They felt high.
- **Drowsy**: They felt drowsy.
- **Anxious**: They felt anxious.

The intensity of the effects was greatest for high, reality, time, surroundings, thought and sound. They were lowest for anxiety and meaning.

This study clearly shows there is a dose–effect relationship between the ketamine dose and the intensity of the ‘psychedelic’ effects. All but one participant spontaneously reported feelings of intoxication and perceptual distortion during the ketamine infusion; one of these persons also reported such symptoms during the placebo infusion. Three participants became moderately dysphoric during the ketamine infusion, but not during the placebo infusion.

Krystal *et al.* (1994) also included VAS of mood states in their study in 18 healthy volunteers after administration of 0.1 or 0.5 mg/kg ketamine hydrochloride i.v. for 40 minutes. They observed a biphasic effect on anxiety, the low dose decreasing anxiety and the high dose increasing anxiety. VAS rating for high was increased dose-dependently.

Hartvig *et al.* (1995) studied the psychotomimetic effect of low doses (0.1 and 0.2 mg/kg i.v.) ketamine in a double-blind randomised crossover study in five healthy volunteers. All subjects having peak plasma ketamine concentrations of 70 ng/ml or above or estimated peak regional brain ketamine concentrations of 500 ng/ml or above experienced psychotomimetic effects. These consisted of pronounced feelings of unreality, altered body image perception, sensations of impaired recognition of the limbs, detachment from the body, and modulation in hearing, characterised by preoccupation with unimportant sounds. The intensity of the effects showed a dose–response relation with the degree of regional brain binding of ketamine.
Vollenweider and coworkers (1997) investigated the differential effects of $S$- and $R$-ketamine and found that $S$-ketamine is responsible for the psychotomimetic effects, whereas $R$-ketamine induced a state of relaxation. Results of a mood rating scale for $S$-ketamine showed increased scores for ‘deactivation’, ‘introversion’, negative and dysphoric feelings and anxiety. All subjects reported distortion of body-image, loosening of ego-boundaries, and alterations of the sense of time and space, variously associated with emotional changes ranging from euphoria (30%), indifference (30%) or heightened anxiety (40%).

In an open uncontrolled study (Hansen et al., 1988), seven individuals working in health care explored the psychotropic effects of ketamine for its use as a possible adjunct in psychotherapy by intravenous, intramuscular and oral self-administration of various subanaesthetic doses. They recorded that their inner experiences were extremely intense and possessed a subjective quality, which made it difficult to put them in writing. To a certain extent, they varied from one subject to another and even for the same subject from one session to another. Nevertheless, all of the subjects had experienced most of the following phenomena:

- A sensation of light throughout the body;
- novel experiences concerning "body consistency" (e.g., being described as made up of dry wood, foam rubber, or plastic);
- grotesquely distorted shape or unreal size of body parts (e.g., extremely large or small);
- a sensation of floating or hovering in a weightless condition in space;
- radiantly colourful visions (e.g., images of moving from one room to another filled with moving, glowing geometrical patterns and figures);
- complete absence of time sense (i.e., an experience of virtual timelessness or eternity);
- periodic, sudden insight into the riddles of existence or of the self;
- occasionally, an experience of compelling emotional consanguinity, at times extending to sensations of melting together with someone or something in the environment; and
- an experience of leaving the body (i.e., out-of-body experience).

In nearly every instance, subjects retained the sense of a sober, witnessing "I" that could both observe and consider as well as be amazed, overjoyed or perhaps anxious, and that could, to a certain extent, later remember the unusual phenomena.

In the EMCDDA report (2002) a more extensive overview of the effects, including the near-dead effect, described by the participants is given.

Effects on psychopathological status - psychiatric comorbidity (psychological and psychiatric assessment)

Studies in healthy volunteers given ketamine and schizophrenic patients have shown that ketamine produces a clinical syndrome with aspects that resemble key symptoms of schizophrenia.

Krystal et al. (1994) assessed both four key positive and three key negative symptoms of schizophrenia in healthy subjects after administration of 0.1 or 0.5 mg/kg ketamine hydrochloride i.v. during 40 minutes. The positive symptoms were conceptual
disorganisation, hallucinatory behaviour, suspiciousness, and unusual thought content. The negative symptoms were blunted affect, emotional withdrawal, and motor retardation. Ketamine produced a dose-dependent increase in scores for both positive and negative symptoms.

Similarly, scores for key symptoms of schizophrenia (conceptual disorganisation and disorganised speech, unusual thought content, emotional withdrawal, psychomotor retardation and blunted affect) were increased by ketamine (Malhotra et al., 1996). Adler and co-workers (Adler et al., 1998; 1999) studied the effects of ketamine on thought disorder and compared these effects with thought disorder in patients with schizophrenia. They found similar scores for 19 of 20 items on the Scale for the Assessment of Thought, Language and Communication. Only the score for the item ‘perseveration’ was lower in schizophrenic patients. However, after Bonferroni correction this difference was no longer statistically significant.

A total dose of 0.56 mg/kg ketamine over 125 minutes was infused in healthy volunteers (n=19) to obtain a pseudo steady state plasma ketamine concentration of 134 ng/ml. Reduced processing negativity and P300 amplitude, psychophysiological anomalies, commonly observed in schizophrenic patients, were recorded. However, no drug effect on mismatch negativity, another parameter commonly reduced in schizophrenic subjects, was found (Oranje et al., 2000).

Vollenweider and coworkers (2000) observed a negative correlation between raclopride’s binding potency in the ventral striatum and S-ketamine-induced euphoria- and mania-like symptoms, suggesting a role for elevated striatal dopamine levels in these positive symptoms.

**Chronic effects**

**Effects on cognition, mood and mental functioning**

Short-term exposure to ketamine appears not induce any long-term adverse effects on cognition, mood or personality. Long-term heavy use of ketamine may be associated with persisting deficits in attention and recall. However, such a condition has been documented only once in the literature.

**Clinical studies in volunteers**

In a follow-up interview in a study by Krystal et al. (1994) of healthy volunteers given ketamine hydrochloride (0.1 or 0.5 mg/kg), no subject had lingering or recurrent physiological or psychological effects, such as nightmares, flashbacks, or perceptual alterations following a test day.

The subjects in the study of Hansen et al. (1988) did not report any long-term side effects of any nature for up to three years following the ketamine sessions. Corssen et al. (1971) studied 30 volunteers from a prison population that were given either ketamine or thiopentone or served as control. Psychological assessment was performed before, at 1 week, 4 weeks and 6 months after substance administration. They could not establish a difference between the three groups.
Studies in patients

Psychological changes were assessed in 221 patients following ketamine anaesthesia and compared with patients receiving other anaesthetics. Psychometric tests were applied repeatedly for more than 1 year (Albin et al., 1970). There were no significant differences between groups in terms of mental performance, hallucinations and behavioural factors.

Seven case reports of prolonged (several weeks to up to 1 year) psychic phenomena after single (or in one case dual) exposure were reviewed by Steen and Michenfelder (1979). In one patient, serious effects persisted for 5 days, in three others there were only minor disturbances for 3 weeks, in two patients severe congenital brain abnormalities were present, and in one patient complaining of hallucinations and “passing out spells” and feelings of unreality and hesitation, it could not be excluded that these symptoms were linked to a single dose exposure to ketamine 1 year earlier, but this seems unlikely.

Studies in recreational users

Siegel (1978) stated that subjects who reported long-term use of ketamine sometimes complained of “flashbacks”, attentional dysfunction and decreased sociability. Positive effects on mood were mentioned as well, which reinforced and maintained substance use. However, standard psychometric tests did not reveal personality changes. The subjects described were mostly polydrug users, those snorting ketamine also using cocaine. Contrarily to the PCP group, that was described in the same paper, a tendency to transient psychosis was not noted.

Amongst 20 recreational substance users studied by Dalgarno and Shewan (1996), lasting psychological effects were not reported. Eleven of them used ketamine less than 10 times, 8 used it between 10 and 20 times and only one user reported use of approximately 100 occasions. The last subject, who was an experienced poly substance user, reported “a total loss of reality” during a month-long ketamine binge, after which he stopped completely without major difficulties. Subsequently, he reported having very lucid dreams similar in nature to the ketamine-induced state. These dreams lessened in intensity and ceased completely within 7 to 10 days of the final ketamine episode. Jansen (1990) described a case in which a subject had persisting impaired recall and attention and a subtle visual anomaly after cessation of long-term high-dose ketamine use.

Morgan et al. (2004) looked at the effect of ketamine in recreational users direct after use and 3 days later. On Day 0, ketamine users were impaired on both source memory and item recognition and scored more highly on schizophrenic and dissociative symptom scales compared to poly substance controls. On Day 3 ketamine users only displayed source memory impairments and these positively correlated with the level of schizophrenic-like symptoms on Day 0. No differences on Day 3 in schizophrenic-like or dissociative symptoms were observed. These findings suggest that repeated use of ketamine produces chronic impairments to episodic memory.
In order to find out if these deficits might be reversible upon reduction or cessation of ketamine use or are long-lasting, the group of Morgan et al. (2004) performed an additional study in which they looked at ketamine users, already tested 3 years earlier. Meanwhile, this group of ketamine users had reduced their frequency of use of ketamine by an average of 88.3%. Performance of ketamine users on tasks tapping semantic memory had improved and this improvement was correlated with their reduction in ketamine use. On tasks tapping episodic memory and attentional functioning, ketamine users still showed deficits compared to poly substance controls. Higher levels of schizotypal symptoms and perceptual distortions were exhibited by the ketamine group, although dissociative symptoms were similar to controls. These findings indicate that semantic memory impairments associated with recreational use of ketamine are reversible upon marked reduction of use; however, impairments to episodic memory and possibly attentional functioning appear long-lasting. In addition, schizotypal symptoms and perceptual distortions may persist after cessation of ketamine use.

Only a very limited number of cases (10) of ketamine dependence over the past 20 years have been described (Bobo and Miller, 2002; Florkowski and Ferfecki, 1987; Lim, 2003; Pal et al., 2002, Critchlow, 2006). Unfortunately the use of terms is not well-defined and therefore one cannot be sure that the cases presented here are really dealing with ketamine dependence. Almost half of the cases deal with healthcare staff (Moore and Bostwick, 1999; Rusek et al., 1988) as they have easily access to this kind of products. Furthermore multidrug use or polysubstance is one of the features these people have in common.

**Tolerance**
Tolerance to ketamine develops quickly and can be high. In one case report, the subject relates the history of his ketamine use. During the first 2 years his consumption developed from an occasional 50 mg oral dose to 500 mg four to five times a day. Switching to intramuscular injection, he was injecting 300-750 mg five to six times a day within a month. The tolerance dissipated on stopping the habit, but redeveloped at the same rate (within a month) after restarting intramuscular injections (Kamaya and Krishna, 1987).

**Abstinence symptoms**
There is no evidence that ketamine causes an abstinence syndrome in humans. The subject described in the case report by Kamaya and Krishna (1987) found stopping the habit extremely difficult, but never experienced a withdrawal syndrome. Amongst 20 recreational ketamine users described by Dalgarno and Shewan (1996), 11 reported to never having experienced mental after-effects and 8 said never to have experienced physical after-effects following a ketamine episode. Of those that did have mental after-effects, three reported a general feeling of well-being, two had a desire for physical contact, two felt mildly depressed and "flat", and two said they were "dopey" (feeling like being under the influence of cannabis). Of those that reported physical after-effects, three reported a general feeling of contentment and happiness, four said they felt mildly "hung over" or drained, three reported vomiting, one said he felt physically and positively changed and one felt nauseous.

Jansen (2000b) states that an elevated mood after a ketamine binge is common, whereas a cocaine-like swing into depression is rare. He suggests that high levels of norketamine
can take days to subside, thereby providing a "deflating cushion". However, for such a theory no evidence is provided. In rats, norketamine-induced anaesthesia and locomotor activity are of shorter duration than when these effects are induced by ketamine. Both ketamine and norketamine are rapidly cleared from blood and brain (Leung and Baillie, 1986).

**Substance-seeking behaviour and dependence**

A distinction may be drawn between experimental (Ahmed and Petchkowsky, 1980) and dependent ketamine use (Kamaya and Krishna, 1987; Hurt and Ritchie, 1994). In dependent users, use of the substance continues despite increasing apparent effects on their work or on their health. Amongst the 20 users described by Dalgarno and Shewan (1996), seven had used ketamine once or twice and only three had used 15 times or more. One user in this group reported that he had believed the experience was "never going to end" and another experienced extreme dissociation. These two never repeated their first-time use. It appears that the dissociative experience discourages some experimental users. Another reason for limited use mentioned in this study was the scarcity of the substance. On the other side of the spectrum, one user in this study group said he believed he had been dependent on the use of ketamine during his heaviest period of ketamine use.

According to Jansen (2000b), tolerance to the effects of ketamine develops, and with higher doses the ability to remember the experience is sharply reduced. Where many stop at this point, others carry on with compulsive binges. These result in cocaine-like stimulation, opioid-like calming, cannabis-like imagery (which also disappears), alcohol-like intoxication, and relief from anxiety, depression, and mental craving (Jansen, 2000b). Jansen states that repeated users of ketamine may rapidly become dependent. This dependence-promoting nature of ketamine may be prominent for those that carry on with compulsive binges. No sound data on the prevalence of long-term use are available.

Three well-known ketamine histories are those of John Lilly (1978), Marcia Moore (1978) and D.M. Turner (1994). The first still seemed to use ketamine at the age of 83, even though at some point in his life elected hospitalisation for ketamine withdrawal. The second, according to her husband, Howard Altounian, became dependent and committed suicide. The third slipped below the waterline in his bathtub, with a half-empty bottle of ketamine on its side.

8. **Abuse potential**

No systematic studies on personality traits or other psychological factors leading to ketamine use or affecting the probability of harm were found. Psychological factors that increase the probability of harm include mood and anxiety conditions leading to self-medication and sensation seeking.

Jansen (2000b) describes several conditions that may drive the use of ketamine. Amongst these is a characteristic of the ketamine experience, which may be described as escape from reality. Few substances offer such a strong experience of entering a different reality, which is not only experienced as differently, but also as no less real than reality without the substance. This possibility for escape and discovery may appeal to some individuals, especially those that have discontent with their ordinary existence.
and are looking for sense and meaning in their life. The ketamine experience offers in this way a psychological reward, which contributes to the development of dependence. In those involved in taking substances as much and as many as possible, the sensation-seeking factor will certainly be important (Laviola et al., 1999). Ketamine, advertised as The Ultimate Psychedelic Journey (Turner, 1994), will appeal to substance users looking for extremes.

9. Therapeutic applications and extent of therapeutic use

Ketamine hydrochloride is used as an analgesic and anaesthetic in human and veterinary medicine, where it has acquired a unique place. Registered indications for ketamine use are listed in Annexe 1 report on WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD.

Important clinical applications are mainly brief procedures in paediatric and ambulatory anaesthesia, its use in the treatment of burning wound patients, obstetrics and for the induction and maintenance of anaesthesia in hypovolemic, pericardial tamponade, constrictive pericarditis, and cardiogenic shock patients (Reich and Silvay, 1989; Bergman, 1999; Haas and Harper, 1992).

Its use in veterinary anaesthesia, especially in small animals, as well as in exotic animals, is widespread. Several Member States (Sweden, Denmark, Germany, Portugal) indicate that ketamine is indispensable for its indications in veterinary medicine.

Outside the EU, the use of ketamine as an anaesthetic in human medicine may have a more prominent place in developing countries, where facilities are much poorer. The ease of use gives ketamine a major advantage under the more difficult circumstances encountered (Green et al., 1996). The impact of ketamine availability on general and African medical practice in Ethiopia, Nigeria, Tanzania and Benin is described in annexes 2 and 3.

The pharmaceutical form of the preparations used in medicine is an injectable solution of the racemic mixture of ketamine hydrochloride in water. The solution is packaged in small glass sealed vials.

In several countries, the racemic mixture has already been replaced by a formulation containing the S-(+)-enantiomer only.

As the molecular action of substances used in medicine is better understood due to new techniques and insights, new indications or applications for well-established products, like ketamine, may emerge.

At this moment, the following new indications for ketamine have been investigated and published:

- analgesia, for instance in patients resistant to opioids (Akin et al., 2005). Also other routes of application are being investigated, like the intranasal route (Bell and Kalso, 2004) – an unexpected by-product from the non-medical use. Another development in this field is the use of lower, so-called subanaesthetic doses (Smith et al., 2001).
• psychotherapy, either as an adjunct to the psychotherapeutic process (Hansen, 1988) or as a chemical adjuvant in the treatment of dependence to alcohol (Krupitsky and Grinenko, 1997) or heroin (Krupitsky et al., 2002, Krupitsky et al., 2007). The treatment of alcoholism is based on the effects of ethanol on the NMDA-receptor complex with which also ketamine interacts (Krystal et al., 2003, Krystal et al., 2003).

10. Listing on the WHO Model List of Essential Medicines

Ketamine is listed as an anaesthetic both in EML 18th ed (2011) and in EMLc 3rd ed (2011).

11. Marketing authorizations (as a medicine)

Ketamine is authorized as a medicine at least in 60 countries including the United States of America and the European Union. See also annexe 1, report of the WHO Questionnaire for Review of Psychoactive Substances for the 35th ECDD

12. Industrial use

Not applicable.

13. Non-medical use, abuse and dependence

The most popular route of administration, when ketamine is used recreationally or experimentally, is the intranasal route, i.e. snorting the powder, or a solution from a vaporiser. Some long-term users may use the intramuscular, subcutaneous or intravenous route as well. In the rave scene, oral administration by way of ketamine-containing tablets occurs as well.

Recreational users snorting the powder, describing the quantity as a ‘typical line’, suggest a quantity between 60 and 250 mg (Dalgarno and Shewan, 1996). Ketamine containing ecstasy-mimic tablets available in Hong Kong SAR could contain amounts varying from 5 mg to 170 mg per tablet. With illicit ketamine, purity of the substance can vary. In Hong Kong SAR, purity of ketamine seized in a month varied from 40-85%.

Ketamine was first marketed in the early 1970s (FDA, 1979), and promoted as a more acceptable alternative to its congener PCP (“Angel dust”) (Dotson et al., 1995). PCP was abandoned, except for veterinary use, because of its adverse effects such as hallucinations and delirium. Although ketamine is not devoid of similar side effects, these are less persistent.

Ketamine misuse was first spotted at the West Coast of the USA in 1971 (Siegel, 1978). In the early 1990s in the UK, several reports of a more widespread recreational use of ketamine appeared (Hall and Cassidy, 1992; McDonald and Key, 1992; Jansen, 1993;
Dalgarno and Shewan, 1996). An inquiry of the EMCDDA has shown that recreational use of ketamine is noted in other EU Member States as well (Arditti, 2000).

Although the contemporary dance drug scene is a global phenomenon with many countries, France, Canada, USA, Scotland, Australia, and cultures (Arditti et al., 2002; Barrett et al., 2005; Chengzheng et al., 2004; Clatts et al., 2005; Gross et al., 2002; Riley et al., 2001) reporting similar developments with ecstasy and other club drug use, the scene, in many respects, is a reflection and expression of local culture. During the last few years the term ‘club drugs’ has been used for defining an heterogeneous group of chemical substances in permanent evolution, that are consumed for recreational purposes. These substances have been extensively used, firstly by the Rave culture and later by the so called Club culture. These movements are characterized by the search of amplified sensations, by means of the combination of electronic music, marathon dancing and substance misuse. After years with a predominating consumption of amphetamine type stimulants in these groups, it seems that the use of another type of substances is increasing, fundamentally substances with hallucinogenic effects, such as ketamine (Abanades et al., 2004).

Besides these more mainstream groups, several smaller groups have been identified in which ketamine is misused. For instance a subset of gay men also taking more sexual risks (Lee et al., 2003), but also homeless and runaway youth (Lankenau and Clatts, 2004; Van Leeuwen et al., 2004). Other harms that require further investigation are the association between ketamine and unsafe sex and injecting behaviours, and use in situations where there is an increased risk of accidental death when the user's cognition is grossly impaired (Degenhardt et al., 2005).

Although a lot of research groups are investigating the use of recreational substances, no solid epidemiological data are present. Top et al. (2004) describe the Australian Illicit Drug Reporting System (IDRS) and its feasibility of monitoring trends in the markets for ‘party drugs’. The trial demonstrated that the system would allow the successful monitoring of markets for party drugs that are relatively widely used, such as ecstasy, but would be less sensitive in monitoring markets for party drugs that are used by small proportions of the total population, such as gamma-hydroxybutyrate (GHB) and ketamine.

Please refer to additional data in Annex 4 and 5

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Copeland and Dillon (2005) give an overview of the health and psycho-social consequences of ketamine use. Information on ketamine is not routinely collected in population surveys and morbidity and mortality data collections. Levels of use in the general population, however, appear to be very low with higher levels in groups with access to the substance, such as medical and veterinarian professionals, and party drug users. There are a number of potential ketamine effects that may be seen as adverse or harmful, with growing evidence of the symptoms of ketamine dependence among recreational ketamine users. A withdrawal syndrome, including psychotic features, is beginning to be described. The use of ketamine with other neurotoxic drugs, such as alcohol, should be avoided. Increased rates of high risk sexual and injecting behaviours
in association with ketamine use, however, have been reported by gay men and marginalised youth in the US. The conclusion of the authors is that ketamine does not appear to currently pose a significant public health risk.

Please refer to additional data in Annex 4 and 5

15. **Licit production, consumption and international trade**

See report on questionnaire to Member States.

16. **Illicit manufacture and traffic and related information**

Due to the difficult chemical synthesis of ketamine so far only diversion from legal sources has been observed.

In letters to the WHO the International Narcotics Control Board (INCB), dated 2005, a number of examples of misuse and trafficking are given.

For an unknown reason this is focused primarily to Asia and Oceania. Countries mentioned are: Australia, Bangladesh, Cambodia, China, the Hong Kong Special Administrative Region of China, India, Malaysia, Singapore, Thailand and Viet Nam. One reason might be the increasing tourism to these countries by Europeans or Americans as it is often more easy to obtain these products overhere. One city in particular has to be mentioned, Goa, as back in the nineteenthies this was also the place were the so called XTC (being mostly MDMA) started its advance into the club and dance scene.

The INCB mentioned also newspaper articles on increased use in the United Kingdom (The Guardian) and Malaysia (The Star). In the latter the use increased from 8% of all drug use in 2002 to 28% in 2003 and 32% in 2004.

Please refer to additional data in Annex 4 and 5

17. **Current international controls and their impact**

Ketamine is currently not under international control by the international drug control conventions.

However in 2006, the Commission on Narcotic Drugs (CND), in its resolution 49/6 called upon Member States to pay particular attention to the emerging problem of widespread misuse of and trafficking in ketamine, in particular in East and South-East Asia, which also affects States in other regions and to consider controlling the use of ketamine by placing it on the list of substances controlled under their national legislation, where the domestic situation so requires.

In 2007, the CND in its resolution 50/3 encouraged Member States to pay particular attention to the emerging problem of widespread misuse and diversion of ketamine, in particular in East and South-East Asia and South America, which also affects States in other regions and to consider adopting a system of precautionary measures for use by their government agencies to facilitate the timely detection of the diversion of ketamine.
It requested the United Nations Office on Drugs and Crime to share the concerns of the CND with the Expert Committee on Drug Dependence of the World Health Organization, and, in that regard, looks forward to the updated review of ketamine in the report of the Expert Committee.

In its Annual Report for 2007, the International Narcotics Control Board (INCB) called on all Governments to implement Commission resolution 50/3 without delay. In its reports for 2008 and 2009 it called for the implementation of both resolutions 49/6 and 50/3.

In 2008, in addition, the Board "decided to request all Governments to provide it with information on the specific legal or administrative measures adopted pursuant to Commission resolution 49/6, including information on measures to control ketamine". As of 1 November 2008, the Board had received the requested information from 63 countries and 4 territories, of which 34 reported that ketamine had already been placed on the list of substances controlled under national legislation, pursuant to CND resolution 49/6, and 32 countries reported that legal provisions or administrative measures had been adopted to implement that resolution. Of the countries and territories that had not yet placed ketamine under control, 9 reported that their domestic situation would require doing so, mainly because of the extent of misuse of the substance. The Board requested that all Governments that have not yet done so furnish it with updated information on their national regulatory control measures for ketamine for publication on the Board’s website. In 2009, a total of 48 Governments reported that ketamine had already been placed on the list of substances controlled under national legislation.

It may be argued that de facto over the years a situation of international control has emerged without any scientific assessment of the situation, due to both CND resolutions and the INCB continuous pressure on Member States.

It should be mentioned that according to the international drug control conventions the CND has no mandate to conclude to international control without a WHO recommendation and the INCB has no mandate at all. The World Health Organization mentioned this at several occasion during the discussions of the Commission on Narcotic Drugs on the INCB Annual Reports.

18. Current and past national controls

See report on questionnaire to Member States. (Annexe 1)

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance
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The 2008 WHO questionnaire for the preparation of the thirty-fifth Expert Committee on Drug Dependence was responded for ketamine by 64 countries.

LEGITIMATE USE

60 countries authorized ketamine as a medical or veterinary product. 8 countries legitimated ketamine for technical use and 2 countries authorized ketamine for other legitimate use. Of the countries that responded to the questionnaire the Czech Republic was the first country to grant market admission in 1970. Burkino Faso was one of the respondents that most recently admitted ketamine to the market in 2002. In 52 countries the registered indication for ketamine is anaesthetics. In Greece and Malaysia it is also used for analgesia, including, neuropathic pain, pain associated procedures, pain management in humans, pain control, adjuvant therapy of status asthmaticus, immobilization, sedation, therapeutic and psychedelic use, for diagnostic and therapeutic reasons, persistent hiccough, priapism and resistant bronchospasm. For a full list of indications as mentioned in the responses see annex ketamine.

In the Netherlands, Norway and Tuvalu it is used off-label for analgesia.

The dosage use varies between 5 mg/ml and 100 mg/ml. Ketamine is injected and the most common dosage that is used is 50 mg/ml.

Iraq has legitimated ketamine for technical use as general anaesthesia for medical use.

30 countries indicated that they import the substance. In 6 countries ketamine is imported and also manufactured in the country. Of the countries that responded to the questionnaire, China is the only country that manufactures ketamine and does not import the substance.

ABUSE

Of the 64 countries responding, 16 countries reported on the use of ketamine in a harmful way and 9 countries reported on the extent of the harmful use. When abused, ketamine is administered orally, smoked, injected or snorted. The latter is the most common way of abuse in Germany and the USA. Other reported ways of abuse are in the form of tablets, capsules, liquid and crystalline.

In Australia 1.1% of the general population used ketamine at least once in their lifetime. In China most abusers also abuse other psychoactive substances. Further reports on the extent of the abuse are reported in Germany and the Czech Republic. In Denmark it is presumed that < 2% of the youth used ketamine. Malaysia reported the abuse among adolescents and teenagers in disco and night clubs. The Republic of Korea reported the use of ketamine as a substitute for MDMA and LSD. In Thailand it is used by adolescents as a club drug, usually together with ecstasy. Finally the USA reported the use of ketamine in parties. They have 700 reports of sale/use by minors in schools, college, nightclubs and "rave" dances. It is also abused in facilitating sexual assaults. A national high school survey was done among eighth, tenth and twelfth grade students from 2004 to 2007. Data indicates that GHB abuse among this population remained relatively stable from 2006 to 2007.
10 countries reported on the extent of public health or social problems associated with the harmful use of ketamine, while 5 countries reported not having information or data related to public health or social problems associated with the harmful use of ketamine.

The Czech Republic reported not having any case of overdose caused by ketamine. Denmark reported not having systematic reporting of either deaths or poisonings caused by ketamine nor has ketamine been a contributing cause to deaths or poisonings. The Republic of Korea reported that ketamine, at low strength injected, can cause attention deficit, learning disorder and memory impairment. At high strength, ketamine can cause mental derangement, amnesia, respiratory problems. Thailand estimated the number of the population reporting ever having used ketamine was about 30,324 people, 0.07% of the population aged between 12-65 years. In the USA, ketamine abuse has been associated with incidents of public intoxication and improper operation of motor vehicles while individuals are under the influence of ketamine. Initially, burglaries of veterinary clinics were the primary source of the drug. Sex offenders mix ketamine into victims’ drinks, without their knowledge, or encourage victims to ingest it themselves. In 2006, an estimated 270 drug-related emergency department (ED) visits involved ketamine. In 2005, there were an estimated 303 ED visits involving ketamine. There was no statistically significant difference between the 2005 and 2006 estimates.

CONTROL
29 countries reported that ketamine is controlled under legislation that is intended to regulate availability of substances of abuse. In Germany ketamine is not subject of the drug control regulations. However in cases of illegal production, circulation, trading or passing of ketamine a violation of the Pharmaceuticals Act (AMG) may be considered. In Greece ketamine is controlled with measures equal to those described in the UN convention on Psychotropic Substances. For ketamine this means that the production, import, transportation, storage and disposal of raw materials or final products are controlled by National Organization for Medicines.

In Norway it is not controlled under legislation that intends to regulate availability of the abuse of ketamine, but when prescribing medicine containing ketamine, the same control measures apply as when prescribing substances such as morphine, pethidine and fentanyl.

In total 19 countries have tracked illicit activities involving the substance. Clandestine manufacturing is reported 3 times. Smuggling is reported 12 times and diversion is also reported 12 times. Other illicit activities are reported twice.

12 countries reported on the quantity of the seizures. The seizures vary from a few grams to thousands of kilos. The biggest reported seizures are from China with 6000 kg and the USA with an average of 3730 kg a year (451 to 1414 per year during 2004-2007). Other seizures are reported in Thailand 360 kg, Germany 240 kg, Malaysia 150 kg, Dominican Republic 26 kg, Myanmar 17 kg, Poland 10 kg and France 9 kg. Smaller seizures are reported in Denmark, Norway and the Republic of Korea.

IMPACT OF SCHEDULING
8 countries reported that if ketamine is placed under more strict international control, the availability for medical use will be affected.

7 countries reported how a transfer will impact the medical availability.
Bhutan reported that there will be an impact of scheduling to some extent. The transfer will impact medical availability as a result of stringent import regulation. The impact in China is the control of the substance as a psychotropic substance since 2001. In Greece it will have an impact on the distribution.

The Netherlands reported that the impact of the transfer will be that the use of ketamine will be less than medical/veterinary acceptable. According to the Republic of Korea the impact of international control, the administrative process in distribution will be more complicated. Tuvalu reported that control will affect the quantities allocated for each country.

**Ketamine - Brand Names**

- Imalgene, Detalar, Ketamine
- Calipsol, Ketamine HCL, Ketamin
- Ketamin DeltaSelect, Ketamin Inresa, Ketamin, O.K. injectionsol
- Ketaset
- Ketalar
- Anesket Vigente Hasta, Ketalar, Ketamina
- Calypsol
- Kanox, Ketamine HCL
- Clorketam, Ketamine
- Pan ketamine
- Roxtexmedia Trittal
- Fetamin-chu 'Fhjita'
- Tekam
- Bioketan, Ketamidor
- Calypsal
- Narketan 10
- Ketamax
- AB Ketamin
- Ketajex, K Mar
- Katanest-S
- Ketamina, Katanest, Vetaketam
- Imalgewe
- Keiran, Kesia, Motorin, Tazet
- Ketolar, Imalgene
- Inducmina
- Kalypspa, Kalypsol
- Ketaflo, Ketaject, Ketaset plus, Vetaket, Vetalar

**Form**

Injected

**Registered Indications for Ketamine**

- Anesthesia
- Anesthetic agent
- Induction and maintenance of anesthesia
- Induction of anesthesia to be maintained with other medicines
- Intramuscular anesthetic
- Short term anesthesiology
- Introduction of anesthesia
- Local anesthetic
- General anesthetic
- Introduction to general anesthesia
- Anesthetic in emergency cases
- Anesthesia for diagnostics
- Anesthesia for short surgical operations
- Anesthetics in short time diagnostic or surgical procedures
- Anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation
- Anesthetics given prior to the administration of other anesthetics
- Anesthesia prior to the administration of other general anesthetic agents
- As supplement to other anesthetics
- Supplement low-potency agents, such as nitrous oxide
- Induce inhalation anesthesia
- (- Nonbarbiturate IV and IM anesthetic especially for short procedures)
- Obstetrics for vaginal delivery or in caesarean section
- Analgesic
- Analgesic agent
- Neuropathic pain
- Pain associated procedures
- Pain management in humans
- Pain control
- Adjuvant therapy of status asthmatics
- Immobilization
- Sedation
- Therapeutic and psychedelic use
- For diagnostic and therapeutic reasons
- Persistent hiccough
- Priapism
- Resistant bronchospasm

S.D. Amanor--Boadu, O.A. Soyannwo
February 2008

Executive Summary

Further to the International Narcotics Control Board (INCB 2006) recommendation that the World Health Organization (WHO) should expedite a review to determine whether ketamine should be placed under international control, the WHO requested an investigation into the impact of ketamine on medical practice in Africa.

Ketamine was first introduced into medical practice as an anaesthetic agent in 1965. It is structurally related to phencyclidines and is presented as the hydrochloride form in the racemic mixture. It is used worldwide but in the developing countries it is a central medicine in anaesthetic practice and is thus used extensively.

The advantage of ketamine over other agents is that it stimulates the cardiovascular system in most instances and does not have appreciable respiratory depressant action. It is analgesic even in sub anaesthetic doses.

Anaesthesia suffers from severe manpower shortages in the developing countries especially in Africa. There are few physician anaesthetists and an insufficient number of nurse anaesthetists. Funding for health care is problematic thus limiting anaesthetic facilities.

Ketamine and thiopentone are the most commonly used anaesthetic agents in the developing countries. They are readily available and are cheap.

Ketamine is most commonly used in secondary health institutions. It is employed in 10-40% of various elective surgical procedures and is decidedly the safer agent in the high risk emergency patient. It has a unique role in obstetrics and in children thus reducing morbidity and mortality.

The alternatives to ketamine are few in the developing are the local anaesthetic agents and these may not be feasible in some surgical cases and in children.

There are no reports of ketamine misuse in any of the countries visited. Scheduling of ketamine may create a barrier to accessibility of this essential medicine and deprive many patients of prompt surgical care. A public health crisis may be created by tight control.
1. **General introduction**

In September 2002 the World Health Organisation Expert Committee on Drug Dependence had a pre-review on ketamine. A critical review of the substance was thereafter requested. (ECDD 2006)

It was concluded that there was no significant public health issues posed by the agent and the proposed international control was therefore unnecessary. It was further suggested that the drug be kept under surveillance to detect trends.

Because of the fear generated that if the medicine is scheduled it may pose a serious threat to the surgical care especially in the developing nations an investigation on its use in the developing countries was ordered.

Ketamine was introduced into medical practice as agent in 1965. It is considered to have a very good safety profile as it generally did not depress the cardiorespiratory system as did the barbiturates and the various inhalational agents in use at that time and until current time.

It is employed as an induction agent, as an agent for the maintenance of anaesthesia both in man and in veterinary practice.

Ketamine in subanaesthetic doses is used for sedation, analgesia and in reversal of opioid tolerance. It is currently a medicine of much research in pain management and neuroprotection.

In its 2006 report, the INCB has proposed to schedule the substance because of a series of misuses of the agent and the public health problem that might pose. (INCB 2007)

2. **Pharmacology of ketamine**

Ketamine belongs to the class of phencyclidines and has been in use since the late 1960s. Its use was first reported in Nigeria in 1971 (Magbagbeola). It produces a unique state of anaesthesia called Dissociative anaesthesia enhancing thalamo-limbic system while suppressing the thalamo-neocortical pathways. While the patient is anaesthetised the eyes may be open and roving and there may be movements of the lips, swallowing and other muscle movements. (Clemens and Nimmo 1981)

It is a potent analgesic with N-methyl-D-aspartate receptor blockade activity. It is also thought to act at the opioid receptor site.

It is readily available as the racemic mixture. The S isomer has been formulated and is thought to be more potent and exhibits fewer side effects than the racemic mixture. S-ketamine is not yet readily available in the developing countries.

It can be given by all routes including the oral route and the neuraxis. The onset of action after an intravenous dose is about 3 minutes and the effects lasts about 20 minutes. After intramuscular dose the effect is observed in 5-10 minutes and may last up to 30 minutes.

The agent is degraded in the liver to an active metabolite nor-ketamine.

**Doses:**
IV route 1-2 mg per kg body weight.
IM, subcutaneous and oral routes 5-10 mg/kg

It is available in 10 mg 50 mg and 100 mg per ml (10ml vials).
It is stable on the shelf and does not require refrigeration.

3. Clinical effects of ketamine

Central Nervous System
It produces Dissociative anaesthesia in a dose dependent manner. It has potent analgesic activity and increases the muscle tone. The eyes may be observed to rove or have nystagmus during anaesthesia. There may also be purposeless movement and the patient may vocalise.

It is equivocal if ketamine is epileptogenic. However, the agent is contraindicated in the epileptic patient. (Gastone et al 1975)

Ketamine increases the intracranial and the intraocular pressures. However there are recent reports of a neuro protective activity possible through the NMDA receptor blocking action which prevents cell death. More investigations are required for the implication of this in neurotrauma. (Kohrs and Durieux 1998)

Recovery from the anaesthetic may be marked by restlessness and irrational talks. The most worrisome effects are the reports of hallucinations often frightening in about 70% of adult patients. This effect is thought not to be common in children. Patients may therefore require more supervision at recovery. Hallucination precludes the use of ketamine in the schizophrenic patient.

Hallucinations are mitigated with benzodiazepines (usually diazepam) and barbiturates which further prolong the recovery of the patient from anaesthesia. Hallucinations are also reduced when inhalational agents are employed in the anaesthetics.
Tolerance develops to ketamine when it is used in repeated dosing as in burn dressing and anaesthesia for radiotherapy in children.

Analgesia
Increasingly the analgesic activity of ketamine is being further investigated. It is analgesic in subanaesthetic doses and is being used in different settings such as in perioperative analgesia, for neuropathic pain and for reversal of opioid tolerance in patients.
It is used in sedation and analgesia in children especially in cancer chemotherapy (Soyannwo et al 2001).

Cardiovascular System
Ketamine provokes the release of catecholamines and is thus stimulatory on the cardiovascular system. There is increased heart rate, blood pressure and systemic vascular resistance after an intravenous dose. (Tweed et al 1972) This effect is highly desirable in the shocked patient and is widely used in this clinical setting. This effect however contraindicates the use of ketamine in the hypertensive patient, the patient with arrhythmias and the patient with ischaemic heart disease.
Respiratory System
When given by slow intravenous injection, the respiratory rate and depth are maintained during ketamine anaesthesia. Respiration is preserved also after im dosing. Some desaturation has been reported when the patients had some airway obstruction immediately after induction. (Pesonen 1991)
Preservation of the respiratory system is useful in situations where there is limited access to the airway as in extrication of trauma victims and when airway skills and apparatus are limited.

Through its sympathetic effect, ketamine is bronchodilatory and may be the agent of choice in patients with asthma.

The laryngeal and the pharyngeal reflexes are also thought to be preserved. This attribute makes it a better agent in field or sub-optimal anaesthetic environment when a patient might be at risk of regurgitation. In a report by Ezra et al. 2000 regurgitation and aspiration occurred only in patients who had Methohexitone anaesthetic in non-caesarean emergency obstetric patients who needed surgery. Ketamine is thus employed in many cases in the developing world in obstetric anaesthesia. The gold standard is that patients at risk of aspiration who need a general anaesthetic should have cuffed endotracheal intubation to minimise risk of aspiration. Tracheal intubation in the obstetric patient is usually difficult and requires expertise. Difficulty with the airway contributed significantly to maternal morbidity and mortality until the current trend of regional anaesthesia became entrenched.

Some of the cadre of anaesthesia care givers in the developing world may not be skilled at safe tracheal intubation should the patient need general anaesthesia. The retention of the laryngeal reflexes in a large proportion of patients during ketamine anaesthesia enables prompt surgical care. The addition of other depressant agents such as benzodiazepines may render the airway vulnerable to aspiration.

Laryngospasm sometimes occur during ketamine anaesthesia but it is more common in children. Excessive salivation and pooling of secretion in the mouth may be contributory. The use of a drying agent such as atropine or glycopyrrolate in premedication is recommended. Laryngospasm often responds to simple airway manoeuvres.

Gastrointestinal tract
Ketamine is pro emetic with varying incidence of 25-40 %. This effect is less than that observed with opioids and is also amenable to antiemetics. It is not hepatotoxic and can be safely employed in the porphyric patient which is an advantage over thiopentone. There is no oxytocic effect but should probably be avoided in non-parturient pregnant women requiring surgery. It crosses the placenta but newborns infants are seldom depressed to the degree seen with other anaesthetic agents.

Musculoskeletal system
Ketamine increases the muscle tone. This effect is marked in infants who may become opisthotonic and suffer respiratory embarrassment as a result. Extreme caution should be exercised when it is used in this group of patients. Increased muscle tone creating difficulty in abdominal operations is seldom a problem in parturient mothers and in
patients with lax abdominal walls. Muscle tone is reduced when benzodiazepines are co-administered.

In summary ketamine is a highly versatile agent employed in perioperative setting as anaesthetic and analgesic, in acute care and in chronic pain management, in trauma and in the field environment. It is cheap and therefore readily affordable for most impoverished nations. Contraindications include hypertensive and IHD, psychiatric conditions, raised intracranial and intraocular pressures and allergy to the medicine.

4. Medical use of ketamine in industrialised countries

The use of ketamine in human medicine is limited in industrialised countries but it is widely used in veterinary practice. The use is limited because of cardiovascular stimulatory effects and the worrisome emergence hallucinations which complicate its use. Ketamine has a relatively prolonged duration of action which is undesirable in current anaesthetic practice where rapid and smooth emergence from anaesthesia, rapid patient turn over and ambulatory surgery is highly desirable and is increasingly practised from both patient and cost angles.

Ketamine is reserved for use in specific cases such as in haemorrhagic shock, and haemodynamic instability. It is a useful agent as a bronchodilator and may thus be indicated in intractable asthmatic patient (Youssef-Ahmed et al 1996)

Its use is being expanded in the field of analgesia. It has been studied for effects in pre-emptive analgesia, as an adjunct to opioid analgesics for postoperative pain management and use in chronic pain states. (Michelet et al 2007, Hocking and Cousins 2003, Nafiu et al 2007)

In the emergency department it is preferred in the sedation of children. (Munro and Machonochie 2007)

Alternatives to Ketamine in Industrialised countries

There are many anaesthetic agents available in the developed countries and they may be classified into intravenous and inhalational agents.

The intravenous agents are in order of popularity
- propofol,
- thiopental,
- midazolam,
- etomidate, and
- opioid analgesics.

Propofol is easily the most popular anaesthetic agent in use today. It has a rapid onset and offset action and has many characteristics suitable for ambulatory surgery. Propofol and midazolam are used in sedation in the ICU. Propofol has cardiorespiratory depressant action similar to thiopental which is a long acting agent but there is surfeit essential anaesthesia manpower in the developing countries to enable safe use of the agents in high risk patients.
Etomidate is safer on the cardiorespiratory systems but has critical depressant effect on steroidogenesis and has been associated with fatalities in the ICU. It is used only when there is compelling indication. Propofol is the most expensive of the agents and cost about 4 USD per ampoule of 200 mg.

Short acting opioid analgesics are almost always part of the anaesthetic and they include
- fentanyl,
- alfentanil,
- sufentanil, and of late the evanescent
- remifentanil.

These agents are potent and require some skills in their use. They are also very expensive.

Long acting opioids such as morphine, meperidine, and other opioids are used.

The Inhalational Agents
Current inhalational agents include
- isoflurane,
- sevoflurane, and
- desflurane.

Halothane is also used but less so than previously because of its longer duration of action, association with hepatitis and arrhythmogenicity. Inhalational agents are also depressant on the CVS and respiratory system but more importantly they require precision anaesthetic machines and ancillary equipment for safe delivery to the patient. In the practice of safe anaesthesia today inhalational agents must be used with electronic monitoring of the inhaled gases.

Local Anaesthetic Agents
More often in current practice local anaesthetic agents are employed in anaesthesia as part of the anaesthetic and also in postoperative analgesia. The available agents include
- lidocaine,
- bupivacaine,
- S-bupivacaine, and
- ropivacaine.

5. Ketamine in veterinary practice
There is a report from the Federation of Veterinarians of Europe 200 which dealt with the issue of ketamine control. The report states “ketamine is very widely used for anaesthesia and analgesia by the veterinary profession. It is an essential anaesthetic for veterinary use because it is the only injectable anaesthetic that is safe and well tested in the full range of species that the veterinarian must treat. This includes both large and small animals, children’s pets and laboratory animals, large wild and zoo animals as well as birds and reptiles. It is safely used by virtually every veterinary practice
throughout Europe and the rest of the world. It has been used safely under POM conditions for many years.”

The report further stated that it would be detrimental to good veterinary practice if opioids and ketamine were placed under the same stringent conditions and that the Federation was not aware of any serious public health problems being reported because of the use of ketamine in vet medicine and therefore questions the need for more stringent controlled measures.

It outlined the strictures a control would create in their practice.

There was a report in 2004 of prosecution of some Russian veterinary doctors who used ketamine in their practice because it was not listed in the country’s medicines list when it was revised in 1998. The doctors were found not guilty after much pressure from animal rights groups and the population.

The Newsletter stated that there was no alternative to ketamine for Vet use in the country and more pressure was exerted to get the medicine back on the routine list. The alternatives to ketamine in veterinary practice include pentobarbital, propofol, inhalational agents such as halothane and isoflurane and the regional anaesthetic agents.

6. **Ketamine use in developing countries**

The December 2007 Supplement edition of the journal ‘Anaesthesia’ published by the Association of Anaesthetists of Great Britain and Ireland was devoted to Anaesthesia in the Developing World. The editorial described anaesthesia in the developing countries as being in crisis. The various problems were presented in sections of the paper. Ketamine anaesthesia in some clinical scenarios were also presented. (Walker et al. 2007)

Ketamine anaesthesia is widely used in the developing world because there is paucity of manpower, money and equipment. Because of the interference with and depression of the vital organ systems by anaesthetic agents and techniques highly skilled manpower are mandatory for safety in anaesthesia.

The poor state of the economy of many developing nations means poor health care financing. While in the developed countries the per capita annual expenditure on health is over USD2000 in Africa and many other developing nations it is below USD100.

Anaesthesia manpower problems in Africa are very acute and have remained so for many years. An analysis of Physician Anaesthetist manpower by the President of the West African College of Surgeons (Yeboah 2005) shows that there is

<table>
<thead>
<tr>
<th>1 anaesthetist</th>
<th>to</th>
<th>number of population</th>
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<tbody>
<tr>
<td>Mali</td>
<td>1,150,000</td>
<td></td>
</tr>
<tr>
<td>Gambia</td>
<td>350000</td>
<td></td>
</tr>
<tr>
<td>Liberia</td>
<td>unknown</td>
<td></td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>5,400,000</td>
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<tr>
<td>Ghana</td>
<td>1,333,333</td>
<td></td>
</tr>
<tr>
<td>Benin</td>
<td>1,320,000</td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>1,900,000</td>
<td></td>
</tr>
</tbody>
</table>

In the UK the ratio is 1 anaesthetist to 5000 population.
It was also lamented the inability to retain our trained workforce many of whom are emigrating to the developed world for better conditions of service and practice. Those who remain are largely employed in the cities where less than 30% of the population reside.

In February 2008, 167 surgeons of different specialities were conferred the specialist certificate by the West African College of Surgeons. Of these new graduates there were only 4 anaesthetists. Anaesthesia is not an attractive specialty. Nurses trained in anaesthesia provide much needed additional manpower. However there are limits to what they can safely practice and legislation compels them in some countries to work under the supervision of the surgeons. In the extreme surgeons may have to supervise anaesthesia administered by theatre attendants who have no basic science education. (Olasinde and Oluwadiya 2005) In Malawi such a cadre are part of the anaesthetic manpower.

In addressing the issue of manpower shortage, the World Federation of the Society of Anaesthetist assist in training in various subregions of the world, voluntary humanitarian organizations such as the Red Cross and the Medecine Sans Frontier, religious groups also offer short assistance in training and short and long term clinical work.

**Equipment**

Anaesthesia is an equipment intensive speciality and the equipment is expensive and is therefore not widely available even in some secondary health care institutions. The sophisticated equipment is also not widely available in the teaching hospitals. Some hospitals in the rural areas have only the EMO anaesthetic machine, many have none.

Anaesthetic machines need anaesthetic gases and these may also be difficult to get in rural areas due to cost, transportation etc. The machines need regular servicing to ensure safe delivery of agents. Electronic monitors, essential for early detection of cardiorespiratory dysfunction are only available in few tertiary centres. Modern anaesthetic agents are expensive for poor countries.

Anaesthesia in the developing world is therefore limited in scope and choice of agents. Ketamine anaesthesia is therefore very useful in such difficult conditions. It is described as versatile. The agent has a wide margin of safety when compared with other anaesthetic agents.

Ketamine is widely used for elective and emergency procedures, in children and adults. It is employed even for general surgical, orthopaedic, obstetric and gynaecologic procedures etc.
Ketamine in obstetrics

Maternal mortality is very high in the developing countries with rates between 800 and 2000 deaths per 100,000 live births in many countries (Fenton et al 2003, Tomta K. et al, 2003). Many factors are responsible including poor anaesthesia resources. Anaesthesia for the obstetric patient is high risk and requires adequate knowledge and skills of the attending care giver. In the situation where there is limited manpower, non-physician care givers should be trained and continuously updated in safe techniques of anaesthesia. Ketamine is useful in the shocked obstetric patient in whom spinal anaesthesia, the accepted safer technique when skilfully delivered, is contraindicated.

Poor anaesthetic facilities are not confined to the rural areas as these problems may also exist in the urban setting. In a study by Amanor-Boadu et al 97% of more than 1600 caesarean sections performed in a hospital that was about 5 kilometres away from a teaching hospital were done under ketamine anaesthesia. In the same hospital Taiwo reported on ketamine anaesthesia without endotracheal tube in the surgical management of 22 children with typhoid perforation.

Ketamine is considered safe because of its non-depressant action on the cardiorespiratory system.

In the Pacific, ketamine anaesthesia is also widely employed for various surgical procedures because of manpower shortages and remoteness of some islands. In the Latin America the anaesthetic manpower is said to be adequate and ketamine is employed sparingly as with Europe and for much of the same indications. Anaesthetic manpower is also adequate in much of India but there may be problems in the rural areas (Clyburn et al 2007).

7. Alternatives to ketamine in the developing countries

The alternatives to ketamine are limited and not as safe within the context of the limited manpower and skills.
There is thiopental, occasionally propofol, benzodiazepines. Opioid analgesics are not always available.

The inhalational agent which has the safety profile of ketamine is di-ethyl ether but it is almost obsolete and may be difficult to source. Ether is commonly used with the EMO machines which are cheap and easy to maintain.

Halothane and isoflurane require expensive machines to deliver and some expertise is required for safe use.

Local anaesthetic agents are also employed to a large extent in anaesthesia in the developing world. They are used for regional anaesthesia such as subarachnoid blocks which is the current practice for obstetric anaesthesia world-wide. Such a technique is contraindicated in the very ill patient as in shock and haemodynamic instability.

Other regional methods such as the epidural technique and plexus blocks require physician skills to administer. Nurses are not trained in these techniques. Local infiltration is frequently practised for body surface procedures.
Regional techniques are not practicable in most children due to lack of cooperation.

8. **Investigations in some African countries**

**Methodology**

Consent was obtained from the Country Ministry of Health and the Chief Executive of a selected hospital.

The Ministry of Health and the WHO regional office in each country to be visited identified three or four hospitals representing the levels of healthcare in the country.

A questionnaire was developed which sought general information on type of hospital, number of beds and the number of medical staff.

Specific questions on anaesthesia included the number of surgeons and the number of anaesthetists both physician and nurses and any other person in anaesthesia service. Questions also included the number of theatres in the hospital, number of anaesthetic machines, the anaesthetic agents available and the number of operations performed annually, number and percentage of anaesthesia performed with ketamine anaesthesia. The theatre records were to be examined to verify and annual reports of the hospitals read.

The pharmacy records of the agents procured and consumed were also employed in the determination of the role of ketamine in anaesthesia. Anaesthesia personnel were asked of the complications and unusual problems they might have encountered with ketamine. Anaesthetists and other health care givers were asked for the knowledge of misuse of ketamine.

The hospitals enrolled were a tertiary/teaching institution, a secondary institution, a mission hospital and a private hospital.

**8.1 Ethiopia**

Ethiopia belongs to the 10 least developed nations in the African continent according to 2007 Human Development Index.

The population is about 77 million and it is the second most populous country in Africa after Nigeria and it is rapidly growing. About 85% of the population live in rural areas with poor health facilities.

The health system is largely provided for by the government. There are 138 hospitals and more than 600 health centres. Private medical establishments abound and some of them offer surgical care but most of the surgical care is undertaken in the government health facilities. Health care workforce is poor with about 1 doctor to 35,493 people according to the, in all there are about 2115 physicians.
Anaesthesia care is especially poor in Ethiopia. In a 1998 review by Teweldebrhan, nurses are the main anaesthesia care givers in Ethiopia and they have a well established School of Anaesthesia which graduates about 30 nurse anaesthetists per annum. In times of strife anaesthesia had been provided by assistants who have no formal nurse education. There are only 17 specialist physician anaesthetists for the whole country as I was informed by the President of the Society of Anaesthetists.

Patients pay for health service from out of pocket.

The WHO Representative through Dr Bekele has made arrangement for me to visit some institutions in the country. I saw the Permanent Secretary of health Dr Hassan Mohammed who also facilitated my visit with letters of introduction to the institutions I planned to visit.

The Institutions proposed were The Black Lion Hospital, Zewditu Hospital, Betezatha Hospital, and Planning and programming Department of the Federal Ministry of Health.

Investigations into ketamine use were conducted at The Black Lion Hospital and Betezatha Hospital, both in Addis Ababa in St Luke’s Hospital, Welleso and Bishoftu Hospital in Oromiya Region.

**Black Lion Hospital**

This is the foremost teaching Hospital in Ethiopia and is the hospital of the University of Addis Ababa. It is 600 bedded and a postgraduate training institution for specialists in various fields of Medicine. It also has a school of anaesthesia for nurse anaesthetists.

There are 6 operating theatres with standard anaesthetic machines. There are 4 anaesthetists and 12 nurse anaesthetists. Approximately 10,000 surgical procedures including obstetrics were performed last year.

The anaesthetic records classify the anaesthetic techniques as general, regional or local. It requires perusal of individual patient case notes to determine the exact anaesthetic the patient had. The Chief Anaesthesiologist thinks about 10% of surgical operations had ketamine anaesthesia.

*Anaesthetic medicine availability*

In addition to ketamine, thiopentone, diazepam, pethidine, halothane, isoflurane and muscle relaxants, and local anaesthetic agents were always available in the hospital. Midazolam and propofol are sometimes available from drug donations. Etomidate was also available when there was a cardiac outreach programme from visiting teams from developed countries.

Anaesthetic agents are supplied from the Central Stores This may have been so because of the different outreach programmes of orthopaedic, maxillofacial, cardiac etc. from different NGOs who come to assist continuously.
The Chief of Anaesthesia thinks ketamine has a special place in anaesthetic practice particularly in children and in the very ill patient.

The List of Drugs for Ethiopia 2002 edition includes inhalational anaesthetic agents Diethyl ether and trichloroethylene which are obsolete abroad but which are still relevant in the 3rd world today. The agents possess some of the advantages of ketamine but availability might eventually be a problem because of the limited demand.

**St Luke’s Catholic Hospital and College of Nursing, Wolisso**

This is a 144 bedded hospital that is owned by the Ethiopian Catholic Church with medical specialists provided by an NGO Doctors with Africa of Italy. The hospital serves a population of 1,192,700. There are 40 and 22 beds for surgery and obstetrics and gynaecology respectively.

There are 10 physicians in all comprising 3 surgeons, 1 ophthalmologist, 1 internist, 1 paediatrician and 4 general practitioners. There is no physician anaesthetist but there are 4 nurse anaesthetists. There are 2 operating theatres with 2 anaesthetic machines equipped with ventilators.

Total number of operations performed in 2007 = 5,189.
Minor operations = 2,589
Major operations = 2,600

40% of the cases were emergencies mostly caesarean sections and trauma.

The theatre records did not indicate the exact number of cases performed with ketamine anaesthesia but the nurse anaesthetist thinks ketamine was employed in 20-25% of the cases.
In Year 2006, the total number of deliveries was 1820 with 519 C/S. About 20% of the C/S had ketamine anaesthesia.

From the pharmacy department anaesthetic agents consumed in 2007 are:
- ketamine: 450 (50mg/ml 10ml vials) vials purchased from ?Action Media
- thiopentone: 50 vials (500mg/vial) Problems of supply.
- halothane: 54 bottles (250 ml/bottle)
- heavy lidocaine: 465 amp.
- heavy bupivacaine: 235 amp.
- 2% plain lidocaine: 388 (50ml amp)
- 2% lidocaine with adrenaline: 465 amp.

Diazepam and meperidine were readily available and were not confined to perioperative use.

No cases of misuse of ketamine have been heard of. No exceptional complications were encountered in surgical use.
Ketamine is considered a very safe anaesthetic and should it not be readily available would constitute a great danger to surgical care in very ill patients who may not tolerate other agents.

**Bishoftu Hospital**

This is a regional hospital catering to a population of about 100,000. There are 100 beds: 20 surgical, 30 obstetrics and gynaecology and the others shared between other specialties.

Staff: 1 surgeon, 1 O&G, and 5 physicians.

No physician anaesthetist but 3 nurse anaesthetists.

There is 1 functional operating theatre with one anaesthetic machine.

The following anaesthetics are always available:
- ketamine and thiopental,
- halothane,
- heavy lidocaine,
- 2% lidocaine,
- diazepam.

No other agents are available for anaesthesia.

Total number of operations for 2007 = 594 cases and they are classified as local or general. There were 160 obstetric cases, 57 gynaecology cases and 377 general surgical cases. 20% of surgical cases are performed under ketamine anaesthesia.

Ketamine anaesthesia plays a major role in care. No cases of misuse have been heard of.

**Bethzatha Hospital**

This is a private establishment in Addis Ababa. It has about 70 beds.

There were immediate records for the latter 5 months of 2007 when I visited and these showed that 650 cases had been performed under general anaesthesia and 110 cases under regional anaesthesia. It was stated that approximately 150 surgical operations were performed every month.

There is a permanent physician anaesthesiologist and 3 locum nurse anaesthetists. There are resident surgeons and physicians and other locum specialists attend the hospital. There is an anaesthetic machine with monitors.

Thiopental and ketamine and local anaesthetics are the main anaesthetic agents available. About 10% of the cases were estimated to have been performed under ketamine anaesthesia. Ketamine anaesthesia is favoured in children.

Ketamine misuse has not been heard of.

Alternatives to ketamine such as etomidate are difficult to come by and are not readily available from the private pharmaceutical agents to purchase.

**8.2 Nigeria**
The Year 2006 Census in Nigeria records the population as 140 million making it the most populous nation in Africa.
On the Human Development index it ranks 158 out of 177.
It runs a 3 tier health system of primary, secondary and tertiary levels of health care.
These are augmented by many private and mission hospitals.
Each of the 36 states of the nation has the 3 levels of health care. Tertiary care is borne by the teaching hospitals while secondary care is delivered by the designated General Hospitals.
There are more than 1000 primary health centres, mission hospitals undertake a large burden of secondary care, while private hospitals are of various categories.
Health care is part funded by government and patients have to pay out of pocket for services. A caesarean section costs about USD 200.

Hospitals in the South West, South East, North East and the North Western parts of the country were investigated for their use of ketamine in the year 2007.

**South West Hospitals**

**Obafemi Awolowo University Teaching Hospital (OAUTH), Ile-Ife.**

This is a 650 bed Teaching Hospital catering to a population of about 1 million people.
It is situated at 2 sites separated by about 20 kilometres

<table>
<thead>
<tr>
<th>Total number of physicians</th>
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<tbody>
<tr>
<td>Number of surgeons</td>
<td>= 60</td>
</tr>
<tr>
<td>Number of physician anaesthetist</td>
<td>= 4</td>
</tr>
<tr>
<td>Number of nurse anaesthetists</td>
<td>= 19</td>
</tr>
<tr>
<td>Other anaesthesia care giver</td>
<td>= 0</td>
</tr>
<tr>
<td>No of theatres</td>
<td>= 7</td>
</tr>
</tbody>
</table>

All theatres have modern anaesthetic machines and other equipment.

Anaesthetics available:
- thiopental,
- ketamine,
- propofol,
- diazepam,
- opioid analgesics,
- halothane, and
- isoflurane.

Total number of surgical operations 2006 (2007 incomplete) = 3421
Total number general anaesthesia = 2857
No of cases performed with ketamine = 63
No performed with loco-regional technique= 564

Quantity of ketamine purchased by pharmacy department = 400 vials (Some surgeons use ketamine for sedation).
Quantity of thiopental = 711 vials.
Total lidocaine = 1560 vials (20-50 ml vials).
No unusual complications due to ketamine.
No known cases of misuse but pilfering sometimes suspected.

Alternatives if ketamine is unavailable. Maybe difficult in view of paucity of invasive monitoring should the other more depressant agents be used in the high risk patient.

**Federal Medical Centre, Abeokuta**

- No. of beds = 160 bedded hospital. 60 beds for surgery and 40 for obstetrics and gynaecology,
- No. of physicians = 110 and this includes 18 interns.
- No. of physician anaesthetists = 5
- No. of nurse anaesthetists = 6
- No. of theatres = 4
- No. of anaesthetic machines = 4

Available anaesthetic agents are thiopental, ketamine, diazepam, morphine.

- Total no. of operations for (2007) = 898
- Operations performed under general anaesthesia = 625
- No. performed with ketamine anaesthesia = 50
- No. of sub arachnoid blocks = 35
- No. of local anaesthesia = 157
- Sedation = 71

No unusual complications of ketamine observed in the cases.
No cases of misuse of the drug heard of.

**Awojobi Clinic, Eruwa.**

The consultant in charge of this private hospital Dr. Yombo Awojobi is much interested in rural surgical practice and has extensive experience. The hospital celebrated its 21st Anniversary in 2007.

It is a 46 bed hospital serving a population of about 100,000.
The hospital is a teaching hospital for the students of the University of Ibadan and medical students have a 4-week rotation in the hospital.

The hospital is staffed by the consultant and a medical officer. There is 1 main theatre and 1 minor theatre. There is no anaesthetic machine and there has never been. There are self-inflating bag valve and mask. The main anaesthetics available are ketamine, diazepam and local anaesthetic agents and analgesics.

In 2007, 797 surgical procedures were performed, 434 of these were performed under ketamine anaesthesia. The rest were performed under loco-regional techniques. The surgeon is well versed in the institution of a spinal

35 caesarean sections were performed and they were with ketamine anaesthesia. When asked for his alternatives to ketamine he responded that there was not any if he was to serve everybody including children.
He then appealed that the total cost of surgery needs to be minimal in the rural setting where people are very poor and ketamine for TIVA markedly reduces operative cost. Ready availability and wide therapeutic index are added advantages. Controlling ketamine would create a public health crisis in the developing countries.

**South East Hospitals**

**Federal Medical Centre UYO**

This is a teaching hospital with 250 beds. There are 20 specialist surgeons and 3 physician anaesthetists 6 specialist anaesthetist in training. Nurse anaesthetist: 11. There are 4 functional theatres and 6 anaesthetic machines.

Available anaesthetic agents were: ketamine thiopentone propofol fentanyl, morphine and meperidine, Halothane the only agent available for inhalation anaesthesia. Lidocaine and bupivacaine were also readily available.

Total surgical procedures performed in 2007 = 1112
Of these there were 460 caesarean sections. General anaesthesia was employed in 60% of the C/S cases and almost all the cases were performed with ketamine anaesthesia. 40% of the cases were performed with subarachnoid block. The other 652 cases had general anaesthesia other than ketamine and regional techniques.

**Commentary**

Further questioning of the anaesthetist in charge revealed that ketamine was the preferred choice of the nurse anaesthetists and they perform the bulk of the work. The nurses are said to be averse to thiopentone because of cardiovascular and respiratory depression.

Ketamine is routinely employed in the obstetric suite and 1 case of fatal vomiting and aspiration was reported to have occurred.

**St Mary’s Hospital, Uruakpan**

It is a mission hospital with 250 beds but much of the service is obstetric. There is 1 specialist obstetrician and 4 medical officers. There is no physician and no nurse anaesthetist. Anaesthesia is administered with ketamine by midwives.

There are 2 theatres and 1 anaesthetic machine which is not being used at all.

The available anaesthetic agents were ketamine, diazepam and lidocaine.

There were about 1000 deliveries in 2007. There were 156 caesarean deliveries all performed under ketamine anaesthesia. It is unknown if any complications occurred with ketamine anaesthesia.
It appears the only alternative to ketamine in this hospital is subarachnoid block after the surgeon or the midwife must have been trained in the technique. No cases of misuse have been reported.

**St Luke’s Hospital, Anua**

This is a 350 bed hospital manned by 6 medical officers who perform surgical operations such as caesarean section, herniorrhapies, and other surgical emergencies.

There are 7 nurse anaesthetists. There are 2 theatres and 2 anaesthetic machines that are functional but are not used. The reasons attributed to non use were the lack of skills for their use. Also the logistics of procurement of anaesthetic gases are cumbersome.

About 2000 operations were performed in 2007 of which there were 600 caesarean sections. More than 90% of the cases were performed under ketamine anaesthesia. When there were contraindications local anaesthetic techniques were employed. No complications were said to have occurred.

**North East Zone**

Five hospitals were investigated in this zone. Ketamine use is as indicated.

<table>
<thead>
<tr>
<th>No.</th>
<th>Hospital</th>
<th>Total Number of Operations in 2007</th>
<th>Number of Operations Done with ketamine</th>
<th>Percentage of cases done with ketamine</th>
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</thead>
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<tr>
<td>1.</td>
<td>Maiduguri Teaching Hospital</td>
<td>1529</td>
<td>327</td>
<td>21</td>
</tr>
<tr>
<td>2.</td>
<td>FMC Nguru (Yobe State)</td>
<td>545</td>
<td>95</td>
<td>17</td>
</tr>
<tr>
<td>3.</td>
<td>FMC Yola (Adamawa State)</td>
<td>775</td>
<td>175</td>
<td>22</td>
</tr>
<tr>
<td>4.</td>
<td>Specialist Hospital Maiduguri (State Govt. Gen. Hosp.)</td>
<td>1469</td>
<td>900</td>
<td>61</td>
</tr>
<tr>
<td>5.</td>
<td>Borno Medical Clinic, Maiduguri (Private)</td>
<td>150</td>
<td>74</td>
<td>49</td>
</tr>
</tbody>
</table>

**Anaesthetic Manpower in Borno State**

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Cadre of Staff</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Physician Anaesthetist</td>
<td>3</td>
</tr>
<tr>
<td>2.</td>
<td>Nurse Anaesthetist</td>
<td>24 (11 of them work in the teaching hospital, 13 in state government hospitals)</td>
</tr>
</tbody>
</table>
North West Zone

Uthman Dan Fodiyo Teaching Hospital, Sokoto

This is a 500 bedded hospital.
There are 17 surgeons and 2 specialist anaesthetists and 7 nurse anaesthetists.
Total Number of operations 2007, 2357
Number of ketamine 116
Number of subarachnoid block 527

Available anaesthetic agents
Thiopental, ketamine, propofol, morphine, meperidine, halothane and isoflurane
No special complications attributable to ketamine use.
There are no reported cases of ketamine misuse. Pentazocine and pethidine misuse have been brought to light.

8.3 Tanzania

The country was visited from February 25-29, 2008.
The WHO Tanzania Office had obtained the permission of the Ministry of Health before hand and letters of introduction to 3 hospitals had been written. The hospitals are Muhimbili Hospital, St Francis Designated District Hospital, Ifakara and Morogoro Regional Hospital, Morogoro.

Demographics of Tanzania
Tanzania is an East African nation with a population 38 million. Human development Index = 0.466 (2011)

From the Annual Health Statistical Abstract (AHSA) 2006 the following information is gleaned. Health care delivery undertaken by government 74%, faith based organizations 22%, private 3% and parastatal 1 %.

The National average of doctor to persons is 1:138,000.
Anaesthetic care is delivered by specialist anaesthetists, non-specialists and anaesthetic nurses. Statistics are lacking on the total number of anaesthesia care givers and the ratio to the populations served.
The AHSA deals extensively with various disease conditions in all age groups, this includes maternal and child health, morbidity and mortality rates, the factors contributing to ill health and mortality but does not address surgical care. There are no National statistics of the number of surgical operations performed. Caesarean sections were not separately dealt with in the chapter dealing with maternal health and safe motherhood.
AHSA however maintains that the Essential Medicines Programme should be strengthened to ensure adequate supply.

Drug supply to the government hospitals
There is an essential drugs list which includes anaesthetic agents. Essential medicines are purchased and distributed by the central government and kept in the Central Medical Stores at Dar-es Salam. Medicines are further distributed to the regions from the
branches of the Stores which are located in 9 zones of the country. Individual hospitals access the medicines from the closest zones.

**Muhimbili Hospital, Dar-Es-Salam**

This is an 840 bedded tertiary and teaching institution which caters for all medical and training specialties. There are 300 physicians in total including trainee specialists. There are more than 30 surgeons but only 6 specialist anaesthetists. Anaesthesia is provided by the 6 specialist anaesthetists, 5 trainee anaesthetists and 32 nurse anaesthetists. There are 5 operating theatres in good working condition 8 theatres are under renovation. There are 7 standard anaesthetic machines for these theatres.

For the year 2007, approximately 9000 anaesthetics were administered and this includes obstetric and gynaecology cases. The broad theatre records indicate general or local anaesthesia. The specific agent would have to be culled from the individual patient records. The number of electives to emergency cases could not be determined. The Head of Department of Anaesthesia stated that ketamine was used in anaesthetics in 10% of elective cases but up to 60% of the emergency cases.

**Obstetric ward**

There are about 217 obstetric and gynaecology beds. Total number of deliveries in 2007 was about 9522. Caesarean section rate was 37% and about 20% of the cases were performed under ketamine anaesthesia.

**Anaesthetics availability**

The following anaesthetic agents and adjuvant were always available in the theatres:

- thiopental
- ketamine
- morphine
- pethidine
- diazepam
- halothane
- isoflurane
- oxygen
- suxamethonium
- pancuronium
- neostigmine
- atropine

**Local Anaesthetic agents**

The following local anaesthetic agents were always available in the theatres:

- plain lidocaine
- lidocaine + adrenaline
- heavy lidocaine
- bupivacaine

**The following were sometimes available**
• midazolam
• propofol (donations), and
• nitrous oxide

Local anaesthetic:
• bupivacaine

Fentanyl, etomidate, vecuronium, atracurium and ropivacaine have never been employed in anaesthesia at Muhimbili Hospital.

Ketamine is most frequently used for induction of anaesthesia and sometimes as the sole anaesthetic.

There is no record and no known cases of misuse of ketamine from the responses from the Head of the Department of Anaesthesia and the Director of Clinical Services. There are reports of pilfering of the medicines presumably for use in private practice but not for self administration. This report was repeated at the 3 hospitals visited in Uganda.

The Head of Anaesthesia was asked what the alternatives would be if there was no ketamine and he said “Anaesthesia without ketamine in this part of the world is unthinkable, especially for the haemodynamically unstable patient, and in trauma etc.

St. Francis designated District Hospital, Ifakara

This is a Catholic mission cum government establishment that serves a population of about 1 million people. It is about 5000 kilometres from Dar-es Salaam and the approach road is un tar red for about 70 kilometres; it is a very difficult terrain. The institution started as a dispensary in 1927 and grew in the 1960s to the 370 bed status. It was designated a government District hospital in 1976 and it is referral centre to about 5 other 100-bedded hospital. It is usually oversubscribed. The Hospital houses the Tanzanian Training Centre for International Health, is affiliated to the Muhimbili Medical school and trains their medical students and has a haemodialysis machine. The government of Tanzania is responsible for the provision of salaries of staff and consumables while the Catholic Mission undertakes all the capital expenditure. The medicines are therefore obtained from the Medical Stores Department.

There are
• 111 surgical beds,
• 56 obstetric and gynaecology beds,
• 11 Neonatal intensive care beds,
• 72 paediatric beds, and
• 93 medical beds.

The total number of physicians =19; 6 surgeons 2 obstetricians, 1 internal medicine 2 paediatricians and 1 anaesthetist. The anaesthetist is of the cadre described as assistant medical officer (AMO). The other doctors are non-specialists AMOs and Assistant dental officers.

Anaesthetic service is undertaken by the AMO and 4 trained nurse anaesthetists.
There are 3 fully functional operating theatres, 1 for minor cases and 2 for major cases. A dedicated obstetric theatre is under construction.

Total number of surgical cases for 2007 =3675. Of these there were 1269 Obstetric cases.
Number of non-obstetric cases = 2152.
Ketamine use was verified for 554 (25%) patients, and 1200 (55.7%) patients had subarachnoid block, the others were done under other general anaesthesia and local anaesthesia.

Number of deliveries 5136. C/S rate about 24%

One thousand and thirty-two (1032) 81.6% caesarean sections were done under subarachnoid block and 237 had general anaesthesia. The type of general anaesthesia was not further classified but the anaesthetist stated that patients in poor physical state had ketamine anaesthesia. Data would require individual patient file scrutiny.

**Anaesthetics availability**
The following anaesthetic agents and adjuvant were always available in the theatres:

- thiopental: 50 vials/month
- ketamine: 100 vials/month (increases if halothane unavailable)
- pethidine: readily available
- diazepam: dito
- oxygen: “
- halothane: 3 bottles/month if available
- diethyl ether: occasionally if no halothane
- suxamethonium: “
- pancuronium: “
- neostigmine: “
- atropine: “

**Local Anaesthetic agents**
- plain lidocaine: 40 amp /month
- lidocaine + adrenaline: 50 amp / month
- heavy lidocaine: 200/month

**The following were sometimes available**
Local anaesthetic: bupivacaine

Midazolam, fentanyl, etomidate, isoflurane, vecuronium, atracurium and ropivacaine have never been available.

No known cases of misuse of ketamine were identified.

When both surgeons and the anaesthetists were asked for the alternative techniques to ketamine anaesthesia, they mentioned regional and thiopental/halothane anaesthesia. They however claimed that the role of ketamine in surgical practice cannot be contested
especially for the very ill patient and for use in minor cases in children most of whom are uncooperative for regional techniques.

**Morogoro Regional Hospital**

This is a 250 bed hospital about 200 kilometres from Dar-es Salaam. This hospital serves a population of about 200,000.

There are 4 physicians comprising 1 surgeon, 1 obstetrician, 1 paediatrician and 1 anaesthetist who is actually an assistant medical officer.

Anaesthetic personnel also include a clinical officer and a nursing officer in training in anaesthesia.

There are 3 operating theatres and a dedicated obstetric theatre. However there is only 1 anaesthetic machine which is an EMO machine for use with diethyl ether anaesthetic.

Total number of minor cases undertaken in 2007 = 693.
Ketamine anaesthetic for minor cases 124 = 17.8 %.
Other cases were with locoregional anaesthesia.

Total number of major cases in 2007 = 740.
Caesarean sections 730, other cases 10.
Ketamine anaesthetic for major cases 138 (18.6 %).
Others cases were mostly with subarachnoid block.
It was worrisome that for eclamptic patients ketamine anaesthesia was also employed because thiopental was unavailable.

Total number of deliveries for 2007 was approximately 7000. Exact figure could not be accessed but the person in charge of the midwifery section thought the monthly deliveries hover around 600 per month.

**The following medicines were always available for anaesthesia care:**
- ketamine: 40 vials per month
- diazepam
- suxamethonium
- plain lidocaine
- lidocaine with epinephrine
- heavy lidocaine
- oxygen from oxygen concentrators

There is limited supply of pethidine.

Thiopental and ether have been unavailable for 2 years. The reasons proffered were that they were not supplied by the Medical Stores Department. Halothane could not be requested for because they did not have an appropriate anaesthetic machine for this potent agent.

Medicines are procured from the Medical Stores Department.

Again no one could recall any cases of misuse of ketamine. Ketamine is considered indispensable for surgical practice.
National Cancer Institute, Ocean Road

I visited this institute out of interest but it is affiliated to the Muhimbili Hospital. It is said to be the only hospital in sub-Saharan African offering comprehensive cancer care. It is the only cancer centre for Tanzania. The hospital cares for all cancers and all ages. Treatment is free. I spoke briefly to the Medical Director and the Palliative Care nurses.

Ketamine is used in the sedation of children for intrathecal cancer chemotherapy and for biopsies.

Visit to medical stores department in Dar-Es Salaam
The WHO Representative through Ms Rose Shija had contacted the Director of the Stores to allow a visit. The Director was away on the day of the visit but her assistant attended us. The Medical Stores supplies all essential medicines requirement by the country. Medicine are sourced through tender and the determinant of who to buy from includes the quality and price.

Ketamine
The suppliers of ketamine are Rotex of Germany and Claris of India. They come as 10ml vials of 50mg/mL.

Monthly consumption in 2007 was 441 issues (an issue is 25 vials) = 11,025 vials per month = 132,300 vials per annum

Ketamine induction dose by the i.v. route is 1-2 mg/kg body weight and maintenance dose is 1-3 mg/kg/hr. Therefore a 70 kg man could have an hour of anaesthesia with a vial of ketamine.

Thiopental
Rotex and Vital care are the suppliers of thiopental to MDS. They come as 500mg/vial.

Monthly consumption in 2007 was 150 issues (an issue= 10 vials) =1,500 vials per month.
Annual consumption was 18,000 vials.

The induction dose of thiopental is 3.5-5mg/ kg. Thus a 70 kg fit man would be induced with 300-500 mg dose of thiopentone which is a vial.

Ether
2007 consumption was 10,500 bottles of 250 ml this was up from 6,000 bottles in the previous years. The demand could not be explained.

Halothane
Halothane consumption was 5,600 bottles of the 250ml.

Diazepam and midazolam
Diazepam and midazolam are not confined to anaesthetic use and were not inquired into.

**Remark**
Medicines maybe sourced from private pharmacies with due attention to the cost benefit of such a move.

9. **Conclusion**
Ketamine plays a major role in anaesthetic service delivery in all the countries visited. Ketamine was most frequently employed in the secondary health facilities but it was also used in high risk cases in the tertiary institutions.

Complications arising from the use of the agent are rare.

There were no reported cases of misuse of the ketamine in any of the hospitals or the health care practitioners I interviewed and interacted with.

There is at this time no justifiable evidence for the control of ketamine.

If ketamine were to be controlled, the rigors of procurement would be similar to that of the opioids.

There would result a public health crisis.
ANNEX 3: Use of ketamine in Benin
(Translated from French)

Prof Diallo Abdoulaye
February 2008

1. Introduction

1.1 Background information on ketamine

**Pharmacology (3,6,7,8,12, 15)**
Ketamine, which was synthesized for the first time in 1962 and introduced first into veterinary medicine and then human medicine in 1965, is an arylcycloalkylamine whose anaesthetizing properties vary depending on the dose. It possesses two isomers with occasionally different pharmacological properties: la ketamine R(-) and ketamine S(+).

Ketamine may be administered by the intravenous (i.v.), intramuscular (i.m.), intrathecal (i.t.), oral (po), rectal (p.r.) and intranasal routes (i.n.).

After administration, it is distributed principally to the highly vascularised organs, with a particular affinity for fatty tissue. It is essentially metabolised by the liver, and 90% of it is eliminated by the kidneys. Conservation of anaesthetic properties by its principal metabolite, norketamine, accounts for its prolonged effects.

It has a dissociative effect on the central nervous system, together with an intense analgesic effect associated with hallucinations and delirium on awakening. It increases intracranial pressure.

Numerous studies have confirmed its neuroprotective effects, its effects on the WDR neurones and on the NMDA receptors, as well as its synergistic effects on morphine receptors.

It causes stimulation of the cardiovascular system, marked by increased heart rate, blood pressure and heart flow. Its effect on the myocardium is disputed and differs depending on the state of the myocardium.

Generally speaking, ketamine is only a mild respiratory depressant, although apnoea may occasionally occur after rapid intravenous injection. Despite maintenance of minute ventilation, respiratory depression cannot be totally excluded. It preserves muscle tone and pharyngeal and laryngeal reflexes are maintained, and it has a bronchodilator effect and unquestionably causes sometimes important hypersecretion of the salivary and bronchial glands.

*Moreover, it induces no or little histamine release and is rarely responsible for allergic reactions.*
The effects of ketamine on the uterus depend on the dose and stage in pregnancy. When administered in ordinary doses, ketamine has no known toxic effect. Venous tolerance is excellent. The neuron lesions occasionally observed after intrathecal administration have frequently been attributed to the associated preservatives. The uncertainty as to its bone marrow toxicity makes it necessary to suspend its use via this route. The nasal route is used above all by those with dependence for illicit recreational purposes. Teratogenic effects have been reported in rats, but no data are available on humans.

**Practical use (3, 15)**

**Dosage**
The recommended intravenous doses to induce anaesthesia range from 2 to 3 mg/kg in adults and from 1 to 2 mg/kg in children of less than three months. The necessary doses via the intramuscular or rectal route are higher (5 to 10 mg/kg).

**Modulation of side effects**
Cardiovascular stimulation, intracranial hypertension, hallucinations, delirium and agitation on awakening may be limited or avoided by the association of suitable doses of benzodiazepines, thiopental, β-blocker, clonidine or of dexmedetomidine. Salivary and bronchial hypersecretion justifies use of antisialagogues such as atropine.

**Principal Indications**
The principal indications are:
- states of shock, as an anaesthetic in paediatrics,
- anaesthesia of burn victims,
- anaesthesia in hostile environments (combat medicine, disaster medicine, incarcerated patients and pre-admission situations).

It may also be used in outpatient surgery, in obstetrics and as a complement to locoregional anaesthesia by the sub-arachnoid route (although this is not advised). Numerous studies have demonstrated its value in anaesthetics and balanced analgesics.

**Contraindications**
There are numerous contraindications, but they may be reduced by carefully adapted modulation. They essentially concern psychiatric illnesses, heart failure, intracranial hypertension, thyrotoxicosis, lesion of the eyeball and intraocular hypertension.

**1.2 Information on Benin**

Benin is a West African country with an area of 112,622 km² and a population of 80,000,000. To the west it borders on Togo, to the east Nigeria and to the north Niger and Burkina Faso. Its former name was Dahomey and its political capital is Porto-Novo, Cotonou being the economic capital. The country's official language is French and the currency is the CFA franc

**1.3 Geographical situation of Benin and of the towns of Cotonou and Abomey**

Like most countries in Africa, Benin is a land of limited resources. Its per capita GDP is $836 and its economy is mainly based on agriculture.
Most of the population live in rural areas.
For administrative purposes, Benin is divided into twelve departments: Alibori, Atacora, Atlantique, Borgou, Collines, Donga, Couffo, Littoral, Mono, Ouémé, Plateaux and Zou. The town of Abomey, the capital of Zou department, is 145 km from Cotonou.

The country's health pyramid matches its administrative divisions and comprises three levels: central, intermediate and peripheral (10).
* The peripheral level represents the health system's most decentralized operational unit and comprises 34 health zones, each of which has a number of first-line public health services. Health facilities are backed up by a referral hospital (which may be public or private), known as the zone hospital, which is the first level of referral in the health zone.
* The intermediate level comprises the departmental hospitals, which include the Abomey departmental hospital (in Zou department).
* At the central level, the Hubert Maga hospital (CNHU) is the country's national referral hospital. It is assisted by specialized high-intensity facilities such as the Lagune Mother and Child Hospital (HOMEL), which is specialized in maternal and child health.

Like other African sub-Saharan countries, Benin suffers from a shortage of qualified health workers (11). Moreover, these scant human resources are ill-distributed throughout the country and the field of anaesthetics-intensive-care is no exception. Because of these circumstances in 1971 the Faculty of Health Sciences was set up to train first of all general practitioners and later specialists.

In order to satisfy needs in anaesthetics-intensive-care, a DES (Diploma in Specialized Studies) in anaesthetics-intensive-care was introduced in the 1996-1997 academic year and the College of Nurses and Midwives in Anaesthetics-Reanimation (ENAFISAR), which was opened in 2002, trains paramedical staff specialized in anaesthetics-intensive-care (10).

In Benin, anaesthetics like all other pharmaceutical products are supplied by a National Essential Medicines Procurement Office (CAME), an autonomous public agency which provides supplies of generic medicines and consumables.

It is important to mention the existence, at the regional level, of ACAME (African Association of Essential Medicines Procurement Offices), grouping more than 15 African countries, whose permanent Headquarters are in Ouagadougou, and which is chaired on an annual revolving basis.

Moreover, there is a growing trend towards the establishment of informed and coordinated group procurement mechanisms, which offer considerable opportunities in terms of supply and quality assurance. The sub-region is currently setting up joint control laboratories.
The current situation of health workers in Benin

<table>
<thead>
<tr>
<th>Socioprofessional category</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialized physicians, including Anaesthetists intensive-care specialists</td>
<td>198</td>
</tr>
<tr>
<td>General practitioners</td>
<td>149</td>
</tr>
<tr>
<td>Dental surgeons</td>
<td>18</td>
</tr>
<tr>
<td>State certified pharmacists</td>
<td>10</td>
</tr>
<tr>
<td>State certified nurses (IDE)</td>
<td>520</td>
</tr>
<tr>
<td>State certified midwives (SFE)</td>
<td>622</td>
</tr>
<tr>
<td>Specialist SFE-IDE</td>
<td>91</td>
</tr>
<tr>
<td>State registered nurses</td>
<td>710</td>
</tr>
<tr>
<td>Nursing assistants</td>
<td>490</td>
</tr>
<tr>
<td>Welfare workers</td>
<td>72</td>
</tr>
<tr>
<td>Practical auxiliaries</td>
<td>54</td>
</tr>
<tr>
<td>Hygiene and sanitation workers</td>
<td>202</td>
</tr>
<tr>
<td>Laboratory and radiology workers</td>
<td>200</td>
</tr>
<tr>
<td>Administrative staff</td>
<td>890</td>
</tr>
<tr>
<td>Drivers</td>
<td>123</td>
</tr>
<tr>
<td>Health service maintenance workers</td>
<td>171</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4520</strong></td>
</tr>
</tbody>
</table>

Source PNSDRH : DRH Benin 2007 (10)

2. Our study

Methodology
At the request of the World Health Organization (WHO), this study on the use of ketamine in French-speaking sub-Saharan Africa has been carried out by Professor Diallo Abdoulaye between 1 and 6 November 2007 in Benin. In accordance with the terms of reference of the mission, the following procedure was observed: site visit, field survey, discussions with senior anaesthetists and other anaesthetics staff, questions-and-answer sessions, administration of a standard questionnaire and examination of the operating theatre registers.

The study concerned 3 medical facilities in Benin:
* the Hubert Maga national university teaching hospital (CNHU).
* the Lagune Mother and Child hospital (HOMEL)
* the Abomey departmental hospital (HDA)
Results

Description of the 3 medical facilities
- CNHU is the national referral hospital, with a capacity of 600 beds and a staff of some 1200. It is the main location for practical training of medical students and student nurses.
- HOMEL is the country's largest maternal and child health centre; it has some 250 beds and a staff of 400. The bed occupancy ratio is very high as a total of 7500 deliveries take place each year, 35% of them caesarean sections.
- HDA, is located on a rural site and has a capacity of 150 surgical beds and almost 300 beds for general medicine and paediatrics. It is the prototype rural hospital in which ketamine is used for 65% of general anaesthetics.

Operating capacity and specialized anaesthetics staff

<table>
<thead>
<tr>
<th>Facility</th>
<th>Operating theatre</th>
<th>Anaesthetists</th>
<th>Anaesthetic nurses (ITSARS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNHU</td>
<td>11</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>HOMEL</td>
<td>4</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>HDA</td>
<td>3</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Availability of ketamine
Ketamine is available in all the facilities visited, all of which had sufficient stocks for one year's operation.

<table>
<thead>
<tr>
<th>Medical facility/Ketamine</th>
<th>Type of ketamine</th>
<th>Presentation</th>
<th>Manufacturing laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNHU</td>
<td>Generic</td>
<td>Vials of 10 ml to 50mg/ml</td>
<td>Panpharma</td>
</tr>
<tr>
<td>HOMEL</td>
<td>Generic</td>
<td>Vials of 10 ml to 50mg/ml</td>
<td>Rotexmedica LDI</td>
</tr>
<tr>
<td>HDA</td>
<td>Generic</td>
<td>Vials of 10 ml to 50mg/ml</td>
<td>Rotexmedica</td>
</tr>
</tbody>
</table>

The medicine is supplied regularly by wholesalers with offices in Benin or by the national procurement offices (CAME). Only CNHU obtains supplies directly from the Panpharma laboratories in France.

Use of ketamine in anaesthetics in the 3 facilities

<table>
<thead>
<tr>
<th>Medical facility/Case</th>
<th>Total number of anaesthetics</th>
<th>Number under ketamine</th>
<th>Percentage</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNHU</td>
<td>1547</td>
<td>202</td>
<td>13%</td>
<td>6 months (January-June 2007)</td>
</tr>
<tr>
<td>HOMEL</td>
<td>9230</td>
<td>1846</td>
<td>20%</td>
<td>12 months (January-December 2006)</td>
</tr>
<tr>
<td>HDA</td>
<td>3164</td>
<td>1317</td>
<td>41%</td>
<td>24 months</td>
</tr>
</tbody>
</table>
**Principal indications mentioned by practitioners**
The indications mentioned are almost always the same: foremost among them are states of shock, peritonitis, intestinal occlusions, caesarean sections with high risk of haemorrhage (placenta praevia, retroplacental haematoma), burst ectopic pregnancies, minor surgery (debridement, sutures, curettage, examination using valves, plaster, removal of nails and burn dressing).

Use of low doses in analgesia was mentioned at both CNHU and at HOMEL. Use as a complementary sedative during locoregional anaesthesia (LRA) is common at all three sites. Examples of such use are operations that last longer than planned and cases of insufficient analgesia after a spinal anaesthesia and/or an epidural.

In paediatric anaesthesia, intramuscular injection is used at the start of surgical procedures, but above all for the anaesthetic itself. This practice was particularly prominent at HDA, which has a large paediatric department.

**Dosage used in the three facilities**

<table>
<thead>
<tr>
<th>Medical facility/Dosage</th>
<th>Dosage</th>
<th>Route</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNHU</td>
<td>3 mg·kg⁻¹ on average</td>
<td>Intravenous bolus dose</td>
<td>Reinjection if needed</td>
</tr>
<tr>
<td>HOMEL</td>
<td>3-5 mg·kg⁻¹</td>
<td>Intravenous bolus dose</td>
<td>Reinjection if needed</td>
</tr>
<tr>
<td>HDA</td>
<td>4 mg·kg⁻¹ on average</td>
<td>Intravenous bolus dose and intramuscular</td>
<td>Intramuscular only in children</td>
</tr>
</tbody>
</table>

**Conditions of use of ketamine**
At CNHU and at HOMEL, the range of equipment available provides considerable room for manoeuvre. These facilities have respirators, multiparameter monitors and a broad and varied range of anaesthetic products.

HDA, which is located in the interior of Benin, has the minimum necessary to ensure anaesthetic safety in the use of ketamine: aspiration system, oxygen, monitoring, perfusion kits, and intubation kit. A respirator is available in the intensive-care department.

Diazepam is used almost systematically to modulate side effects; atropine is used when needed.

If a tracheal tube is needed, curare is given. Pancuronium is the most readily available curare.

Midazolam and fentanyl were mentioned as belonging to the anaesthetics used at CNHU and HOMEL.

All the practitioners questioned were sufficiently familiar with ketamine. However, they categorically said that its use by non-anaesthetists was dangerous.
Illicit use is uncommon, apart from use in a small number of undocumented illegal abortions.

### Complications observed

<table>
<thead>
<tr>
<th>Type of complication / medical facility</th>
<th>CNHU</th>
<th>HOMEL</th>
<th>HDA</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed awakening</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Surge in blood pressure</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Properly controlled modulation allows these side effects to be diminished</td>
</tr>
<tr>
<td>Hallucinations - Agitation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Congestion</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>-</td>
<td>-</td>
<td></td>
<td>4 cases in 2 yrs Attributed to the patients' condition?</td>
</tr>
</tbody>
</table>

### Possible alternatives to use of ketamine

<table>
<thead>
<tr>
<th>Medical facility/alternative</th>
<th>Alternative 1</th>
<th>Alternative 2</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNHU</td>
<td>Propofol + Analgesic</td>
<td>Etomidate</td>
<td>Maximum balance</td>
</tr>
<tr>
<td>HOME L</td>
<td>Etomidate + Thiopental</td>
<td>Etomidate + Propofol</td>
<td>Maximum balance</td>
</tr>
<tr>
<td>HDA</td>
<td>Thiopental (available),</td>
<td>Etomidate</td>
<td>Not very satisfactory</td>
</tr>
</tbody>
</table>

### 3. Comments

The situation in Benin is identical to that in other countries in French-speaking sub-Saharan Africa such as Burkina Faso, Mali and Niger (11): there is a severe shortage of specialized staff. Moreover, the few specialists available are concentrated in the capital cities. The specialty of anaesthesics - intensive-care is no exception to this rule, as is confirmed by the fact that of the 10 anaesthetists practising in Benin, 7 are in Cotonou.

These three facilities were selected on account of their different profiles, which allow us to get a good idea of how ketamine is actually used in Benin. While CNHU and HOMEL are relatively well equipped (top of the range respirators, monitors and a broad and varied range of anaesthetic products) at HDA, only the bare minimum is available: simple anaesthetic apparatus with a halogen well, oxygen supply, aspirator, perfusion kits and intubation kit).

Outside zone hospitals, it is rare to find permanent specialized anaesthetists, and this makes the use of ketamine dangerous on these sites.

Ketamine is available wherever anaesthesia is used in the facilities visited. This was also the finding of a report published in 1999 by Professor Adnet Pascal, Diallo A et coll., who found it in 72% of nursing practices in rural areas (1). This figure has gradually increased (4).
Current stocks of ketamine and adjuvants are adequate at both the central and peripheral levels. The generic forms used mean that the cost is even more affordable (2, 4). Although the cost varies from one country to another in the sub-region, as a rule it is unquestionably moderate, despite the low GDP of the countries concerned.

These price differences are attributable to economic liberalization, non-harmonization of countries customs and tax policies and to the diversity of suppliers. While HOMEL and HDA obtain their supplies from the National Procurement Office, CNHU directly purchases its ketamine from Panpharma France. This is made possible by the managerial autonomy of our hospitals.

Mali provides an even more striking example: the two national hospitals sell ketamine 500mg to patients at very different prices: CFAF 630 at Point G hospital and CFAF 970 at the Gabriel Touré Hospital. (1 Euro = CFAF 655.957)

The generics supply system is made easier thanks to these national procurement offices. The sub-regional procurement offices and the informed and coordinated procurement system (AIC) will give our countries the opportunity further to improve supplies and to ensure stability and product quality.

The two adjuvants commonly associated with ketamine are also available in generic form at affordable prices (13, 9).

### Comparison of prices in three countries in the sub-region

<table>
<thead>
<tr>
<th>Product/ average CFAF price</th>
<th>Benin</th>
<th>Burkina Faso</th>
<th>Mali</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine 500 mg</td>
<td>550</td>
<td>520</td>
<td>800</td>
<td>Diversity of prices within and between countries</td>
</tr>
<tr>
<td>Diazepam 10 mg</td>
<td>75</td>
<td>70</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Atropine 0.5 mg</td>
<td>50</td>
<td>52</td>
<td>105</td>
<td></td>
</tr>
</tbody>
</table>

Stockouts are now a distant memory in all three facilities. The principal indication is anaesthesia of fragile patients in a hostile environment. In the view of the practitioners interviewed, misuse of ketamine is limited to a few abortions, very often carried out under hazardous conditions. The different accidents occurring after these clandestine operations are not declared.

There is currently little information about recreational use of ketamine.

The range of choice of anaesthetics is as broad at the central level and at the Hubert Maga National University Teaching Hospital (CNHU) in Cotonou and at Lagune Mother and Child Hospital (HOMEL), as it is limited at the peripheral level, such as the Abomey departmental hospital (HDA). This explains why from 12% at CNHU, the proportion of anaesthetic procedures using ketamine rises to 20% at HOMEL, and to 41% at Abomey (HDA). Moreover, in this hospital, out of 2026 general anaesthetics (GA) administered over 2 years, 1317 (i.e. 65%) used ketamine. Here, the possible alternative general anaesthetic is thiopental (30%).
Dosage is relatively well controlled, although it is sometimes determined empirically depending on the case and on weight. At the central level, because of the range of choice available, and of use of balanced anaesthesia, the dosages are lower. In contrast, in rural areas, the doses administered are somewhat higher. This could be accounted for by the frequency of congestion linked to salivary and bronchial hypersecretion, justifying the use of atropine, mainly because of its antispasmodic effect. Its systematic use is subject to caution (13).

Relatively satisfactory alleviation of the hallucinations, delirium and agitation constantly encountered is obtained with diazepam. Midazolam and clonidine might be proposed to reinforce the existing arsenal (9).

As a whole, it has been possible to control the side effects observed, at both the central and peripheral levels. However, over two years four deaths have been reported at HDA; the patients were very fragile patients for whom a final life-saving attempt was ethically appropriate. It is more likely that the deaths were due to the poor condition of the patients rather than to the use of ketamine.

Despite their level of experience, it would be advisable for teams of anaesthetists to follow periodic training courses on this complex product, in respect of which the indications, dosage, side effects and modulation techniques are constantly evolving. This would be a sure means of breaking with empiricism and routine and avoiding many unpleasant surprises.

We should make practical use of the properties of ketamine S, as we now know that with this isomer the numerous side effects are reduced.

In the opinion of the practitioners questioned, the alternatives proposed for use ketamine are less satisfactory: very frequently, the alternatives are thiopental, etomidate and propofol. Of these three products, only thiopental is widely available in generic form in Africa. Availability of the two others in generic form (which has already been announced) is not yet effective on our markets.

Intravenous administration of ketamine is widespread. The intramuscular route (i.m.) is used almost exclusively in children, in which case it is relayed, as soon as a route is found, by intravenous injections or inhalation of halogenated products. However, as children are very susceptible to salivary and bronchial hypersecretion, episodes of congestion are frequently observed.

Use of the oral route in adults and of the rectal route in children has already been mentioned, although these are exceptional. The nasal route, widely used elsewhere, is uncommon in French-speaking sub-Saharan Africa, as is intrathecal administration (15). Whatever the case, a minimum number of precautions must be observed in using ketamine: respiratory support equipment (oxygen, intubation and aspiration equipment . . .) and qualified staff. For this reason, use of ketamine, especially by non-specialists, is hazardous or even dangerous beyond the level of departmental hospitals such as the Abomey hospital (HDA).

Anaesthesiologists, anaesthetic nurses and technicians specialized in anaesthesia-intensive-care (ITSAR) need to undergo periodic re-training if they are to perform better.
4. Conclusion

Ketamine is an anaesthetic that is available in Benin at an affordable price. It is highly appreciated for anaesthetizing patients whose condition is delicate, for anaesthesia in difficult circumstances and for numerous surgical and obstetric procedures (14, 15).

There is an acute need to standardize its supply, at both the national and subregional levels. In this connection, the establishment of Procurement Offices needs further to be reinforced to ensure regular supplies and quality.

Refresher training for specialized staff must be regularly planned.

However, provision of ketamine S must be speeded up, although use of ketamine by staff who are not specialized anaesthetists is to be proscribed.

5. Recommendations

In the light of the available scientific data, of the specific conditions in developing countries - particularly in Africa, and bearing in mind the limited human resources available - in terms of both number and quality - in the field of anaesthetics, the following recommendations should be made and followed:

1) In-service training should be organized on the use of ketamine for practitioners as a whole and for practitioners in Africa in particular;

2) Availability on the African pharmaceutical market of generic forms of the ketamine S isomer should be speeded up, as it has fewer side effects and is thus more beneficial;

3) Maximum use should be made of the benefits offered by the essential medicines procurement offices and the system of informed and coordinated procurement networks;

4) Use of ketamine by non-specialized anaesthetics-intensive-care staff should be proscribed in both urban and semi-urban or rural settings;

5) Use of ketamine should be avoided in medical facilities unable to offer minimum precautions (in terms of safety): oxygen, intubation and aspiration equipment and modulation medicines.
6. Bibliography


15. WHO EXPERT COMMITTEE ON DRUG DEPENDENCE Reports
   - Thirty-fourth Report 34th ECDD 2006/4.3 ketamine Critical review of KETAMINE

7. **List of abbreviations**

- ACAME: Association Africaine des Centrales d’Achats de Médicaments Essentiels (African Association of Essential Medicines Procurement Offices)
- GA: General anaesthetic
- LRA: Locoregional anaesthetic
- AIC: Achats Coordonnés Informés Coordonnés (Informed and coordinated procurement)
- CAME: Centrale d’Achat de Médicaments Essentiels (Essential Medicines Procurement Office)
- CFAF: Currency in the French-speaking community in Africa (1 Euro = CFAF 655.987)
- CNHU: Hubert Maga National University Teaching Hospital
- HDA: Abomey departmental hospital
- HOMEL: Lagune Mother and Child Hospital
- IDE: State certified nurse
- IM: Intramuscular route
- IT: Intrathecal route
- IV: Intravenous route
- GDP: Gross domestic product
- SFE: State certified midwife
- IN: Intranasal route
- PO: Oral route
- PR: Rectal route
- WDR: Wide Dynamic Range
- NMDA: N-methyl-D-aspartate
Annex 4: Abuse of Ketamine in the United States

In 2000, Monitoring the Future (MTF), a U.S. secondary school survey, sponsored by the National Institute on Drug Abuse, added a question regarding the abuse of ketamine by students in the U.S. The following table summarizes the annual prevalence of ketamine abuse among eighth, tenth and twelfth grade students from 2007 to 2011. For several years, the prevalence of ketamine abuse in these age groups has remained steady.

### Ketamine Annual Prevalence Use Reported by MTF (Percent of Students)

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>8th Grade</td>
<td>1.0</td>
<td>1.2</td>
<td>1.0</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>10th Grade</td>
<td>0.8</td>
<td>1.0</td>
<td>1.3</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>12th Grade</td>
<td>1.3</td>
<td>1.5</td>
<td>1.7</td>
<td>1.6</td>
<td>1.7</td>
</tr>
</tbody>
</table>

The table below provides information on ketamine exposures as reported in American Association of Poison Control Centers’ National Poison Data System (NPDS), formerly known as the Toxic Exposure Surveillance System (TESS); this database is composed of information from 57 poison centers throughout the U.S.

### Ketamine Exposures Reported by NPDS (National Poison Data System)

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Exposures</td>
<td>114</td>
<td>158</td>
<td>154</td>
</tr>
<tr>
<td>Intentional Exposures</td>
<td>25</td>
<td>39</td>
<td>47</td>
</tr>
<tr>
<td>Treated at a Health Facility</td>
<td>46</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Serious Outcome*</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Exposures resulted in life-threatening or continued long-term medical conditions.

Note: Ketamine exposures include analogs

The Drug Abuse Warning Network (DAWN) emergency department (ED) visits for ketamine from 2007-2009 are listed in the table below.

### DAWN Emergency Department (ED) Data (2007 – 2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>ED Visits - Ketamine</th>
<th>ED Visits – Total Illicit Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>291</td>
<td>1,301,085</td>
</tr>
<tr>
<td>2008</td>
<td>344</td>
<td>1,335,206</td>
</tr>
<tr>
<td>2009</td>
<td>529</td>
<td>1,304,301</td>
</tr>
</tbody>
</table>

Note: Data after 2009 are not currently available

DEA reports indicate that a major source of illicit ketamine in the United States is Mexico, via smuggling into the United States. Additionally, diversion of legitimate shipments and smuggling provide significant amounts of ketamine to the illicit market. There is no evidence of clandestine manufacture.

**Total quantity of seizures**
According to the System to Retrieve Information from Drug Evidence (STRIDE), a DEA database to systematically collect drug analysis results from DEA and other federal laboratories, a significant amount of ketamine is still being encountered on the illicit market. The table below provides information from DEA and other federal laboratories regarding ketamine cases, exhibits and seized material.
Annex 5: Abuse of Ketamine in China, Macao SAR and Hong Kong SAR

1. Chinese Central Government
Ketamine abuse especially from illicit manufacturing is an important problem. Every year China seizes illegally produced ketamine (5.3, 4.9 and 5.04 tons in 2009, 2010 and 2011 respectively). Synthesis is mostly from hydroxyl imines precursors. In mainland China, the reports of ketamine use is increasing; 77815, 94840, 107803 and 135500 reports in 2008, 2009, 2010 and 2011 respectively. Ketamine misusers are mainly young people and adolescents. In 2011 young people less than 35yrs accounted for 86.5% of misusers. According to INCB report (2011), 99% of all ketamine seizures took place in Asia. Misuse and trafficking are prominent problems in these areas. China is concerned that the data on misuse from Asia are incomplete.¹

2. Macao Special Administrative Region of China
Ketamine became more popular after 2005. It overtook heroin and became the most popular abused drug in 2010, especially among teenagers. Approximately 50 - 60% of young abusers (under 21yrs) abuse ketamine regularly. Family and social problems related to the ketamine abuse are being reported. The dependence of ketamine is serious and is a party drug or a recreational drug as mentioned in the report. People abuse ketamine in discos or karaoke, and also at home regularly, which means that ketamine is abused in the same pattern as ICE and heroin. Ketamine related crime also increased dramatically after 2005. Seized Ketamine in 2005 was about 13 kg which was almost 18 folds compared to 2004 (0.7 kg). Cross border trafficking became one of the serious teenager crimes. Ketamine related health problems are also reported in recent years, especially urinary tract dysfunction after long term abuse of ketamine.

More information can be obtained from
Annual Reports on Drug Control in Macao:
Central Registration System for Drug Abusers of Macao:
http://www.antidrugs.gov.mo/anti/web/en/mo_commit_ent.jsp

Based on available data, ketamine causes serious public health and social problems in Macao SAR.

3. Hong Kong Special Administrative Region, China
The abuse of ketamine by young people has aroused serious public health and social concerns. Ketamine remains the most commonly abused psychotropic substance in Hong Kong SAR, especially among young drug abusers. Table 1 shows that, over the years, ketamine abuse accounted for approximately 70% to 80% of reported abuse among young substance abusers in Hong Kong SAR. As shown in table 2, seizure of ketamine also remained high.
Ketamine is classified as dangerous drugs under the Dangerous Drugs Ordinance, Cap. 134 and is subject to strict control on trafficking, manufacture, possession, supply, import and export. As for other such drugs, illicit trafficking, manufacture, possession, supply, import
and export of ketamine will attract a maximum penalty of a fine of HKD 5 million and life imprisonment.

Table 1 Ketamine abuse over years

<table>
<thead>
<tr>
<th>Year</th>
<th>2005 (%)</th>
<th>2006 (%)</th>
<th>2007 (%)</th>
<th>2008 (%)</th>
<th>2009 (%)</th>
<th>2010 (%)</th>
<th>2011 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of reported ketamine abusers under the age of 21</td>
<td>1368 (60.05)</td>
<td>1876 (72.8)</td>
<td>2392 (79.76)</td>
<td>2962 (85.26)</td>
<td>2834 (83.65)</td>
<td>2241 (79.72)</td>
<td>1395 (69.54)</td>
</tr>
</tbody>
</table>

The percentage is ketamine abusers among all drug abusers in Hong Kong SAR.

Table 2 Ketamine seizures

<table>
<thead>
<tr>
<th>Year</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine seized (kg)</td>
<td>296.1</td>
<td>1006.1</td>
<td>96.4</td>
<td>423.3</td>
<td>472.3</td>
<td>164.2</td>
<td>276.3</td>
</tr>
</tbody>
</table>

Ketamine is a psychologically compelling substance of misuse. It can produce dependence. Recent evidence suggest that it is associated with a multitude of physical and psychiatric complications, some of which could be serious and irreversible. The harmful effects on the mind and mental health range from attention deficit, deteriorating memory, cognitive impairment, muscular incoordination, depression and hallucination. Long-term ketamine toxicity might involve neurodegenerative processes similar to those of Alzheimer’s disease. Furthermore, ketamine abuse may damage many important bodily functions including cardiovascular, respiratory, gastrointestinal, reproductive and immune systems. Findings from research studies in Hong Kong SAR suggest that habitual abuse of ketamine may result in significant urinary bladder dysfunction and renal impairment. The two research reports, “Long-term ketamine abuse and apoptosis in Cynomologus monkeys and mice” and “Research on urological sequelae of ketamine abuse” provide data related to these issues.

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1 The data provided by the countries when requested by WHO are included in the questionnaire report.
2 The figures only partially reflect the situation in Hong Kong SAR, as reporting of drug abuse is not compulsory in Hong Kong SAR.
3 Long-term ketamine abuse and apoptosis in Cynomologus monkeys and mice
4 Research on urological sequelae of ketamine abuse