Critical review of KETAMINE

Introduction

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 periode 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 abovementioned 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 computersearch has been performed in the following databases Pubmed, Toxline, Psycinfo and Embase.

Conclusions

Ketamine is an arylcycloalkylamine structurally related to cyclidines, like eticyclidine, phencyclidine, rolicyclidine and tenocyclidine.

It is a NMDA-receptor-antagonist used as an anaesthetic in both human and veterinary medicine. Furthermore a number of effects on various neurotransmitter systems have been described.

Ketamine can produce a state of dependence as shown in various animal models. This is supported by some human data as reported by the WHO. Although one should keep in mind that monitoring of adverse effects in patients is quite different from monitoring effects in recreational users. Due to its pharmacological effects it produces a depression of the central nervous system, resulting in hallucinations, disturbances in thinking and perception and also in motor function.

There is evidence that ketamine is abused, but looking at the figures one can hardly consider this to constitute a public health and social problem. Especially when comparing ketamine to the other cyclidines.

The substance is difficult to synthesize, so illegal production is unlikely. Preparations are mainly used in hospitals and veterinary clinics, so it is not expected that diversion will take place on a large scale.

Summarizing all the available information international control is not really necessary, but keeping the drug under surveillance could be considered.

1. Substance identification

INN:

Ketamine, Ketamine hydrochloride;

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;

Research names :

CI-581; CL-369; CN-52,372-2.

CAS Number :

Free base: 6740-88-1

Hydrochloride salt: Current: 1867-66-9; Previous: 81771-21-3; 96448-41-8; 42551-62-2

Proprietary names:

Anaket, Anasket, Anesketin, Brevinase, Brevinaze, Calypsol, Calypsovet, Chlorketam, Imalgene, Inducmina, Kalipsol, Katalar, Keta, Keta-HamelnKetaject, Ketalar, Ketalin, Ketalor, Ketamav, Ketamax, Ketamil, Ketaminol Vet, Ketanarkon, Ketanest, Ketanest-S, Ketaset, Ketasol, Ketava, Ketaved, Ketavet, Ketmine HCl, Ketolar, Ktmin, Narkamon, Narketan, Pan-Ketamine, S-Ketamin, Tekam, Vetalar Vetaket, Vetus Ketha-Thesia.

Street names

A number of street names for ketamine can be found in the literature, like: Ketamine, K, K-Hole, Kaddy, Kate, Ket, Vitamin K, Special K, Super K, Kéta K, Kit Kat, Cat valium, Liquid E, Liquid G, Flatliners, Tac et Tic, Jet, Super acid, 1980 acid, Special LA coke, Super C, Purple, Mauve and Green (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.

2. Chemistry

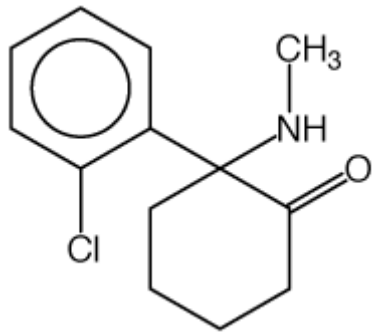
Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) is an arylcycloalkylamine structurally related to phencyclidine (PCP). Ketamine hydrochloride is water-soluble, white crystaline and has a pKa of 7.5 (Budavari *et al.*, 1989). Its free base, ketamine, has a lipid solubility 10 times that of thiopentone. The commercially available pharmaceutical form is an aqueous solution for injection of the racemic mixture of the hydrochloride salt. However, in some countries, e.g. the Netherlands the S-enantiomer is marketed.

Chemical formula

Free base: $C_{13}H_{16}ClNO$

Hydrochloride salt: $C_{13}H_{17}Cl_2NO$

Structural formula



Ketamine contains a chiral centre at the C-2 carbon of the cyclohexanone ring, so that two enantiomeres exist S-(+)-ketamine and R-(-)-ketamine. The S-one being the pharmacologically more active one. More and more the S-(+) enantiomere is used in the commercially available preparations.

Molecular weight

Free base: 237.73

Hydrochloride salt: 274.18

1.15 mg of the hydrochloride salt is equivalent to 1 mg of the free base.

Melting point

Free base: 92-93 °C

Hydrochloride salt: 262-263 °C

Synthesis, precursors, excipients and impurities

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).

Ketamine that is used recreationally, is mostly diverted from the pharmaceutical supply to hospitals, veterinary clinics or the pharmaceutical distribution network. Precursors mainly used for its illicit production are cyclohexanone, methylamine and chlorobenzene

(EUROPOL-EMCDDA, 2000). Sources on internet rate the synthesis of ketamine as difficult. A specific route described on internet involves the precursors cyclopentyl bromide, *o*-chlorobenzonitrile, and methylamine. A considerable amount of additional reagents and solvents is needed for the four-step synthesis described.

At the same place it is mentioned that two ketamine analogs have been found on the black market: the compound missing the 2-chloro group on the phenyl ring, and its N-ethyl analog. According to this internet site, both of these compounds are considered most likely more potent and longer lasting than ketamine. Using the same synthesis route as described for ketamine, the precursors benzonitrile and ethylamine instead of *o*-chlorobenzonitrile and methylamine would be involved.

When the drug is diverted for recreational use, the original pharmaceutical form is often abandoned. The most popular form for ketamine is a powder, which is snorted. The powder is prepared by evaporation of the original solution. This powder is usually sold in small plastic or paper bags. Additionally, the ketamine solution may be transferred to a vaporizer, from which it can be administered intranasally. It may also be present in tablets for oral use. As with all illegally sold drugs the concentration and presence of adulterants are mostly unknown and therefore represents an additional public health risk. When tablets contain ketamine, these tablets are often sold as ‘ecstasy’. Other substances reported to be present in ketamine-containing tablets are pseudoefedrine, ephedrine, cafeine, amphetamine, methamphetamine and MDMA.

3. General pharmacology

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

Pharmacodynamics

Ketamine is a dissociative anaesthetic (Domino *et al*, 1966). Originally, the dissociation component refers to a functional and electrophysiological dissociation of thalamo-neocortical and limbic systems (Reich and Silvay, 1989; Haas and Harper, 1992). Later, 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 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 indicated 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 (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) has 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 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 nucleus accumbens (NAc) led the authors to conclude that ketamine increases NAc dopamine efflux not by block of dopamine uptake, autoreceptors or NMDA receptors, but by mobilization 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 euphorigenic, addictive 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 R-ketamine. This correlates to 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).

Secondary pharmacology

Effects on 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 respiratory system

Ketamine is a mild respiratory depressant. It causes a shift of the CO_2 dose-response curve to the right, in a dose-related manner, but does not change the slope of the curve. Respiratory drive to CO_2 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 laryncheal 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).

Routes of administration

Clinically, the drug usually is 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).

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 vaporizer. 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. The United States report also use by smoking.

Dosages

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).

Recreational users snorting the powder, describe the quantity as a 'typical line', suggesting a quantity between 60 and 250 mg (Dalgarno and Shewan, 1996). 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. Toxicology, including adverse reactions in humans

The clinical safety profile of ketamine is largely based on the 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 drug user than for clinical practice.

Animal

Single-dose toxicity

Single dose acute toxicity shows an LD50 between 140 (intraperitoneally in the neonatal rat) and 616 mg/kg bw orally in the mouse (EMEA, 1997). In adult mice and rats LD50 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 also were dose-related elevated. Histological changes in the liver were minor (EMEA, 1997).

Reproduction function

Rats were injected during the premating 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-foetal 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 foetal 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 addicted 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-amino butyric acid (GABA) at *N*-methyl-d-aspartate (NMDA)] and $GABA_A$ receptors during the synaptogenesis period, also known as the brain growth-spurt period. Transient interference (lasting >= 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 an Sister Chromatid Exchange 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(+) enantiomere of ketamine in a standard battery of validated in vitro and in vivo tests did not reveal any evidence for a genotoxic potential. Provided that the genotoxicity findings with the S(+) enantiomere 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 mentioned before the combination of cocaine with ketamine is currently popular among young drug abusers and has been associated with increased risk of human immunodeficiency virus (HIV) infection. 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).

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) α_2-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 (α_2-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 partyscene.

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, drug 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). In a review on internet reports from heavy users of ‘dissociatives’ (i.e. dextromethorphan, ketamine and PCP) are summarized. Effects after frequent use mentioned were “jolts” or “shocks” when moving their 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.

Human

Clinical experience

Ketamine is considered 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 included 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 9 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 9 and brief respiratory depression in 4 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).

Sympaticomimetic effects

Serious side effects like hypertension and lung oedema have been reported (Murphy, 1993). Such adverse effects appear to be rare and may be related to the combination of ketamine with other drugs of abuse.

This may be due to the sympathicomimetic properties of ketamine. Inhibition of central catecholamine reuptake 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 sympaticomimetic 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 only ketamine was 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 intravenous dose for anaesthesia or 1.3-2.5 times the recommended intramuscular dose for anaesthesia. The intravenous 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 when administering through the intramuscular 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 drug 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 cardiostimulant effects, like cocaine and amphetamines, are indicated as drugs that may increase ketamine toxicity. Benzodiazepines can have favourable effects in clinical practice as co-administration prevents the occurence 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 artice 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.

Recently 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 astma as co-morbidity factor cannot been excluded.

The WHO Uppsala Monitoring Centre (UMC) reported, out of 1277 reports from adverse effects from world wide PMS-data 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 intoxicant will have severely impaired self-control, which poses a risk for injury of 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, like: general stiffness, increase of body temperature (38 °C), hepatic crises, myalgia and mydriasis.

5. Pharmacokinetics

The reported volume of distribution varied from 1.5 to 3.2 l/kg. The clearance was in the range 12-28 ml/(kg.min). Volume of distribution and clearance for S-ketamine are 9 and 14% greater than those for R-ketamine are, 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 are, 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 majority 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-lifes are ranging 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 is 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 circuit (as CK or Calvin Klein) these findings should lead to further investigations into the possible risks for users of this combination.

6. Dependence potential

Behavioral studies in animals

Self-administration

Animal models of addiction are used to test the induction of drug-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 addiction. 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 methamphetamine 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 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 drugs then 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 appeared that drug intake tends to increase slightly with increases in unit dose in each species. However, the increase is of a lesser degree than that generally occuring 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 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 opiates 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-addictive 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, dependence 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 i.v. 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. Re-administering the compounds, the rates increased rapidly to control rates, providing evidence of reversal of withdrawal. Cross-dependence 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)

Behavioral studies in man

Acute effects

Studies investigating the pathophysiology of schizophrenia, using ketamine as a model substance, and studies investigating the psychotropic effects of ketamine in their own right, have provided a good characterisation of 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 drug 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.

Effects on emotional status, behavioral 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 i.v. an escalating dose of ketamine by 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

COLORS: 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 ketamine dose and intensity of 'psychedelic' effects. All but one participant spontaneously reported feelings of intoxication and perceptual distortion during the ketamine infusion; one of these persons also reported these 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 of 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 disorganization, 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 disorganization and disorganized 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 Bonferoni 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 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 to 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

On a follow-up interview in a study by Krystal *et al.* (1994) in 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 one week, 4 weeks and 6 months after drug 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 one 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 one 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 five days, in three others there were only minor disturbances for three 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 one 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 drug 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 drug 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 polydrug 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 seven to ten 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-drug 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 three 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 polydrug 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.

Dependence potential in humans

Only a very limited number of cases (9) 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). Unfortunately the use of terms is not well-defined and therefore one can not 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 two 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 have 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).

Drug-seeking behaviour and addiction

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 drug continues despite increasing apparent effects on their work or on their health. Amongst the 20 users described by Dalgarno and Shewan (1996), 7 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 drug. On the other side of the spectrum, one user in this study group said he believed he had been addicted to 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, opiate-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 addicted. This addictive nature of ketamine (in the sense of psychological dependence) 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 addicted and committed suicide. The third slipped below the waterline in his bathtub, with a half-empty bottle of ketamine on its side.

Psychological factors that increase the probability of harm (e.g., mood and anxiety conditions leading to self-medication, sensation seeking)

No systematic studies on personality traits or other psychological factors leading to ketamine use or affecting the probability of harm were found.

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 drugs 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 drug. 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 addiction.

In those involved in taking drugs 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 drug users looking for extremes.

7. Epidemiology of use and abuse, with an estimate of the abuse potential of the substance

Ketamine was first marketed in the early 1970's (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 abuse was first spotted at the West Coast of the USA in 1971 (Siegel, 1978). In the early 1990's in the UK, several reports of a more wide-spread 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 abuse. 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 drugs 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 abused. 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 behaviors, and use in situations where there is a heightened 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 drugs 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-hydroxy-butyrate (GHB) and ketamine.

Out of a global database of 1277 reported adverse effects, covering a 2 year period, the UMC reported 5 cases of withdrawal syndrome (0.4 %), 21 cases of drug abuse (1.6 %) and 7 cases of drug dependence (0.5 %) (unpublished, communication to WHO, 2005).

The 2005 WHO Questionnaire for the preparation of the Expert Committee was responded for ketamine by 74 countries. 20 countries report abuse, 21 report that there is no abuse, 2 countries suspect abuse, but without proof and the other countries do not answer the question.

Australia reports a prevalence of 0.3% over the last 12 months and an 1.0 % lifetime use among people over 14 years old. Two thirds of them are male. Acute side effects are seen, but very few cases of fatal overdoses.
The prevalence in the Czech Republic is 0.8% over the last 30 days, 1.7% over the last 12 months and 6.7% lifetime use.
In Switzerland 9 out of 20 cases of poisoning were abuse cases; an additional 3 were possible abuse cases. From 1997-2005 9 cases of abuse were reported.
In Thailand the prevalence is estimated to be 0.1% of the population of 12-65 years.
In the United States of America the prevalence is reported by MTF as follows:

	2000	2001	2002	2003	2004	2005
8th Grade	**1.6**	1.3	1.3	1.1	0.9	0.6
10th Grade	2.1	2.1	**2.2**	1.9	1.3	1.0
12th Grade	2.5	2.5	**2.6**	2.1	1.9	1.6

Data are expressed as percent of students reporting use during the past year. Peak use year appears in bold print

Belgium saw 6, 10 and 40 cases of ketamine abuse in 2003, 2004 and 2005. In China there is recreational use among young people. Costa Rica had 3 cases in the last 2 years.
In Finland there is only abuse on a minor scale, as in France, where it is used at 'techno' parties, but rarely encountered; two cases of use as a rape drug ("chemical submission") were registered in France. In India it is only reported in one state. Ireland had 25-35 cases in 2004 and 2005. In Japan it is used in clubs to an extend that is not known. Several acute intoxications were seen. In Mauritius were two reports of use as rape drug, but they were not substantiated by the police. In Peru it is used on rave parties. In Sweden is limited evidence on social problems as to the abuse. In East-Timor it is used among small numbers of international staff. Urugay reports dependence after abuse.

8. Nature and magnitude of public health problems

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 drug, 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.

9. National control

Only three countries out of 74 report that they brought the substance under control: Australia, Belgium and the United States, the latter under Schedule III of the Controlled substances Act. the Lybian Arab Jamarhiriya "has been considering" the scheduling. Countries reported by the INCB to have brought the substance under control are Malaysia, Myanmar, the United Kingdom. Brunei Darussalam is reported to be considering its scheduling. Since 1997, France scheduled the raw material, but not the vials.

10. Therapeutic and industrial use

Ketamine hydrochloride is used as an analgesic and anaesthetic in human and veterinary medicine, where it has acquired a unique place. It is on the market in 70 out of the 74 countries that answered the questionnaire; in most countries as an anaestesic, in some countries also as an analgesic. A typical description of the indication reads:

> " Used for restraint or as the sole anesthetic agent in diagnostic or minor, brief surgical procedures that do not require skeletal muscle relaxation in humans. " (Ketalar, USA)

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 Third World countries, where facilities are much poorer. The ease of use gives ketamine a major advantage under these more difficult circumstances (Green *et al.*, 1996).

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 the S(+)- enantiomer.

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 opiates (Akin et al, 2005). Also other routes of application are investigated, like the intranasal route (Bell and Kalso, 2004). A kind of not expected 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 addiction to alcohol (Krupitsky and Grinenko, 1997) or heroin (Krupitsky et al, 2002). 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).

11. Production, consumption and international trade

Ketamine is produced commercially in a number of countries including Belgium, China, Colombia, Germany, Mexico, and the United States. Ketamine production is a complex and time-consuming process, making clandestine production impractical. (information US DoJ)

12. Illicit manufacture and illicit 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 abuse and trafficking are given.
For an unknown reason this is focused primarily to Asia and Oceania. Countries mentioned are: Australia, Bangladesh (609kgs diverted in 2002 after an import from Hungary), Cambodia, China, the Hong Kong Special Administrative Region (SAR) of China, Taiwan Province of China (65 kgs), 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 over here. One city in particular has to be

mentioned, Goa, as back in the nineteen eighties this was also the place were the so called XTC (being mostly MDMA) started its advance into the club and dance scene.

In the Annual Reports Questionnaire (ARQ) for 2003 submitted by Governments to UNODC, six Governments reported seizures of ketamine (Australia, Greece, Hong Kong SAR of China, Macao SAR of China, Malaysia and the Philippines. The largest seizures were reported by Malaysia (82.5 kg) and Hong Kong SAR (51 kg).
In the Annual Reports Questionnaire (ARQ) for 2004 submitted by Governments to UNODC, four Governments reported seizures of ketamine (Australia, Belgium, Hong Kong SAR of China, and Macao SAR of China. The largest seizures were reported by Hong Kong SAR (46.44 kg).

In the Questionnaire, only few countries report larger scale illicit activities, mainly Australia, which country reports that illicit activities with ketamine are significant, including importations and inclusion in MDMA and MA tablets as adulterant; 2-10 seizures annually in the period 2001-2005. Thailand reports seizures: 164 kgs in 2004 and 98 kgs in 2003.
In the USA there is no evidence of clandestine manufacture, but the substance is diverted from legitimate shipments; injection fluid is evaporated and sold as powder in bags et cetera. Also the substance was found to be smuggled from China via Mexico. In the period 2000-2005 there were 39 - 139 cases detected annually.

13. Current international controls in place and their impact

At present, no international controls are in place.
If such controls would be enforced, 11 out of 74 countries said that it would give problems with the availability for human medical use and/or for veterinarian use. This could be for instance because of increased administrative efforts that would be needed, or the application would be restricted to certain professionals, which would mean that in remote areas patients could not be treated. In veterinary medicine the unavailability would be a problem, because there is no replacement for the medicine.

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