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**REPORT OF AN
INFORMAL CONSULTATION
ON STRATEGIES FOR PREVENTION OF
HEARING IMPAIRMENT
FROM OTOTOXIC DRUGS**

Geneva, 21-23 November 1994

**Programme for the Prevention of Deafness
and Hearing Impairment (PDH)**

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INTRODUCTION

An informal consultation on "Strategies for Prevention of Hearing Impairment from Ototoxic Drugs" was held in WHO Headquarters in Geneva from 21 to 23 November 1994.

This meeting was convened within the framework of action of the WHO Programme for the Prevention of Deafness and Hearing Impairment (PDH); a list of participants is attached as Annex 1.

The meeting was opened by Dr G. Torrigiani, Director of the Division of Communicable Diseases. In his address, he pointed to the need for further data on ototoxicity, and the necessity to find suitable mechanisms for limiting the incorrect or unnecessary use of ototoxic drugs. The full text of the opening statement is in Annex 2.

Professor P. W. Alberti and Professor S. K. Kacker were elected as Chairman and Rapporteur respectively.

The proposed agenda was adopted without change (Annex 3).

1. MECHANISM AND CAUSES OF OTOTOXICITY

The participants commenced by considering the scope and purpose of the consultation (Annex 4) and existing definitions.

Ototoxicity refers to the harmful effect of a drug, or chemical substance, on the organ of hearing and/or balance.

Hearing impairment from ototoxic drugs is commonly caused by a small variety of drugs, chemical substances or heavy metals, as follows :

Table 1

Aminoglycosides	Gentamycin, streptomycin, kanamycin, amikacin, tobramycin, neomycin, netilmicin, polymyxin-B
Macrolides	Erythromycin, azithromycin, clarithromycin
Loop diuretics	Furosemide, bumetanide, ethacrinic acid
Salicylates	
Antimalarials	Quinine, chloroquine (high dosage)
Non-steroid anti-inflammatory drugs	Naproxen, indomethacine (no definite findings)
Anti-neoplastic drugs	Cisplatinum, bleomycin, carboplatinum
Chelating agents	Desferoxamine
Topical otological preparations	Antibiotic solutions: Neomycin Aminoglycosides Polymyxin-B Chloramphenicol Fosfomycin Anti-inflammatory: Propylene-glycol, hydrocortisone Antiseptic: Chlorhexidine, povidone-iodine (?) Acidifying: 2% acetic acid solution (?)
Chemical agents	Heavy metals: Mercury, lead (Industrial pollution, cosmetics). Solvents: Toluene, styrene Others: Arsenic, cobalt, cyanides, benzene, propylene-glycol, potassium bromide

In this consultation the focus was on ototoxic drugs.

The most common cause of hearing impairment from ototoxic drugs is the systemic or topical administration of aminoglycosides. Their extensive use, and abuse, are a major concern. The damage may be cochlear, vestibular, or both, resulting in hearing loss and unsteadiness. Although gentamycin and streptomycin are usually primarily vestibulo-toxic, their effect on the cochlea may produce severe hearing loss.

The mechanism of damage is either by direct action of the drugs on the hair cells or, less commonly, by affecting the stria vascularis, leading to degeneration of their supporting cells, resulting from metabolic changes due to toxic action of the above-mentioned agents: the degeneration may stop at any stage if the toxic action is blocked by removing the toxic agent, with variable recovery of hearing and balance.

However, the reversibility is usually agent- and dose-related. The most common causative agents, the aminoglycosides, usually produce permanent damage; their mechanism of action is in two stages:

- 1st stage = biochemical damage only
- 2nd stage = cell death

From the reported data, the key role of prevention is obvious.

2. EPIDEMIOLOGY, DETERMINANTS AND RISK FACTORS

2.1 Epidemiological data

Epidemiological data on ototoxic deafness and hearing impairment are unfortunately not available from most developing or developed countries. In fact, there are no reliable reports on the public health aspect of ototoxicity from the regions of Africa, the Americas or the Eastern Mediterranean.

2.1.1 EUROPEAN REGION

The only available source of information seems to be a national survey, carried out in Italy in 1991. The prevalence of hearing loss (>40dB) was about 4% and the specific prevalence of ototoxic damage was 1.9% (some 104 500 persons) (Quaranta, pers.comm.). According to this survey, ototoxicity is an underestimated source of deafness, which is totally avoidable with control in the use of ototoxic drugs and prevention of exposure to chemical and physical agents.

2.1.2 SOUTH-EAST ASIA REGION

A hospital study carried out in India in 1994 reported that, among 51 patients treated with streptomycin, 100% suffered from dizziness, 52.9% had hearing impairment, 33.3% had tinnitus and in 61.7% a mild or profound hearing loss was detected.

No other information of epidemiological significance on ototoxicity is available.

2.1.3 WESTERN PACIFIC REGION

Findings from a national sample survey, carried out in China in April 1987 in 30 provinces and municipalities with 1 576 316 examinations, show that 1.7% (26 518 cases) had hearing impairment and, among these, 3.7% was due to ototoxic damage; if these data are extended to the whole population in China, there could be 20 000 000 patients suffering from hearing impairment and, among these, 744 000 cases caused by ototoxic damage.

Reviewing some earlier surveys, an increase of ototoxic damage, as part of the overall burden of hearing impairment, could be found from 1954 (1%) to 1979 (28.4%); a recent campaign of public awareness on ototoxic drugs has reduced significantly the incidence of ototoxic hearing loss.

2.2 Determinants and risk factors

Considering available information, it seems that most common determinants for ototoxic damage are:

- personal and familial susceptibility;
- age (particularly extremes of life);
- daily dosage, duration and route of ototoxic drug administration;
- long-term exposure (i.e., total cumulative dose) to ototoxic chemical and physical agents.

Routes of administration of ototoxic drugs are also important determinants in the onset of hearing damage: the most dangerous seems to be intraspinal, followed by intravenous and intramuscular administration, and percutaneous in the treatment of burns; oral administration is considered relatively safe, at least for aminoglycosides, because of the low absorption rate from the intestinal tract.

Among risk factors, there is epidemiological evidence for:

- pregnancy;
- renal failure;
- hepatic failure;
- noise in working environment;
- concomitant administration of other ototoxic drugs, in particular diuretics.

The following table outlines particular risk factors in relation to ototoxic drugs:

Table 2

SUBSTANCE	DETERMINANTS & RISK FACTORS
Aminoglycosides	<ul style="list-style-type: none"> - Pregnancy - Renal dysfunction - Synergy with loop diuretics - Genetic/familial predisposition <p>In these conditions may be ototoxic even when given in normally acceptable dosage</p> <p>Caution: when used in infants and the elderly, and in those with a family history of ototoxic hearing loss; some may produce significant vestibular damage with normal hearing</p>
Cytotoxic drugs Cisplatin Carboplatinum (less ototoxic)	Risk not relevant in view of specific life-saving indications
Antimalarials Quinine Chloroquine	<ul style="list-style-type: none"> - Usually safe, unless long-term use or unusually high dosage - Ototoxic danger only in intensive parenteral treatment of cerebral malaria
Diuretics Thiazides and similar "loop" diuretics	<p>Potentiate ototoxic drugs and may also be ototoxic in their own right</p> <p>Caution: when used with aminoglycosides</p>
Salicylates	<ul style="list-style-type: none"> - Mildly ototoxic - Reversible hearing impairment <p>Caution: watch for idiosyncratic reactions, and not for use in children < 12 years of age</p>
Macrolides Erythromycin Azithromycin Clarithromycin	<ul style="list-style-type: none"> - Ototoxic only if given IV in high dose - Usually reversible hearing impairment
Analgesics	No known ototoxic effect
Otological preparations Antiseptics (ibitane, povidone-iodine, savlon, etc.) Other ear drops	<ul style="list-style-type: none"> - Potentially ototoxic if applied in presence of ear drum perforation and normal middle-ear mucosa - No proven ototoxic effect in usual dosage

3. STRATEGIES FOR PREVENTION AND CONTROL

3.1 Public education

The lack of general knowledge about the risk of ototoxic damage and insufficient public education on ototoxicity are great obstacles to preventive action. The utility of public and health education is also highlighted by the results of the survey in China (reduction of ototoxic deafness or severe hearing impairment after a public awareness campaign).

The aim of public education should be to provide individuals with information in order to enable them to use medicaments in an appropriate way.

Public information should make people conscious of the risk arising from the abuse or improper use of ototoxic drugs, related to dosage and duration of their administration. General knowledge of the interaction of concomitant therapies would be useful to prevent the synergistic effects of two ototoxic drugs. A large amount of documentation is available from the WHO Action Programme on Essential Drugs and the Division of Drug Management and Policies, which could be used as guidelines for educational campaigns.

3.2 Professional education

A large proportion of hearing impairment related to ototoxic drugs results from their inappropriate or indiscriminate use by multipurpose health care providers. The ototoxic potential of drugs should be stressed during the training of such staff, with regular refresher courses to update relevant knowledge. Otolaryngologists could provide the leadership, guidance and support in the introduction, development and conduct of such training in their respective countries.

In order to highlight drugs with particular ototoxic activities to the medical profession, a special clause is recommended to be included in the WHO List of Essential Drugs at its next revision in 1995; an overview of ototoxic drugs should be prepared for the WHO *Drug Information* series.

Information on ototoxicity could be given to paediatricians, internists, general practitioners, nurses, multipurpose health workers and, of course, pharmacists. The relevance of audiometric checks should be emphasized: (i) in at-risk patients following long-term therapies with ototoxic drugs; (ii) in non-risk patients under therapy with drugs that can potentiate the ototoxic effect of other drugs, for which medical prescription is not always needed.

3.3 Regulation/legislation

There are no restrictions in most developing countries limiting the availability of ototoxic drugs.

In China, aminoglycosides are available on prescription; in India, there are strict rules for their delivery, but regulations are not enforced. In many countries, ototoxic drugs are also sold "over the counter" without the need for prescription from a recognized health care provider.

Legislation should be introduced in countries where it does not as yet exist, to control the availability of these drugs, also when provided as a "gift" in emergencies and disaster situations. Where legislation exists, it should be strictly enforced.

In order to prevent the abuse or inappropriate use of ototoxic drugs, special attention could be given to drug indications, dosage and reduction of the "over the counter" trend.

3.4 Management

The most effective action to prevent ototoxic damage from drugs is to spread knowledge among people and health workers, to stop misuse of ototoxic drugs. Furthermore, for medical staff it should be stressed that, as a general rule and when available, non-ototoxic alternative drugs should be used, even if their cost may be higher.

There are situations in which potentially ototoxic drugs must be administered. Under such circumstances, the following should be observed: (i) proper dosage and duration of therapy; (ii) an appropriate route of drug administration; (iii) a continuous monitoring of the patient, with particular attention to audiometric values and serum drug level where feasible.

These measures should be quite effective in preventing deafness or hearing impairment from ototoxic damage; but when these procedures are not feasible, the general knowledge and awareness of early symptoms are of great importance. Furthermore, legislation and the restriction of the availability of major ototoxic drugs on medical prescription, together with a careful control of drugs delivered in emergencies and disaster situations, are powerful tools for prevention.

With regard to ototoxic chemical agents, it is useful to refer to the International Programme on Chemical Safety documents¹ and to ILO General Conference (77th session, 6 June 1990) recommendation No.177, concerning safety in the use of chemicals at work. The problem is a major one, and there is good evidence for the synergistic cochleotoxic effect of noise and particularly of toluene, a widely used industrial chemical.

4. EDUCATIONAL MATERIAL

Posters and brochures are suggested useful educational materials and, for their production, collaboration with interested nongovernmental organizations (NGOs) should play an important role. Posters should be used in schools and health centres, hospitals and other suitable public places. Newspaper articles could highlight the problem and its prevention.

When available, media communication, such as through television or radio, could be successfully used. Newsletters could be used for professional education, trying to reach also the multipurpose health workers.

¹ Environmental Health Criteria, for example Nos: 1 (mercury); 2 (lead); 12 (noise); 13 (carbon monoxide); 19 (hydrogen sulfide); 26 (styrene); 30 (principles for evaluating risks to progeny associated with exposure to chemicals).

5. RESEARCH NEEDS

National surveillance systems are needed in most developing countries to set up a monitoring system for ototoxic damage. The main obstacle seems to be the unavailability of audiometers (conventional or high frequency), which are essential to obtain reliable data. A pro-forma for a screening survey of ototoxic damage should be prepared, which could be suitable also for general practitioners; a model form for field tests is in Annex 5. More research is needed to find out if there is any substance that could reduce damage from ototoxic drugs during their administration.

Also needed is a determination of safe dosage and duration of treatment with potentially ototoxic drugs in high-risk groups.

CONCLUSIONS AND RECOMMENDATIONS

Preamble

Ototoxicity refers to the harmful effect of a drug or chemical substance on the organ of hearing and/or balance.

The global magnitude of the problem of hearing impairment or deafness due to ototoxicity is not accurately known, but it is probably responsible for 3-4% of all deafness in children in developing countries and for a substantial part of hearing impairment in adults, including also developed countries. Furthermore, there are indications that ototoxic hearing loss is increasing in some parts of the world and adding to the burden of needless hearing impairment.

Hearing impairment from ototoxic drugs or substances is mainly caused by a few commonly used aminoglycoside antibiotics and other medicaments, including antimalarials and cytostatics; however, chemicals such as solvents, used in an industrial or domestic setting, can also have such effects, sometimes with reduced hearing being part of a general neurotoxic effect, at times acting synergistically with noise.

Hearing loss due to ototoxicity is generally irreversible but **avoidable** in most instances, given proper preventive action through rational use of drugs in the health care system and by the consumers.

1. Ototoxic drugs

By far the most common cause of hearing impairment from ototoxic damage by drugs is due to injectable aminoglycosides. Gentamycin is cheaper than newer available alternatives and hence is in more common use and widely available. The global resurgence of tuberculosis is leading to greater use of streptomycin.

It is recommended that the use of aminoglycosides be restricted to trained health personnel only. Particular caution should be exercised in their concurrent use with other ototoxic agents, especially injectable loop diuretics and when treating high-risk groups, such as in pregnancy, in cases of renal disease and at the extreme ages of life.

2. Monitoring

There are specific indications where essential drugs with ototoxic potential have to be used either systemically or topically. In such circumstances, careful monitoring can help to prevent possible hearing loss from ototoxicity. As a minimum, it is recommended that such monitoring include surveillance of proper dose and duration of treatment, as well as assessment of symptoms; if feasible, audiometry should be carried out when indicated, as in high-risk groups.

3(a) Professional education and training

A large proportion of hearing impairment attributable to ototoxic drugs reportedly results from their inappropriate or indiscriminate use by health care providers of various categories; this is often the result of lack of awareness on the part of the prescribers.

It is recommended that these health care personnel be given training, during their basic and continuing education courses, on the rational use of drugs, particularly those with ototoxic potential. Otolaryngologists could provide leadership, guidance and support in the introduction, development and conduct of such training in their respective countries.

3(b) In order to highlight for the medical profession those drugs which are particularly ototoxic, it is recommended that a special clause on ototoxic side-effects of those drugs concerned be included in the WHO List of Essential Drugs at its next revision in 1995; in addition, an overview of ototoxic drugs should be prepared for the WHO *Drug Information* series. Other suitable material should also be prepared in collaboration with interested nongovernmental organizations and professional bodies.

4(a) Public education

Ototoxicity may also result from a lack of awareness of the general public and the individual patient of the potential damage to hearing caused by certain medications. It is important that the public be made aware of such possible complications, of the need to take medications only in consultation with their health care providers in the prescribed doses and duration, and to report back to the health care provider in the event of any untoward effect on hearing or balance.

4(b) There is a need for the production of health education material to acquaint the public of the hazard of ototoxic drugs. A considerable amount of documentation is available from the WHO Action Programme on Essential Drugs which could serve as guidelines in producing such material. It is recommended that these be adapted as appropriate, in the development of health education material relevant to ototoxicity, by the WHO Programme for the Prevention of Deafness and Hearing Impairment in its collaboration with interested nongovernmental organizations.

5. Regulation and legislation

It was reported that in many countries drugs with ototoxic effects were freely available and sold "over the counter" without the need for a prescription from a recognized health care provider.

It was recommended that legislation be introduced in countries where this does not exist at present, to control the sale of ototoxic drugs. In countries where legislation exists, there is a need for its stricter enforcement.

6. Donated drugs

The receipt of donations of a variety of medicines from different sources is commonplace in countries faced with disaster situations, e.g. natural disasters, armed conflicts, etc. It is likely that these consignments could include ototoxic medications, especially antibiotics. It is recommended that caution be exercised when dispensing or administering such drugs to these populations, in accordance with guidelines from WHO and the emergency relief organizations concerned.

7. Research

There is a great need for more research on ototoxicity, in particular on its epidemiology and main causes in different settings, including its genetic predisposition; the role and potentially harmful effects of topical antibiotic and antiseptic preparations in ear care also deserve further attention in this perspective.

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ANNEX 2

**SPEECH BY DR G. TORRIGIANI
DIRECTOR, DIVISION OF COMMUNICABLE DISEASES**

Ladies and Gentlemen:

On behalf of Dr Nakajima, Director-General of the World Health Organization, I welcome all of you to Geneva and to this important and timely Informal Consultation on Strategies for Prevention of Hearing Impairment from Ototoxic Drugs.

Avoidable hearing impairment and deafness are an important public health problem, particularly in a number of developing countries, as a major cause of sensorineural hearing loss.

Although infectious conditions such as otitis media account for the largest proportion of conductive hearing loss, damage to hearing caused by ototoxic medication has been increasingly reported from countries in recent years.

In the last few decades, a large array of drugs with ototoxic potential has been added to our therapeutic options. Among these, antibiotics such as aminoglycosides have been largely incriminated in producing hearing loss. While many of these drugs have been life-saving, their indiscriminate use has led to hearing deficits that have affected the quality of life of the individuals treated.

There are several reasons for their injudicious use. Self-diagnosis and self-medication are amongst such causes. The easy availability of some of these drugs "over the counter" and without a physician's prescription favours self-medication with potentially harmful drugs. Another reason is the dispensing of these drugs by pharmacists and other paramedical and professional persons who are not fully aware of their hearing-threatening propensity and who cannot keep track of the patient's consumption of the medicament in question.

A particularly worrying example is the administration of some of these medications to pregnant mothers, thereby affecting the unborn baby. Their prolonged use in patients with liver or kidney failure is another example of injudicious use.

Preventive interventions should be based on strategies that educate the individual patient, the public, professionals and policy-makers.

First of all, individuals and the public must be made aware of the hazards that these drugs pose to hearing.

Professionals, including paraprofessional personnel, should receive training at the undergraduate and postgraduate levels, and in continuing education courses, on the rational use of drugs in general and those with ototoxic potential in particular.

Annex 2

When treatment with such drugs becomes imperative, due to the unavailability of substitutes, the patient's hearing needs to be closely monitored so that treatment could be stopped in time, and possible remediable measures instituted early.

Policy-makers must ensure that existing legislation with regard to the restricted sale of these drugs is enforced and, where such laws do not exist, laws limiting ready availability, except on a physician's prescription, should be introduced and enforced.

Operations research on knowledge, attitudes and practices of the public and the professionals could be carried out, to help design educational and training material and messages about the hazards to hearing of such drug use. There may be other examples in this field, where valuable experience has been gained which could benefit the solving of the present issue.

I trust that the outcome of this informal consultation will provide practical guidelines to countries faced with the problem of ototoxic hearing loss, to help prevent and control this cause of needless hearing impairment and deafness.

I wish you a fruitful meeting and a pleasant stay in Geneva.

ANNEX 3

AGENDA

Opening of Meeting

Election of Officers

Adoption of Agenda

1. Mechanisms and causes of ototoxicity
2. Overview of global data on hearing impairment including specific information on ototoxic hearing loss
 - (i) epidemiological data
 - (ii) determinants and risk factors
3. Strategies for prevention/control
 - (i) education: - public
 - professional
 - (ii) regulation/legislation
 - (iii) management
4. Educational material
5. Research needs
6. Conclusions and Recommendations

Closure

ANNEX 4**SCOPE AND PURPOSE**

Ototoxicity refers to damage and dysfunction of the inner ear structure resulting from exposure to drugs and/or chemical substances.

Such exposure is a common cause of sensorineural hearing loss, particularly in developing countries. It generally results from indiscriminate use of medications that have ototoxic propensity. In industrial settings, it may also result from exposure to specific chemical agents that may damage the inner ear.

This informal consultation would review the available data on the prevalence and incidence of ototoxic hearing loss, possible risk factors and determinants and outline measures to prevent and manage hearing loss resulting from this cause.

An expected outcome of the consultation would be the preparation of guidelines for developing educational material pertaining to the prevention and control of ototoxic hearing loss.

ANNEX 5

OTOTOXICITY FORM

Date:

Name:

Age:

Sex:

No.:

City:

File No.:

Occupation:

History of the case:

1. Renal - for dialysis
2. TB
3. ICU
4. Oncology

Presence of: (A) Renal disease ☐ (B) Liver disease ☐ (C) Metabolic disease, etc. ☐

Drugs	taken	Dose	Route	Duration
				Days-weeks-months
1.				
2.				
3.				
4.				
5.				
6.				

Exposure to noise

Family History

Traditional medicine

Previous treatment with similar medication: Yes ☐ No ☐Ear complaint

Before treatment

During or after treatment

- Earache
- Discharge
- Hearing loss
- Tinnitus
- Imbalance

Yes ☐ No ☐ R-LYes ☐ No ☐ R-LEar examination

Before treatment

After treatment

- Tympanic m. perforation
- Discharge
- Ear surgery

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Hearing test

- PTA
- BERA
- Otoacoustic emission
- Tympanometry

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