J. periodont. Res. **8**; Suppl. 12: 55–57, 1973

Some toxicological observations on chlorhexidine

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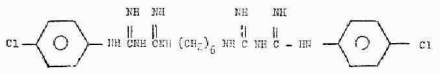
In reviewing the toxicological evaluation of chlorhexidine it may be apposite to briefly mention the historical background leading to its commercial introduction as a general antiseptic agent. During the late 1940's in the laboratories of I.C.I. a search was made for water soluble polymeric substances which might possess anti-viral activity. Most of those examined were polysaccharides and other non-ionic compounds together with a few anionic compounds. In an attempt to explore the alternative activity of cationic polymers a series of polybiguanides was synthesised. Although possessing the required physico-chemical characteristics they had no antiviral activity and were therefore put aside. Some time later they were re-assessed for antibacterial activity against the already established cationic compound cetrimide (Cetavlon*) and were found to be more potent than cetrimide against a wide range of organisms. For reasons of its inherent antibacterial activity chlorhexidine was eventually selected as the chosen biguanide (Fig. 1) and given the trade name 'Hibitane'. A detailed account of the antibacterial properties of this compound is presented elsewhere in this Symposium by Dr. T. D. Hennessey. It was first marketed in the United Kingdom in 1953 as an antiseptic cream which was soon followed by an obstetric cream and, for veterinary use, an udder wash.

Chlorhexidine is a strong base and is most stable in the form of its salts. The salts which were originally employed were the acetate and hydrochloride both of which suffer however from relatively poor water solubility, (Table I) and were largely replaced by the digluconate in 1957. Since that time chlorhexidine has been employed for a wide range of applications a selection of which are listed in Table II.

The earliest toxicological evaluation of chlorhexidine quickly established a marked difference between intravenous and oral LD_{50} values. For example, in mice, the i.v. LD_{50} value for the digluconate is 22 mg/kg whereas the corresponding oral figure is 1800 mg/kg. This pattern is repeated in rabbits and calves. Chlorhexidine it not effective against systemic infections following parenteral dosing. Therefore, its use is restricted to prophylactic antisepsis by topical or oral application. This relatively simple evaluation of toxicity was followed by chronic tests in rats over three month, one year and two year periods. The format



Chlorhexidine (Hibitane)

Fig. 1.

* 'Hibitane' and 'Cetavlon' are Trade Marks, the property of Imperial Chemical Industries Limited.

Table I

The solubility of chlorhexidine salts in water

20°C Salt	% W/V Solubility
Base	0.08
Acetate	1.90
Hydrochloride	0.06
Digluconate	> 50

Table II

Some clinical uses of chlorhexidine

Use	Formulation	Application
Skin infection	Solution	Topical
Wounds	Solution	Topical
Burns	Solution	Topical
Throat infection	Lozenge	Oral
Obstetrics	Cream	Topical
Bladder irrigation	Solution	Topical
Instrument sterilisation	Solution	Immersion
Dentistry	Tincture	Topical
Oesophagitis	Lozenge	Oral
General disinfectant	Various	Various

of these studies is shown in Table 3. The only change seen in these tests was the appearance of giant cells in the abdominal lymph nodes; no tumors or any other toxic manifestations were seen in any of the tissues examined. It should be pointed out that these results were obtained some fifteen years ago at a time when the systematic evaluation of the toxicity of new drugs was in its infancy.

Table III

Chronic toxicity testing of chlorhexidine (rat)

Duration (months)	No. of animals	dose* mg/kg
3	36	50/100/200
12	72	40 —› 230
24	48	125/158

* dose expressed as mg per kg free base.

These original tests were supplemented with evaluations of teratology and reproductive effects (rats), skin sensitisation (rat) and eye irritation (rabbit). The outcome of these studies was wholly satisfactory in that no teratological or reproductive changes were found. Human use has established that concentrations of digluconate greater than 2 % may cause dermal discomfort and that concentrations of up to 0.2 % are tolerated by the eye.

The introduction of any new drug into human medicine is always, from a toxicity standpoint, a move into the unknown. Despite the most exhaustive safety testing in a wide range of animal species, there will always remain the possibility that man may react adversely to the new entity. This may be the result of different metabolism, absorption characteristics or organ sensitivity. The toxicologist can therefore only provide a confident guess rather than an unequivocal statement of safety. The fullest evaluation in man can only come with prolonged human experience of the drug.

In this respect, we are fortunate in being able to review the results of nearly twenty years experience with chlorhexidine. During this period there have been no reports of ill effects following its ingestion. In other words the record of chlorhexidine is particularly clean, no doubt because it is so poorly absorbed. On rare occasions solutions of up to 1 litre of 1 in 5000 chlorhexidine have been accidentally adminstered intravenously. The consequence of this was haemolysis resulting from the ensuing hypotonicity, rather than a direct effect of chlorhexidine. Exchange transfusion led to complete recovery of the patients.

Less than ten cases of sensitisation implicating chlorhexidine have been recorded and, in some of these, it was not clearly established whether other factors were causative.

Some confusion has recently presented

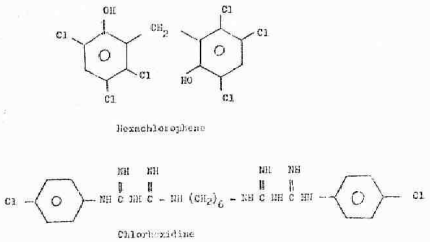


Fig. 2.

itself regarding the toxicity of chlorhexidine to the central nervous system in relation to the antibacterial agent hexachlorophene which has been shown to produce toxic effects in children, monkeys and rats. As Fig. 2 clearly demonstrates there is a distinct difference between the chemical structure of these two compounds: chlorhexidine is a strong organic base and hexachlorophene is a chlorinated phenol. It has been shown by Winrow (accompanying paper) that, in common with most tissues, cerebral levels of chlorhexidine in animals following dosing with radiolabelled material are extremely low. However, direct injection into the cerebrospinal fluid of monkeys produces, like most antiseptics, a toxic reaction (Weston Hurst 1955).

In the last two years great interest has arisen in the use of chlorhexidine in oral hygiene and in particular for the control of dental plaque and gingivitis. With the prospect of long term, indeed life-time, oral application of chlorhexidine we thought it necessary to review existing toxicological data in the light of currently acceptable toxicological standards. For this reason the long term chronic toxicity testing following administration to rats in the drinking water is being repeated with the more sophisticated techniques now available.

In summary, we have established both by previous animal toxicity tests and by long clinical experience that chlorhexidine has an unusually low level of toxicity in animals and man. For this reason, we therefore feel that the clinical evaluation of chlorhexidine in oral hygiene can proceed safely.

Reference

Weston Hurst, E. 1955. Adhesive arachnoiditis and vascular blockage caused by detergents and other chemical irritants; an experimental study. *J. Path. Bact.* **70**: 169–178.

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Discussion III

Rindom-Schiött: Dr. Magnusson, the mice were not anesthetized when they were given chlorhexidine, so may it have been by accident that they got the compound into the respiratory tract and up in the nose?

Magnusson: I can only relate the fact that all animals reacted perhaps to the bitter taste with coughing and sneezing.

Rindom-Schiött: They reacted maybe also to the volume?

Magnusson: Well, I should say that in the gluconate series, we had an acceptable volume of ½ ml dosed very slowly and the reaction was the same.

Briner: Dr. Magnusson, do you normally prevent the animals from recycling their own faeces?