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Acute toxicity of radiation-sterilised propylene glycol

SIR,—Certain drugs that are subject to hydrolysis when dispensed as an aqueous solution are prepared, for pharmaceutical purposes, as a solution in propylene glycol. Such solutions may be difficult to sterilise as many of the drugs concerned are affected by heating; bacteriological filtration is tedious due to the viscous nature of the solvent and there is always a risk that the aseptic precautions necessary for the filling and sealing of the final containers may fail. Radiation sterilisation may offer a useful alternative method: it can be applied to the preparation in its sealed container.

The present investigation was stimulated by the need to sterilise a solution of di-isopropylfluorophosphonate (dyflos, DFP) in propylene glycol (1 mg/ml). The dyflos is prepared with labelled phosphorus atoms (^{32}P) and the solution is intended for parenteral use in clinical studies of blood cell turnover. Preliminary studies indicated that the potency of the dyflos itself was only very slightly affected by radiation sterilisation (Charlton, personal communication) but no information was available on the effect of radiation sterilisation on the toxicity of propylene glycol.

A sample of redistilled propylene glycol was divided into two parts, one of which was irradiated with 2·5 Mrad of gamma radiation—the dose used for sterilisation of medical equipment (Burt & Ley, 1963).

Groups of 3 male and 3 female adult SPF albino rats were given either irradiated or unirradiated propylene glycol by intraperitoneal injection at the following doses: 9·4, 11·1, 13·0, 15·3, 18·0 and 21·1 ml/kg body weight. The LD50 values were calculated from the mortality after 5 days using the method of Finney (1952). The LD50 values, with the 95% fiducial limits were for the irradiated material 13·7 (12·5–15·1) and for the control material 14·2 (12·4–16·1) ml/kg weight; differences between groups are not significant.

Irradiated or unirradiated propylene glycol was given to groups of 5 male and 5 female mice (C3H strain) by intraperitoneal injection to a dose of 5 ml/kg weight. Before injection, 1 part of propylene glycol was diluted with 2 parts of normal saline. This dose is about half the median lethal dose in mice (Lampe & Easterday, 1953) but although all mice showed signs of intoxication (lack of co-ordination of movements followed by deep narcosis and, in a few cases, convulsions), no mice died within 7 days of injection. During the week after injection with propylene glycol no differences were observed in general health, weight changes, or food and water intake between the groups receiving irradiated or unirradiated material. All the mice were killed and examined 7 days after injection; apart from evidence of inflammation of the peritoneal cavity, presumably caused by the injection, no abnormalities were observed in mice of either group.

These results show that sterilisation of propylene glycol with a dose of 2·5 Mrad of gamma radiation does not increase its acute toxicity and this information may be of interest to others who may be contemplating radiation sterilisation of other pharmaceutical preparations formulated with propylene glycol.

J. R. HICKMAN

U.K.A.E.A. Research Group,
Isotope Research Division (A.E.R.E.),
Wantage Research Laboratory,
Berkshire.
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Influence of urine pH and flow rate on the renal excretion of chlorpheniramine in man

SIR,—The renal excretion of amphetamine and methylamphetamine has been shown to be dependant upon the pH of the urine and is sufficiently pH-sensitive to reflect the diurnal rhythm of urinary pH (Beckett & Rowland, 1964, 1965; Beckett, Rowland & Turner, 1965). We now report that, using a specific assay for unchanged drug based upon gas liquid chromatography (Beckett & Wilkinson, to be published) the renal excretion of the antihistamine, chlorpheniramine and its (+) and (−) isomers, shows a dependance not only upon urinary pH but also upon the rate of urine flow.

The oral administration to normal male subjects, of an aqueous solution of 10 mg chlorpheniramine base as the maleate, resulted in a fluctuating excretion rate. The total amount of unchanged chlorpheniramine excreted in 24 hr was 4·5–11·5%. In contrast to the results reported for amphetamine and methylamphetamine (Beckett & Rowland, 1964; 1965; Beckett & others, 1965), maintaining the urine acid (pH 5·00 $\pm$ 0·50), or alkaline (pH 8·00 $\pm$ 0·50), by administration of ammonium chloride or sodium bicarbonate, respectively, did not abolish the fluctuations (see Fig. 1), although there was a difference in the total amount of drug excreted. When the urine was acid, 20·0–26·5% unchanged drug was excreted in 24 hr, whereas only 0·3–0·4% was excreted when the urine was alkaline.

Under constant acid urine conditions the fluctuations in the rate of excretion appeared to be related to changes in the rate of urine flow; a high flow rate resulted in a high excretion rate (see Fig. 1). The volume-dependent fluctuations were abolished when the urine flow rate was maintained above 150 ml/hr by water loading the subjects (see Fig. 1). Under these conditions the excretion rate decreased exponentially except for a rise 10–15 hr after administration of the dose; the reason for this departure from exponential excretion is under investigation. The excretion pattern of both the (+)- and (−)-isomers was similar to that of the racemate.

These results may be explained by assuming that the tubular epithelium of the distal convoluted kidney tubules is selectively permeable to the unionised base (Schanker, 1962). The rate of reabsorption of the drug from the tubular fluid will thus depend on the ratio of concentration of unionised base within the tubules and that in the peritubular fluid (Milne, Scribner & Crawford, 1958; Weiner & Mudge, 1964). The concentration of unionised base in the tubules may be altered by a change in the pH of the tubular fluid, as the pK_a of chlorpheniramine is 9·16 (Marshall, 1955), or by alteration in the fluid volume.