Antifertility mode of action of α-chlorohydrin—interaction with glyceraldehyde-3-phosphate-dehydrogenase

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α-Chlorohydrin (3-chloro-1,2-propanediol) induces temporary sterility in a variety of mammalian species apparently by interference with enzymes involved in the glycolytic pathway (Mohri, Suter, Brown-Woodman, White & Ridley, 1975). The most susceptible enzyme appears to be glyceraldehyde-3-phosphate-dehydrogenase and the suggested mechanism involves the phosphorylation of α-chlorohydrin within the sperm, the 1-phosphate ester of α-chlorohydrin being the proximate inhibitor. The mouse and rabbit are insusceptible to the antifertility action of α-chlorohydrin, so that it seemed of interest to test the sensitivity of rabbit muscle glyceraldehyde-3-phosphate-dehydrogenase to this substance. We have synthesized the 1-phosphate ester of α-chlorohydrin and demonstrated that the rabbit muscle enzyme is susceptible to this, which raises the question as to why rabbit sperm should not be rendered infertile by α-chlorohydrin. α-Chlorohydrin contains an asymmetric carbon atom and its optical isomers have recently been synthesized in this Unit (Jackson & Robinson, 1976; Jackson, Fitzpatrick, Rooney & Gibson, 1977). The antifertility activity is specifically associated with one isomer, namely the S(+) compound. The susceptibility of the rabbit enzyme to racemic and isomeric forms of α-chlorohydrin, the kinetics and nature of interactions, will be discussed.

References

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A chronic dose-ranging kinetic study of salicylate in man

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Salicylic acid (SA) pharmacokinetics are dose dependent due to saturable metabolism (Levy, Tsuchiya & Amsel, 1972); detailed characterization has been derived primarily from single dose studies. Limited pharmacokinetic data are available following the more usual clinical practice of chronic administration. We have conducted a chronic oral dose-ranging study of SA pharmacokinetics in two healthy male volunteers. Each initially took 300 mg soluble aspirin dissolved in water, every 8 h until steady state was reached, as judged by monitoring plasma SA concentration. Within an 8 h dosing interval at steady state timed samples of saliva, blood and urine were collected. The dose of soluble aspirin was then increased by 300 mg and the process repeated until one subject was receiving 1200 mg every 8 h and the other 1500 mg.

SA in saliva and plasma was measured fluorometrically (Graham & Rowland, 1972); total urinary salicylate was measured by the method of Levy & Procknal (1968). Plasma SA binding was determined by ultracentrifugation at 37°C in all samples collected during the study and in pre-dose samples, to which varying amounts of SA were added.

Dose dependency was clearly evident (Table 1). The time-averaged steady state SA plasma concentration ($\bar{C}_p$) increased 10 fold for only a 4–5 fold increase in dose. Diminished plasma SA binding with increasing plasma SA concentration tended to mask the full effect of saturable SA metabolism; the corresponding time-averaged steady state unbound SA plasma concentration ($\bar{C}_u$) increased by 30 fold. Within each 8 h period of intensive sampling the amount administered was recovered in urine, confirming that steady state had been reached. These preliminary data form the basis of a model of salicylate kinetics applicable to chronic medication.