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.

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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.

Table 1 Time averaged steady state concentrations of salicylic acid in plasma ($\bar{C}_p$) and saliva ($\bar{C}_s$) after chronic administration of soluble aspirin (ASA). $\bar{C}_u$ is the unbound plasma concentration

	Subject A			*Subject B*		
Dose of ASA (mg)	*Plasma*		*Saliva*	*Plasma*		*Saliva*
	$\bar{C}_p$ (mg/l)	$\bar{C}_u$ (mg/l)	$\bar{C}_s$ (mg/l)	$\bar{C}_p$ (mg/l)	$\bar{C}_u$ (mg/l)	$\bar{C}_s$ (mg/l)
300	13.0	1.0	0.6	12.3	1.0	0.5
600	57.2	7.0	2.4	30.3	2.3	1.0
900	123.1	20.5	6.1	58.7	8.3	1.9
1200	158.1	29.9	7.1	93.3	17.3	4.1
1500	—	—	—	146.9	36.0	6.0

A positive linear correlation existed between SA concentration in saliva and the total SA concentration in plasma ($r=0.915$; $P<0.001$), as well as with the unbound SA concentration in plasma ($r=0.820$; $P<0.001$), suggesting that saliva may prove useful in monitoring salicylate therapy. The time-averaged steady state SA saliva concentrations ($\bar{C}_s$) are shown in the table. Plasma binding of SA was systematically lower in samples obtained during chronic administration of soluble aspirin than in control samples, an observation not explained by changes in albumin concentration which remained constant throughout.

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Comparative effects of a new orally active antidysrhythmic agent, Organon 6001, on the cardiac action potential of human ventricular muscle and sheep Purkinje fibres

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Organon 6001 (3α-amino-2β-hydroxy-5α-androstan-17-one hydrochloride) has been shown to reduce ventricular dysrhythmias arising from coronary artery ligation in anaesthetized dogs (Marshall & Parratt, 1975). It has class 1 antiarrhythmic activity in rabbit cardiac muscle (Salako, Vaughan Williams & Wittig, 1976). The following studies were undertaken to determine if it has similar effects on human ventricular muscle.

Small pieces of ventricular myocardium were obtained from children undergoing corrective open-heart surgery for ventricular septal defects. No patient had received any cardiotonic, antiarrhythmic or diuretic medication prior to surgery. The muscle was perfused with Tyrode solution (K^+ 4.0 mM) and was driven at a frequency of 1 Hz. Intracellular action potentials were recorded with glass microelectrodes filled with 3 M KCl solution.

The control parameters for the human muscle preparations were: resting membrane potential (RMP) 82.6 ± 0.5 mV, action potential height 112.5 ± 0.6 mV, maximum rate of depolarization (MRD) 265 ± 7 V/s;