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.

Supported in part by Bristol Myers Products. We thank G.J. Fleming, D.M. Johns and S.E. Watson for technical assistance.

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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;

Table 1 The effect of Organon 6001 on cardiac muscle action potentials

Dose of Organon 6001	Human ventricular muscle				Sheep Purkinje tissue			
	n	MRD (V/s)	90% repolarization time (ms)	ERP (ms)	n	MRD (V/s)	90% repolarization time (ms)	ERP (ms)
Control	25	304 ± 20	265.9 ± 6.5	292 ± 2	22	424 ± 17	315.2 ± 2.3	318 ± 9
4 mg/l	21	246 ± 17** (−19)	256.4 ± 2.7 (−3)	284 ± 16 (−3)	24	302 ± 20* (−29)	257.7 ± 1.5* (− 18)	278 ± 12 (- 13)
Control	30	233 ± 12	343.6 ± 2.0	377 ± 15	28	429 ± 25	377.0 ± 3.3	349 ± 46
8 mg/l	27	168 ± 13* (−27)	329.8 ± 1.9 (−4)	370 ± 17 (−2)	24	283 ± 23* (−34)	306.5 ± 1.3* (− 19)	293 ± 34 (- 16)
Control	26	284 ± 20	297.5 ± 8.0	341 ± 31	16	361 ± 33	327.6 ± 1.5	328 ± 16
16 mg/l	31	172 ± 18* (−39)	293.1 ± 6.3 (−1)	329 ± 34 (−10)	16	184 ± 19* (−49)	286.1 ± 6.1* (− 13)	309 ± 24 (- 6)

Values are means ± s.e. mean with the percentage change from controls in parentheses.
n = number of observations obtained from two or three preparations at each dose level. *$P < 0.001$; **$P < 0.025$.

time to 50% and 90% repolarization, 201.6 ± 2.7 and 289 ± 3.3 ms respectively (means of 150 observations in 8 preparations). These parameters do not differ significantly from those of lower mammals. The effects of Organon 6001 (4–16 mg/l) were compared with those obtained using sheep Purkinje fibres bathed in Tyrode solution containing K^+ 5.4 mM. The results are summarized in Table 1. Organon 6001 had no effect on RMP of either tissue, or, except in the highest concentration used in the Purkinje studies, on action potential height. A dose-dependent decrease in MRD was produced by the drug in both tissues; a significant reduction in time to 90% repolarization was seen only in Purkinje tissue. The effective refractory period (ERP) in human ventricular muscle and the ERP/action potential duration ratio in Purkinje tissue was not significantly altered by the drug.

In preliminary experiments on human ventricular muscle lignocaine (8–16 mg/l) decreased MRD to a lesser extent than did Organon 6001, but it significantly prolonged the ERP. No significant effect was seen at a concentration of 4 mg/l.

I am most grateful to Professor P. Caves for so readily making available human ventricular tissue. K.A.K. is an Organon Research Fellow.

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