Coronary artery ligation in anaesthetized rats as a model for the assessment of antidysrhythmic activity; the effects of lignocaine, propranolol and ORG 6001

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Ligation of the left coronary artery in rats provides a relatively simple model for the assessment of antidysrhythmic compounds (Kenedi & Losonci, 1973). Using this model we have compared the effectiveness of lignocaine and propranolol with that of the recently developed aminosteroid ORG 6001 (3α-amino-5α-androstan-2β-ol-17-one hydrochloride; Marshall & Parratt, 1975; Vargaftig, Sugrue, Buckett & Van Riezen, 1975).

Male Sprague-Dawley rats (250–450 g) were anaesthetized with pentobarbitone sodium (6 mg/100 g, intraperitoneally). Carotid arterial pressure and the electrocardiogram were recorded continuously and all drugs were administered intravenously prior to ligation. After thoracotomy, the animals were ventilated with room air and a silk ligature placed under the coronary artery as described by Selye, Bajusz, Grasso & Mendell (1960). Animals were discarded in which this procedure itself produced dysrhythmias or a sustained fall in arterial blood pressure. On ligation, there was a transient decrease in arterial pressure and considerable ventricular ectopic activity for approximately 30 min, including bursts of ventricular tachycardia and fibrillation which reverted spontaneously to sinus rhythm. Table 1 shows the results obtained with the three compounds. Lignocaine and ORG 6001 were effective in reducing the number of ventricular extrasystoles and the incidence and duration of ventricular tachycardia and fibrillation. Propranolol was rather less effective than ORG 6001 in reducing the number of extrasystoles but, like the aminosteroid, prevented ventricular fibrillation.

We conclude from these results that this model is a valuable one to use in the screening of drugs for possible antidysrhythmic activity.

The advantages of such a small animal model are its simplicity, inexpensiveness and the greater speed with which compounds can be examined, compared with similar but larger animal models.

References

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Table 1. Total number of ventricular extrasystoles, together with the incidence and duration of ventricular tachycardia (VT) and ventricular fibrillation (VF), in the first 30 min following coronary artery ligation in anaesthetized rats

	n	*Ventricular ectopic count*	*Incidence of (VT)*	*Total duration of (VT (s))*	*Incidence of (VF)*	*Total duration of (VF (s))*
Controls	26	1155 ± 137	26/26	67 ± 12	16/26	62 ± 16
ORG 6001 (5 mg/kg)	6	315 ± 116*	4/6	25 ± 8	3/6	34 ± 26
ORG 6001 (10 mg/kg)	7	230 ± 106*	5/7	10 ± 4	0/7	0
Lignocaine (10 mg/kg + 2.5 mg/kg^{-1} h^{-1})	6	432 ± 124**	3/6	6 ± 1	1/6	65
Lignocaine (10 mg/kg + 5 mg/kg^{-1}h^{-1})	7	548 ± 191**	4/7	13 ± 5	1/7	11
Propranolol (2 mg/kg)	5	894 ± 227 (4) 4230 (1)	4/4 1/1	50 ± 17 365	2/4 1/1	4 ± 3 17
Propranolol (5 mg/kg)	6	679 ± 212	6/6	43 ± 22	0/6	0

* $P < 0.01$, ** $P < 0.02$.

Values expressed as mean ± s.e. mean for *n* animals. ORG 6001 and propranolol were given intravenously 15 min pre-ligation. Lignocaine was given as a single intravenous bolus injection followed by a continuous infusion, commencing 5 min pre-ligation.

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Ranitidine (AH 19065): a new potent, selective histamine H_2-receptor antagonist

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Until now, an imidazole or an equivalent heterocyclic moiety has been thought to be an important feature in potent H_2-antagonists (Ganellin, Durant & Emmett, 1976). The purpose of this communication is to describe an H_2-antagonist which lacks this feature and whose exceptional potency may result in clinical advantage. The substance is N-{2-[[[5-(dimethylaminomethyl)-2-furanyl]methyl]-thio]ethyl}-N'-methyl-2-nitro-1,1-ethenediamine (AH 19065).

The H_2-antagonist activity of AH 19065 was determined using the guinea-pig isolated right atrium preparation suspended in Krebs solution at 32°C and gassed with 95% O_2:5% CO_2. Cumulative dose-response curves for histamine-induced increases in atrial rate were determined before and in the presence of AH 19065 (3.2×10^{-7} M – 3.2×10^{-6} M) or cimetidine (1.2×10^{-6} M – 1.2×10^{-5} M). Each drug concentration was tested on at least 6 preparations. Both drugs were competitive antagonists as shown by the dose-related, parallel displacements of the histamine dose-response curves and by the slope of the regression of log (DR-1) against log drug concentration. The slope for AH 19065 was 0.99 (95% confidence limits 0.83 – 1.16) and for cimetidine was 1.05 (0.80 – 1.29), both values being not significantly different from unity. The pA_2 values for AH 19065 and cimetidine were 7.20 (7.01 – 7.45) and 6.55 (6.32 – 6.91) respectively. AH 19065 is therefore about 4 times more active than cimetidine in this test.

The H_2-antagonism of AH 19065 on the guinea-pig atrium is a selective effect because concentrations up to 0.96×10^{-4} M had no effect on β-adrenoceptor-mediated chronotropic responses to isoprenaline. On the guinea-pig isolated ileum preparation AH 19065, at concentrations up to 3.2×10^{-4} m, did not antagonise the actions of histamine or bethanechol, indicating that AH 19065 is devoid of significant H_1-antagonist or anticholinergic activity.

AH 19065 and cimetidine were compared as inhibitors of gastric acid secretion in the rat and dog. In the perfused stomach preparation of the anaesthetized rat (Parsons, 1969) AH 19065 (0.03 – 1.0 mg/kg i.v.) and cimetidine (0.3 – 3.0 mg/kg i.v.) produced dose-related inhibitions of histamine-induced secretion. AH 19065 was about 5 times more potent than cimetidine, the antisecretory ED_{50} values being 0.13 (0.08 – 0.22) mg/kg and 0.73 (0.45 – 1.06) mg/kg respectively.

When tested against histamine-induced secretion in 5 conscious dogs with Heidenhain pouches AH 19065 (0.03 – 0.30 mg/kg i.v.; 0.1 – 1.0 mg/kg orally) and cimetidine (0.1 – 1.0 mg/kg i.v.; 0.3 – 3.0 mg/kg orally) caused dose-related inhibitions of secretion. The onset and duration of action of the two drugs were similar but AH 19065 was about 4 times more active than cimetidine, the oral ED_{50} values being 0.23 (0.17 – 0.29) and 0.96 (0.80 – 1.15) mg/kg respectively.

Ranitidine (AH 19065) is a selective H_2-antagonist *in vitro* and a potent, orally active inhibitor of histamine-induced gastric acid secretion *in vivo*.

References

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