Table 1 Effect of clonidine on preganglionic splanchnic nerve activity, blood pressure and heart rate in the cat

	Cumulative dose of clonidine (μg/kg)	*Sympathetic nerve activity (counts/min)*	*Blood pressure (mmHg)*	*Heart rate (beats/min)*
Before drug	–	2470 ± 98	123 ± 7	196 ± 8
After drug	2.5	1600 ± 120	112 ± 7	174 ± 9
	5	722 ± 89	113 ± 4	158 ± 6
	10	234 ± 71	121 ± 7	155 ± 6

Each value is the mean ±s.e. of 10 consecutive readings.

determined threshold. Throughout each experiment, nerve activity was counted for a period of 1 min every 3 min and heart rate and blood pressure noted during each measuring period.

Experiments commenced with a control period during which nerve activity was recorded until 10 similar readings had been obtained. Control experiments in five cats showed that there was no decline in sympathetic activity for at least 2 h after stable control readings had been obtained.

The effects of clonidine on sympathetic nerve activity, heart rate and blood pressure were tested in five cats at doses of 2.5, 2.5 and 5 μg/kg i.v., given at 30 min intervals. Each dose was infused at 0.5 (μg/kg)/min to avoid marked pressor effects. Since the effects of clonidine at 2.5 μg/kg were known to persist for more than 90 min, the results were expressed as the responses to the cumulative dose administered.

Clonidine induced dose-dependent bradycardia but had little effect on blood pressure. Sympathetic nerve activity was reduced by 35.4, 70.8 and 90.5% in response to cumulative doses of 2.5, 5 and 10 μg/kg of clonidine respectively. The cumulative dose of clonidine necessary to produce 50% inhibition of spontaneous sympathetic activity was calculated to be 3.4 μg/kg i.v.

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Antagonism by ICI 66082 of the effects of electrical stimulation on the right ansa subclavia of the dog

J.D. HARRY, M.F. KNAPP* & R.J. LINDEN

Cardiovascular Unit, University of Leeds LS2 9JT

It has been reported previously that the effects on the heart of sympathetic nerve stimulation cannot be antagonized completely by β-adrenoreceptor blocking drugs in doses which do not produce any direct depressant effect on the heart (e.g. for propranolol see Donald, Ferguson & Milburn, 1968). ICI 66082 (4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide) is a new β-adrenoreceptor blocking drug with no other action on the heart in doses up to 20 mg/kg (Harry, Knapp & Linden, 1973). In this investigation an attempt was made completely to block the effects of sympathetic nerve stimulation by using high doses of ICI 66082.

Dogs were anaesthetized with chloralose, artificially respired and the chest opened in the mid-line. Both ansae subclaviae were clamped for 5 min and then stimulating electrodes were placed on the cardiac end of the right ansa subclavia. The vagus nerves were sectioned in the neck. The right ansa subclavia was stimulated with supramaximal pulses (15 volts; 5 ms) at two frequencies, one (0.5-3 Hz) which produced increases in heart rate ranging from 36-66 beats/min, and the other (7-15 Hz) which produced maximal increases in heart rate ranging from 110-160 beats/minute. In each experiment the effects of the two rates of stimulation were recorded before ICI 66082 was given and in the presence of increasing doses of ICI 66082, given intravenously. The results of these experiments are summarized in Table 1.

The results demonstrate that the effects of stimulation of the right ansa subclavia at the lower frequency (0.5-3 Hz) could be completely antagonized by ICI 66082 but that it was not always possible completely to block the effects of stimulation at the frequency of 7-15 Hz, at which the maximal response had been obtained. Maximum

Table 1 Effects of ICI 66082 on the responses to stimulation of the right ansa subclavia of the dog

Cumulative dose of ICI 66082 (mg/kg)	*No. of experiments*	*Reduction in response of increase in heart rate to stimulation at:*	
		0.5-3 Hz	*7-15 Hz*
		% Reduction compared to control	*% Reduction compared to control*
0.5	10	98 ± 0.6	72 ± 9.9
1.0	7	97 ± 0.8	80 ± 7.9
2.0	5	99 ± 0.7	89 ± 2.2
5.0	14	99 ± 0.4	92 ± 3.1
10.0	8	99 ± 0.4	93 ± 2.5

The results are the reduction (mean: ±s.e. mean) in response of an increase in heart rate to stimulation after giving ICI 66082, expressed as a percentage of the response before ICI 66082.

blocking effect, which was sometimes not complete, was achieved with 2.0 mg/kg ICI 66082.

It is concluded that it is not always possible to achieve complete blockade of the effects of maximal stimulation of sympathetic nerves to the heart even with very high doses of ICI 66082.

M.F. Knapp is an ICI Research Fellow.

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2-2′ Pyridylisatogen tosylate: an antagonist of the inhibitory effects of ATP on smooth muscle

M. HOOPER, M. SPEDDING*, A.J. SWEETMAN & D.F. WEETMAN

School of Pharmacy, Sunderland Polytechnic, Sunderland SR1 3SD

Taenia caeci preparations were obtained from female guinea-pigs in the weight range 250-600 g. The preparations were arranged in 10 ml isolated organ baths filled with McEwen's solution maintained at 35 ± 1°C and oxygenated with 95% O_2 : 5% CO_2. After an equilibration period of 30 min, drug-induced relaxations were recorded on a smoked drum using an isotonic frontal-writing

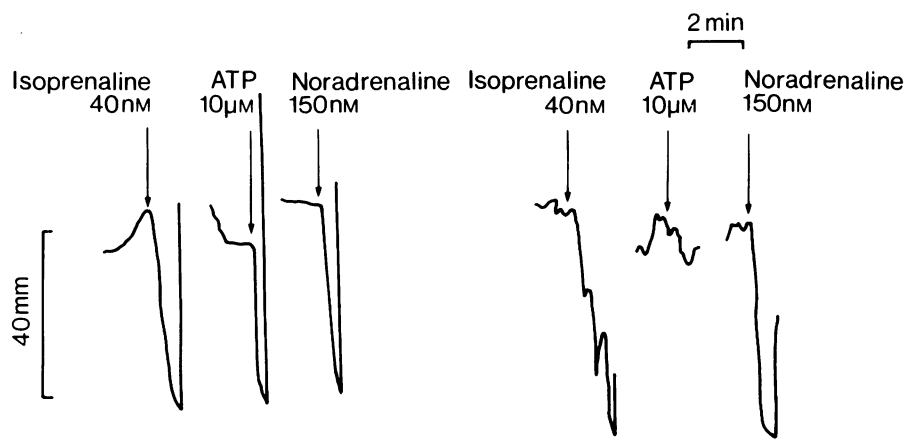

Fig. 1 Blockade of the ATP-induced relaxation of the taenia caeci by 2-2′pyridylisatogen. The drugs were administered on a 5 min cycle. Between panels (a) and (b) the preparation was exposed to 2-2′pyridylisatogen (50 μM for 25 min) which relaxed the tissue: the tone was restored with histamine (70 nM).