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Cardiovascular studies with impromidine (SK&F 92676), a new very potent and specific histamine H_2-receptor agonist

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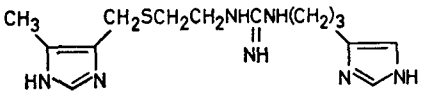
Impromidine (SK & F 92676) has recently been identified as a potent and specific histamine H_2-receptor agonist. The present paper describes some cardiovascular studies with the drug. Impromidine lowers blood pressure in cats and rats by interaction with H_2-receptors. During continuous intravenous infusions of impromidine, the fall in blood pressure is due to a reduction in total peripheral resistance; cardiac output increases during hypotension. The responses to impromidine are similar to responses to histamine in mepyramine-treated cats. Impromidine administered intra-arterially also causes vasodilatation in the femoral and mesenteric vasculature by interaction with H_2-receptors. Impromidine stimulates all measured parameters including coronary flow in the isolated working heart of the guinea-pig. Dose-response curves to impromidine were displaced to the right in the presence of cimetidine.

Selective agonists and antagonists have been described for both histamine H_1- and H_2-receptors. Recently, a new potent and specific histamine H_2-receptor agonist, impromidine (I : SK&F 92676) has been described (Durant et al 1978). Impromidine is a potent gastric acid secretagogue in animals and causes maximal secretion at doses which have little effect on the cardiovascular system (Durant et al 1978) suggesting that the compound may be useful as a diagnostic agent in man for the estimation of maximal secretory capacity of the stomach in patients with gastrointestinal disease. Preliminary studies in man have been reported (Hunt et al 1978).

In addition to their activity as gastric acid secretagogues previously described, histamine H_2-receptor agonists, 4-methylhistamine and dimaprit also produce cardiovascular responses (Owen 1975; Flynn & Owen 1975; Flynn et al 1977) although the



Scheme 1. *N*-[3-(imidazol-4-yl)propyl]-*N'*-(2-[(5-methylimidazol-4-yl)methylthio]ethyl)guanidine.

doses required to elicit these responses usually exceed the doses required to stimulate acid secretion. Impromidine also produces cardiovascular responses which are described in the present paper.

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METHODS

Cats of either sex, 2·3–3·3 kg, were starved overnight but allowed free access to water. The animals were anaesthetized by an intraperitoneal injection of sodium pentobarbitone, 60 mg kg^{-1}. Supplementary doses of sodium pentobarbitone were given intravenously as required. The trachea was cannulated.

Studies on the depressor activity of impromidine in cats

Blood pressure was measured from a catheter tied into one carotid artery. Impromidine, histamine and histamine antagonists were administered via catheters tied into both brachial veins.

Haemodynamic studies in cats

Blood pressure was measured from one femoral artery and cannulae were tied into the opposite femoral vein and one brachial vein for the administration of drugs. Cardiac output was measured using an electromagnetic flow probe (Statham) fixed around the ascending aorta and measuring left ventricular output minus coronary blood flow. The ascending aorta was approached via the appropriate intercostal space having established its likely position by palpating the thorax to determine the position of the heart. The cat was maintained by artificial respiration from the time when the thorax was opened. Heart rate was recorded using a rate-meter driven by the blood pressure pulse signal. Impromidine was administered by intravenous infus-

ions over a range of doses. Each infusion was of 5 min with an interval between infusions whilst all measured parameters recovered.

Vasodilator studies with impromidine in cats

The vasodilator activity of impromidine was established in the acutely denervated vasculature of the hind-limb (femoral vascular bed) and the superior mesenteric vasculature using the technique as described by Flynn & Owen (1975).

Cardiovascular studies in rats

Experiments were made in male rats, 250 g, anaesthetized by intraperitoneal injection of sodium pentobarbitone 60 mg kg^{-1}. The trachea was cannulated. Blood pressure was measured from one carotid artery. Impromidine was administered via a catheter tied into one jugular vein.

Isolated working heart of the guinea-pig

The preparation was set up as described by Flynn et al 1977. Full dose-response curves to impromidine and histamine were obtained in separate preparations. In further experiments, parallel line assays using paired data were carried out in order to compare the potencies of impromidine with histamine on all parameters. Similarly, parallel line assays were carried out in the same experiments in order to obtain dose ratios for impromidine in the presence of cimetidine, compared with control.

Statistics

Comparison of potency of impromidine with histamine and displacement of impromidine dose-response curves by cimetidine were calculated using an analysis of variance.

Drugs

Impromidine was used as the trihydrochloride and solutions prepared in saline.

RESULTS

Depressor activity of impromidine

Impromidine caused dose-dependent falls in blood pressure over the dose range 1×10^{-10} to 1×10^{-8} mol kg^{-1}. In other studies, histamine has been shown to elicit similar depressor responses over the dose range 1×10^{-10} to 1×10^{-7} mol kg^{-1} (e.g. Black et al 1975).

Depressor responses to impromidine were antagonized by intravenous infusions of cimetidine, 4×10^{-7} and 2×10^{-6} mol kg^{-1} min^{-1} (see Fig. 1). The antagonism by cimetidine was dose-dependent with

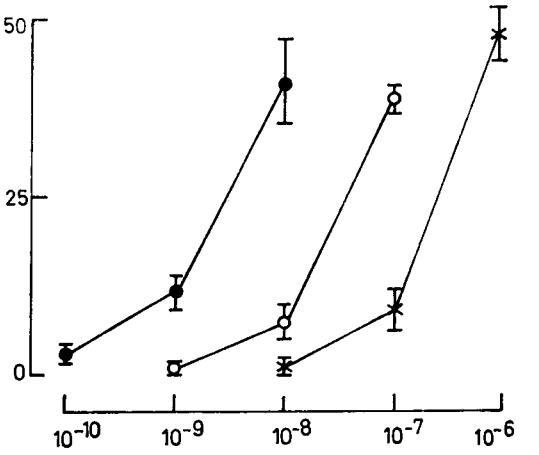

FIG. 1. Anaesthetized cat blood pressure. Displacement of the depressor dose-response curve for impromidine by treatment with cimetidine. Dose (abscissa: mol kg^{-1} i.v.) response curve before cimetidine (●—●) during infusion of cimetidine, 4×10^{-7} mol kg^{-1} min^{-1} (○—○), and 2×10^{-6} mol kg^{-1} min^{-1} (x—x). Means from 4 cats. Ordinate: depressor response (mm Hg).

dose ratios of 7·08 (3·70–13·56, 95% confidence limits) at 4×10^{-7} mol kg^{-1} min^{-1} and 44·82 (23·27–86·34, 95% confidence limits) at 2×10^{-6} mol kg^{-1} min^{-1} cimetidine. Treatment with either mepyramine, 1 mg kg^{-1}, or chlorpheniramine, 1 mg kg^{-1}, had no effect on the depressor responses to impromidine whether given in otherwise untreated cats or in cats after a large displacement of the dose-response curve during infusions of cimetidine, 2×10^{-6} mol kg^{-1} min^{-1} (Fig. 2).

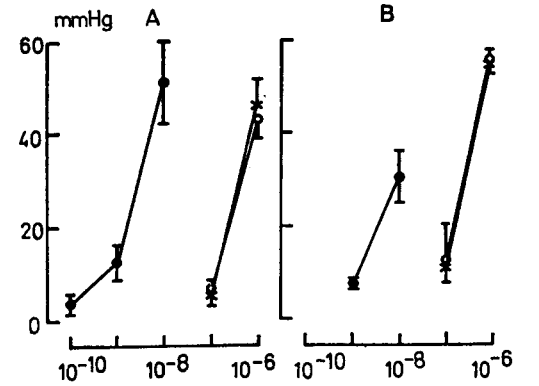

FIG. 2. Anaesthetized cat blood pressure. Failure of either mepyramine, or chlorpheniramine, to antagonize depressor responses (ordinate) to impromidine. Responses to impromidine before treatments (●—●), during infusion of cimetidine, 2×10^{-6} mol kg^{-1} min^{-1} (○—○), and cimetidine plus mepyramine, 1 mg kg^{-1} (Panel A) or cimetidine plus chlorpheniramine, 1 mg kg^{-1} (Panel B) (x—x). Means from 4 cats in each group. Abscissa: mol kg^{-1} i.v.

To compare the relative potency of impromidine and histamine as histamine H_2-receptor agonists in the cardiovascular system, a 2 × 2 assay was made in three cats pretreated with mepyramine (to block the histamine H_1-receptor activity of histamine). The dose response curves for both impromidine and histamine were parallel and the potency of SK&F 92676 was 5·82 (2·04–15·02) times that of histamine.

Haemodynamic studies

Intravenous infusions of impromidine to cats caused marked haemodynamic changes when administered over the dose range $3{\cdot}16 \times 10^{-10}$ to 1×10^{-8} mol kg^{-1} min^{-1}; full-dose response curves are shown in Fig. 3. Impromidine caused slow, well sustained and blood flow. Heart rate increased in 4 cats out of 6 and small increases in stroke volume usually occurred. The maximum changes in heart rate and stroke volume were not very large. The responses to infusions of impromidine were antagonized by cimetidine 2×10^{-6} mol kg^{-1} min^{-1}. Cimetidine caused displacement of the impromidine dose-response curve (Fig. 3) with dose ratios of 83·3 (55·6–125, 95% confidence limits) for the fall in blood pressure, 90·9 (50–200, 95% confidence limits) for the increase in aortic blood flow and 100 (71·4–142·9 95% confidence limits) for the fall in total peripheral resistance. The changes in heart rate and stroke volume caused by impromidine were smaller and more variable and dose-ratios have not been calculated.

The haemodynamic response to impromidine closely resembles that to histamine in mepyramine-treated cats. Impromidine is more potent than histamine under the conditions of these experiments. Precise calculations of their relative potency has not been made as the two agonists were given to different groups of cats but the dose-response curves for blood pressure, total peripheral resistance and aortic blood flow indicate that impromidine is approximately 30 times more potent than histamine (the histamine cats had been pretreated with dose-dependent decreases in blood pressure and total peripheral resistance and increases in aortic mepyramine to permit comparison of the H_2-receptor agonist activity of the two compounds).

Vasodilator studies

The above results indicated that impromidine caused a general decrease in peripheral vascular resistance when given systemically. Local intra-arterial injections of impromidine also caused vasodilatation in the acutely denervated femoral and superior mesenteric vasculatures. In both vascular beds the threshold dose for vasodilatation was approximately 1×10^{-10} mol kg^{-1} and dose-dependent responses could be measured up to $2{\cdot}5 \times 10^{-9}$ mol kg^{-1} in the femoral vasculature and 3×10^{-9} mol kg^{-1} in the superior mesenteric bed. The responses to impromidine in both vascular beds were slower in onset and of substantially greater duration than responses to histamine or dimaprit. In both vascular beds, the vasodilator responses to impromidine were antagonized by cimetidine 2×10^{-6} mol kg^{-1} min^{-1} (Fig. 4).

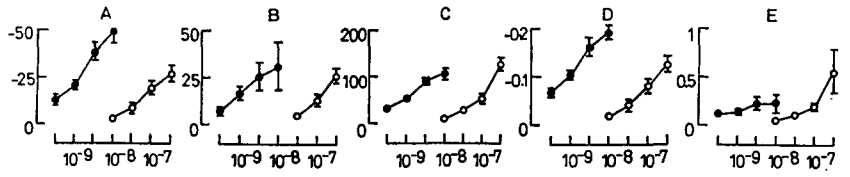

FIG. 3. Haemodynamic responses to impromidine in anaesthetized cats. Control dose-response curve to impromidine in untreated cats (●—●) and antagonism of impromidine responses by cimetidine, 2×10^{-6} mol kg^{-1} min^{-1} (○—○). Means from 6 animals. Ordinates: A, blood pressure (mm Hg); B, heart rate (beats min^{-1}); C, aortic blood flow (ml min^{-1}); D; T.P.R. (units); E, stroke volume (ml). Abscissa: infusion rate (mol kg^{-1} min^{-1}).

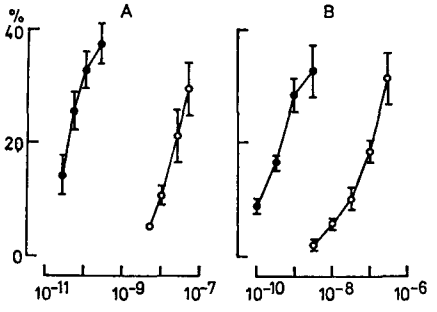

FIG. 4. Vasodilatation in cat femoral and mesenteric vasculature. Vasodilator responses to intra-arterial impromidine in the acutely denervated femoral vasculature (Panel A) and the acutely denervated mesenteric vasculature (Panel B). Responses in untreated cats (●—●) and during infusion of cimetidine, 2×10^{-6} mol kg^{-1} min^{-1} (○—○). Means from 4 cats per group. Ordinate: reduction in perfusion pressure (%). Abscissa: mol kg^{-1} i.v.

Depressor responses in rats

Intravenous infusions of impromidine caused dose-dependent falls in blood pressure in rats over the dose-range $1{\cdot}5 \times 10^{-9}$ mol kg^{-1} min^{-1} to $1{\cdot}5 \times 10^{-7}$ mol kg^{1} min^{-1}. Treatment with cimetidine, 2×10^{-6} mol kg^{-1} min^{-1}, reduced the fall in blood pressure caused by impromidine. Similarly, bolus injections of impromidine 1×10^{-8} to 1×10^{-6} mol kg^{-1} also lowered blood pressure. Cimetidine displaced this dose-response curve to the right.

Isolated working heart

Impromidine increased all measured parameters of cardiac function over the dose range 1×10^{-10} to $3{\cdot}16 \times 10^{-7}$ mol (Fig. 5). Responses to impromidine were of longer duration than histamine responses of similar magnitude. For dP/dt max, sinus rate and LVP max, an unpaired comparison indicated that the dose-response curves for impromidine were to the left of, were parallel with, and had similar maximum increases to the corresponding histamine dose-response curves. For coronary flow, aortic flow and those parameters calculated for these values (i.e. total cardiac output and external pressure work) the dose-response curves for impromidine lay to the left of the histamine dose-response curves but had significantly lower maxima. The potencies of impromidine relative to histamine on all measured parameters are shown in Table 1. The greater potency of impromidine (i.e. 10–15 times histamine) was similar for contractility, aortic flow, cardiac output and external work but impromidine was more potent to increase sinus rate and coronary flow. Following the administration of impromidine, the time to peak increase in dP/dt max preceeded the time to peak increase in heart rate for doses giving similar maximum responses. Like histamine, the threshold dose of impromidine to increase contractility was less than for rate; the maximum contractility response also occurred after a lower dose than that needed for the maximum rate response.

Cimetidine, $3{\cdot}16 \times 10^{-6}$ M, antagonized responses to impromidine. Dose-ratios measured for all parameters with cimetidine $3{\cdot}16 \times 16^{-6}$ M were similar to the dose-ratios obtained with histamine in the presence of the same concentration of cimetidine (for histamine the whole experiment was made in the presence of mepyramine 1×10^{-7} M). Dose ratios are shown in Table 2.

DISCUSSION

Impromidine is a potent and highly selective histamine H_2-receptor agonist.

The cardiovascular responses to impromidine were largely as might be expected from a histamine H_2-receptor agonist as comparisons with dimaprit (Flynn et al 1977) or histamine in mepyramine-treated animals made clear. The cardiovascular responses to impromidine were antagonized by treatment with cimetidine confirming activity as an H_2-receptor agonist. Thus, impromidine given intravenously, lowered arterial blood pressure and decreased peripheral vascular resistance. It also caused

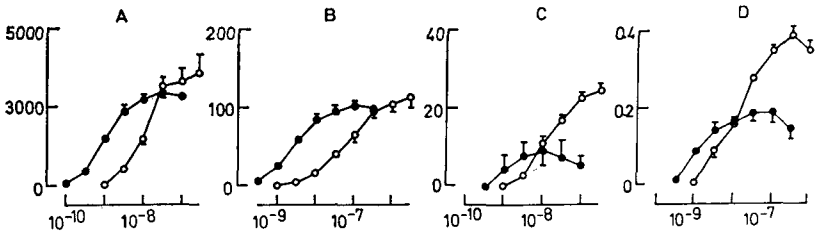

FIG. 5. Isolated working heart. Comparison of responses of the heart to impromidine (●—●) with responses to histamine (○—○). Ordinates: A increase in dP/dt max, mm Hg s^{-1}, B increase in sinus rate, beats min^{-1}, C increase in coronary flow, ml min^{-1} g^{-1}, D increase in external pressure volume work, kg m $min^{-1}g^{-1}$. Abscissa: histamine and impromidine (mol).

Table 1. Potencies of impromidine on measured parameters of guinea-pig cardiac function in vitro, relative to histamine.

Parameter	Potency relative to histamine (=1) with 95% confidence limits
dP/dt max (contractility)	16·2 (11·8–22·1)
Sinus rate	26·5 (19·6–40)
Coronary flow	76 (31–235)
Aortic flow	9·2 (5·2–14·6)
Cardiac output	10 (5·8–15·9)
External pressure volume work	11·7 (8·2–16·1)
L.V.P. max	13·7 (8·4–21·3)

Results were obtained from paired data (n = 3).

Table 2. Cardiac effects of cimetidine $3{\cdot}16 \times 10^{-6}$ M on responses to impromidine compared with effects on histamine (histamine in the presence of mepyramine 10^{-7} M).

	Dose ratio	
	Impromidine	Histamine
dP/dt max (contractility)	7·0 ± 1·1	7·6 ± 1
Sinus rate	5·4 ± 2	8·1 ± 0·5
Coronary flow	9·2 ± 3·4	18·8 ± 3·6
Aortic flow	6·2 ± 1·3	7·8 ± 1·5
Cardiac output	7·1 ± 2·3	8·5 ± 1·4
External pressure volume work	7·8 ± 1·8	9·6 ± 1·1

Results are means ± s.e. mean (n = 3).

vasodilatation when given intravenously, or by close intra-arterial injection to both the femoral and superior mesenteric vasculature. The onset and duration of the local vasodilator responses to impromidine differed somewhat from responses to histamine or dimaprit over the range of doses giving comparable peak responses; onset of response was slower and the duration greater than has been seen with other histamine receptor agonists (Flynn & Owen 1975; Flynn et al 1977).

The haemodynamic studies indicated that for impromidine, like other histamine H_2-receptor agonists, depressor responses are due to peripheral vasodilatation. Thus, although there is some increase in cardiac output, peripheral vasodilatation is sufficient that blood pressure falls. The threshold infusion rate to elicit peripheral vasodilatation was similar to, or slightly less than, the infusion rate to elicit maximal acid secretion (Durant et al 1978). The mechanism of the increased cardiac output in anaesthetized cats caused by histamine and histamine-like agonists is still under investigation and it remains to be determined whether this is a direct effect on the heart or secondary to other effects, e.g. reflexes associated with the depressor responses. Whatever the mechanism, the response to impromidine closely resembled that to dimaprit and to histamine in mepyramine-treated cats. The effects of systemically administered histamine on heart rate in anaesthetized cats are complex and tend to be very variable. Histamine increases heart rate in anaesthetized cats by release of catecholamines from chromaffin tissue, an H_1-receptor mechanism and the cat heart is not very responsive to the direct effects of histamine (Owen 1975; Flynn et al 1979). All the haemodynamic responses to impromidine were antagonized by cimetidine; the dose ratios calculated for the three parameters which responded consistently to impromidine were similar.

The dose-dependent increases in all measured parameters of cardiac function produced by impromidine in the isolated working heart were essentially similar to those produced by histamine, although responses to impromidine were of greater duration than responses to histamine. The positive effects of histamine on the isolated working guinea-pig heart preparation have been shown to be mediated via H_2-receptors (Flynn et al 1979); histamine H_1-receptors mediate a negative inotropic effect (Zavecz & Levi 1978; Flynn et al 1979). The longer duration of action of impromidine on contractility is probably because the positive inotropic response is not opposed by the negative (H_1-receptor) effects associated with histamine administration.

The full dose-response curves for impromidine on contractility and sinus rate were parallel to those for histamine, with similar maximum increases, indicating that impromidine is a full H_2-receptor agonist on these parameters.

The lower maximum effect of impromidine when compared with histamine, on aortic flow (and parameters derived from aortic flow) is probably due to the greater temporal separation of the contractility and rate responses to impromidine. For impromidine and histamine, the increase in the force of contraction precedes the increase in the rate of contraction. This separation is clearer for impromidine than for histamine. In this preparation, increases in aortic flow result from both the increased force of contraction tending to increase stroke volume plus the increased rate of contraction which increases aortic flow without increasing stroke volume (Flynn et al 1979).

Impromidine appeared to be more potent than histamine as an H_2-receptor agonist. Direct comparison of impromidine with histamine as depressor agents (bolus injections in mepyramine-treated cats) showed that impromidine was about 6 times more potent than histamine. When the two agonists were administered in different groups of cats by intravenous infusion, impromidine appeared to be about 30 times as potent as histamine. This difference may reflect different rates of metabolism for impromidine and histamine.

Impromidine also caused a fall in blood pressure in rats. The threshold infusion rate for hypotension was very similar to the infusion rate eliciting maximal gastric acid secretion in rats (Durant et al 1978) and further dose-dependent falls in blood pressure were measured during infusions of large doses.

In conclusion, impromidine has been shown to elicit substantial cardiovascular responses in experimental animals consistent with activity as an H_2-receptor agonist. The responses to impromidine were antagonized by treatment with cimetidine. The threshold dose of impromidine to elicit cardiovascular responses was similar to that which causes maximal secretions of gastric acid (Durant et al 1978).

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