THE CARDIOVASCULAR EFFECTS OF ERGOMETRINE IN THE EXPERIMENTAL ANIMAL IN VIVO AND IN VITRO

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SUMMARY

The cardiovascular effects of ergometrine have been examined using animal models in vivo and in vitro. In rats in vivo the pressor effects of a standard dose of ergometrine were found to be dependent upon the anaesthetic used for the procedure. The pressor action of ergometrine was greater when urethane, an anaesthetic which produces both sympathetic and parasympathetic activity, was used. The in-vitro experiments, using isolated rabbit aorta and portal vein, failed to explain the phenomenon; they suggested that ergometrine has a direct action on the alpha-adrenoceptor in rabbits. No evidence was found to suggest that ergometrine inhibits noradrenaline uptake or its release from the nerve terminals.

Several reports concerning the vascular effects of ergometrine in man have been published.

Cassady, Moore and Bridenbaugh (1960) found that combinations of methoxamine with ergometrine were more likely to result in hypertensive incidents than combinations of methoxamine with other oxytocic drugs. It was observed by Baillie (1963a,b) that hypertensive patients, particularly younger women or those with toxaemia, appeared to have enhanced sensitivity to the pressor actions of ergometrine. More recently, in normotensive patients, ergometrine alone has been shown to reduce venous compliance of the forearm of male volunteers (Brooke and Robinson, 1970) and to constrict the blood vessels of the finger and skeletal muscles of the forearm in pregnant females (Johnstone, 1972).

In view of these reports we have investigated the cardiovascular effects of ergometrine in closer detail using animal models in vivo and in vitro. We were looking particularly for interactions with noradrenaline and with anaesthetics which stimulate or depress autonomic function.

METHODS

Rat arterial pressure.

Female Wistar rats (200–300 g) were anaesthetized with either urethane 1 g/kg or pentobarbitone 40 mg/kg. The left carotid artery was cannulated and arterial pressure was monitored using a pressure transducer connected to a Grass 79G polygraph. A record of heart rate was obtained from a rate meter triggered from the arterial pressure recording.

Drugs, dissolved in 0.2 ml saline, were administered via the jugular vein. Each dose was washed in by a further 0.2 ml of saline.

Rabbit aorta and portal vein.

Male and female rabbits of mixed strain were used. The rabbits were killed by a blow on the head, and the thoracic aorta or the hepatic portal vein removed. Spirally cut strips of either aorta or portal vein were set up at 37 °C in Krebs solution gassed with 5% carbon dioxide in oxygen.

The characteristics of spiral strips of rabbit aorta have been fully described by Furchgott and Bhadrakom (1953). The spirally cut portal vein has been described by Kelly (1971) who found that this preparation had considerably less myogenic activity than the longitudinal strip described by Hughes and Vane (1967).

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Responses of the tissues were measured isotonically using an "Ether" strain gauge connected to a Smiths RE520 potentiometric recorder.

The activity of ergometrine on these two prepara-
tions was compared with noradrenaline, which acts principally on α-adrenoceptors, and tyramine, which acts by releasing noradrenaline from the nerve terminals. Cumulative concentration response relationships were obtained using a 5-min contact time on the aorta and a 2-min contact time on the portal vein.

Cumulative concentration response relationships to the three agents were also obtained on portal vein strips exposed 1×10⁻⁵ M cocaine and on portal vein from rabbits pretreated with reserpine 2 mg/kg for three days.

Interactions with noradrenaline were examined by obtaining concentration response curves to noradrenaline in the presence of various concentrations of ergometrine and vice versa.

Finally, interactions between ergometrine and the α-adrenoceptor blocking agent, phentolamine, were examined and the pA₂ value for phentolamine against ergometrine was obtained by the method of Arunlakshana and Schild (1959). A pA₂ value is a measure of antagonist potency and is defined as the negative logarithm of the concentration of an antagonist which will reduce the response produced by a concentration of agonist 2x to that produced by a concentration x. From theoretical considerations based on the law of mass action, Arunlakshana and Schild (1959) suggested that antagonism could be considered competitive if it fulfilled certain requirements. Firstly, the antagonist should cause a parallel displacement of the log concentration effect curve of the agonist to the right. Secondly, there should be no diminution of the maximum response to the agonist. Finally when log (dose ratio —1) is plotted against the negative log concentration of antagonist a straight line should result with a slope of —1. In these circumstances pA₂ — pA₁₀ = 0.95. The interaction between phentolamine and ergometrine has been examined with these requirements in mind.

Results are expressed as mean values ± SE and significance levels were calculated using the Student t-test.

RESULTS

Rat arterial pressure.

The initial mean arterial pressure in a group of 10 rats anaesthetized with urethane was 80.7 ± 5.1 mm Hg and the heart rate was 264 ± 15 beats/min. Corresponding values in pentobarbitone-anaesthetized rats were 122 ± 4.2 mm Hg and 286 ± 20 beats/min (n=5).

It was possible to obtain a dose-related pressor response to both noradrenaline and vasopressin in rats anaesthetized with both agents. Maximum responses to ergometrine were considerably less than responses obtained with moderate doses of vasopressin and noradrenaline. The maximum response to ergometrine occurred with 160 ng in urethane-anaesthetized rats and 320 ng in the pentobarbitone-anaesthetized rats. In view of this maximum effect of ergometrine it was not possible to obtain meaningful potency ratios between noradrenaline, vasopressin and ergometrine. Thus the effects of standard doses of the three drugs have been compared on the arterial pressure of rats treated with the two anaesthetics. The doses selected were 80 ng noradrenaline, 160 ng ergometrine and 5 mU vasopressin and the results obtained are shown in table I.

Only the effects of ergometrine were significantly different (P<0.001) on the two preparations. Ergometrine was a more potent pressor agent when the rat was anaesthetized with urethane.

No consistent changes in heart rate were seen with any of the pressor agents.

Propranolol 200 μg had no significant effect on the arterial pressure or heart rate of rats anaesthetized with pentobarbitone. However, in rats anaesthetized with urethane, heart rate was reduced by 63 ± 9 beats/min and the arterial pressure increased by 26.9 ± 3.1 mm Hg. Under both anaesthetics the mean arterial pressure response to noradrenaline 40 and 80 ng, ergometrine 80 and 160 ng, and vasopressin 2.5 and 5 mU were slightly enhanced.

Phentolamine 10 mg, had similar effects under both anaesthetics. In urethanized rats phentolamine produced a decrease in the mean arterial pressure of 33 ± 3.9 mm Hg (n=6). After phentolamine, with both anaesthetics, there was no response to doses

**Table I. Comparison of the pressor effects of standard doses of noradrenaline ergometrine and vasopressin in rats anaesthetized with urethane or pentobarbitone. Results are expressed as mean ± SE.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Increase in blood pressure (mm Hg)</th>
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<tbody>
<tr>
<td></td>
<td>Urethane (n=7)</td>
</tr>
<tr>
<td>Noradrenaline bitartrate 80 ng</td>
<td>25.7 ± 2.5</td>
</tr>
<tr>
<td>Ergometrine maleate 160 ng</td>
<td>16.9 ± 2.3</td>
</tr>
<tr>
<td>Vasopressin 5 mU</td>
<td>20.3 ± 3.2</td>
</tr>
</tbody>
</table>

* Significantly different from response in urethane-anaesthetized rats (P<0.001).
of noradrenaline up to 640 ng or to ergometrine from 40 to 2000 ng. The response to vasopressin was only slightly reduced.

In-vitro Studies.

Intrinsic activity.

Log molar concentration response relationships for noradrenaline, ergometrine and tyramine on the rabbit aorta and portal vein preparations are shown in figure 1. Three points are illustrated by this figure. Firstly, although the portal vein preparation is less sensitive to noradrenaline and more sensitive to tyramine than the aorta, both preparations are equally sensitive to ergometrine. Secondly, on the venous preparation, ergometrine is almost equipotent with noradrenaline. Thirdly, the maximum response to ergometrine on the vein and to tyramine on both preparations is considerably less than the maximum response to noradrenaline.

Effects of reserpination and exposure to cocaine.

Similar results were obtained using both the reserpinized portal vein and the vein exposed to a noradrenaline uptake blocking concentration of cocaine (45 min exposure to $1 \times 10^{-5}$M cocaine; Kelly, 1971). The responses to noradrenaline, ergometrine and tyramine obtained using these tissues are shown in figure 2. The control responses to the three agonists obtained in the two series of experiments have been bulked since there was no significant difference between them. However, it should be pointed out that the control responses in the cocaine experiments were obtained on the same preparation as the test responses whereas separate, but concurrently examined, preparations were used for the reserpinized tissue controls.

The reserpinized vein and the cocaine-treated vein are more sensitive to noradrenaline, less sensitive to tyramine, and have the same sensitivity to ergometrine as untreated vein.

Interactions with noradrenaline.

Low concentrations of ergometrine which had no demonstrable agonist action had no effect on the responses of either the aorta or the portal vein to noradrenaline. Higher concentrations of ergometrine gave responses, together with noradrenaline, somewhat less than might be expected if simple summation of effects had occurred. Indeed if the higher concentrations of ergometrine were added to a tissue maximally contracted to noradrenaline, a concentration-dependent inhibition of contraction was seen. This is shown in table II together with the effects of these concentrations of ergometrine on the portal vein preparation maximally contracted to potassium ion. On this preparation it was found that the contractions to potassium were not modified by a concentration of phentolamine which significantly reduced the response to noradrenaline. Although ergometrine did suppress the potassium maximum this was significantly less than the suppression of the noradrenaline maximum.
FIG. 2. Comparison of the responses of the normal, reserpinized and cocaine-exposed rabbit portal vein to noradrenaline, ergometrine and tyramine in vitro. Results are expressed as percentages of noradrenaline maximum responses and are means ±SE.

- normal rabbit portal vein ($n=12$).
- portal vein obtained from rabbits pretreated with reserpine 2 mg/kg daily for 3 days ($n=6$).
- portal vein exposed to $1 \times 10^{-4}$M cocaine for 45 min ($n=6$).

TABLE II. Effects of ergometrine on maximum contractions to noradrenaline and potassium obtained on the rabbit portal vein preparation.

Results are expressed as means ± SE of six experiments.

<table>
<thead>
<tr>
<th>Concentration of ergometrine</th>
<th>Noradrenaline</th>
<th>Potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1.48 \times 10^{-4}$M</td>
<td>3.7 ± 3.5</td>
<td>6.4 ± 3.5</td>
</tr>
<tr>
<td>$2 \times 10^{-4}$M</td>
<td>14.4 ± 3.3</td>
<td>10.8 ± 3.1</td>
</tr>
<tr>
<td>$8 \times 10^{-4}$M</td>
<td>32.8 ± 2.1</td>
<td>18.8 ± 2.4*</td>
</tr>
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</table>

* Significantly different from noradrenaline value ($P<0.001$).

Interactions with phentolamine.

The effects of increasing concentrations of phentolamine on the cumulative concentration response curve to ergometrine obtained on the rabbit portal vein are shown in figure 3. The curve is progressively shifted to the right although there does appear to be some diminution of the maximum response. In a series of seven experiments the mean $pA_2$ value for phentolamine against ergometrine was $8.3 \pm 0.14$. The mean $pA_2-pA_{10}$ value was $0.96 \pm 0.15$. Thus there is some indication that the antagonism of ergometrine by phentolamine may be competitive, although the diminution of the ergometrine maximum response demonstrates that not all of the criteria for competitive antagonism are fulfilled.

FIG. 3. Antagonism of ergometrine by phentolamine on the rabbit portal vein preparation in vitro. The results illustrated are from one experiment.

C, no phentolamine
1, $3.15 \times 10^{-4}$M phentolamine.
2, $6.3 \times 10^{-4}$M phentolamine.
3, $1.26 \times 10^{-3}$M phentolamine.
DISCUSSION

Barrett (1971) showed that the cardiovascular effects of some drugs varied with the anaesthetic used for the procedure. It was concluded that this was the result of the varied effects of the anaesthetics upon autonomic function.

Urethane is an anaesthetic which increases autonomic function and has been shown to release adrenaline from the adrenal medulla (Spriggs, 1965). Pentobarbitone, on the other hand, is believed to depress autonomic function and depress release of adrenaline from the adrenal medulla (Barrett, 1971; Spriggs, 1965).

In our experiments propranolol was shown to depress heart rate and increase arterial pressure in the rat anaesthetized with urethane, but not in the rat anaesthetized with pentobarbitone, thus confirming the findings of Barrett (1971). We have also shown that the rat anaesthetized with urethane is more sensitive to the pressor effects of ergometrine, whereas the sensitivity to noradrenaline and vasopressin is similar to that in pentobarbitone-anaesthetized rats.

Increased sensitivity to ergometrine in conditions of high autonomic tone could account for the clinical observations of Baillie (1963b), who reported that young hypertensive patients were particularly sensitive to the pressor effects of ergometrine.

The pressor effects of ergometrine were not reduced by propranolol, but were completely abolished by phentolamine in a dose which abolished the action of noradrenaline, but not that of vasopressin. Similar results were obtained with both anaesthetics. Thus it seems that the pressor actions of ergometrine are mediated via the alpha-adrenoceptor.

The rabbit aorta preparation and the portal vein preparation differ in that the former has a very sparse adrenergic innervation (Shibata et al., 1971). Kelly (1971) found that the potentiation of noradrenaline by an uptake blocking concentration of cocaine was much less on the aorta than on the portal vein. Thus, when noradrenaline is added extrinsically to the aorta, most of the drug acts directly on the alpha-adrenoceptors, whilst on the portal vein, a more densely innervated tissue, more noradrenaline is taken up into the nerve terminal and less acts directly on the receptors. Similarly tyramine is less active on the aorta because there is less intrinsic noradrenaline in the tissue for it to release. The fact that ergometrine has a similar potency on both preparations suggests, firstly, that it is not exclusively taken up into noradrenergic nerves, and secondly, that it does not act exclusively by releasing noradrenaline. There was no reduction in sensitivity to ergometrine in tissues which had been depleted of noradrenaline by reserpine or in tissues where uptake into noradrenergic neurone had been inhibited by cocaine.

One further point about the results obtained with reserpinized preparations requires comment. The noradrenaline sensitivity of the reserpinized rabbit portal vein was increased, but the sensitivity to ergometrine was not increased. It has been demonstrated that the supersensitivity which occurs in reserpinized tissues involves a number of agonists which suggests that it is non-specific in nature (Trendelenburg and Weiner, 1962). However, Hudgins and Fleming (1966) have demonstrated that reserpinization may lead to a partial non-specific supersensitivity on some preparations. They demonstrated, on the reserpinized rabbit aorta, that sensitivity to noradrenaline, acetylcholine and potassium ion was increased, but sensitivity to histamine, 5-hydroxytryptamine and angiotensin was unchanged. Nevertheless our observation that supersensitivity occurs to noradrenaline, which acts on alpha-receptors, and not to ergometrine, which also appears to act on alpha-receptors, is interesting and requires further study.

It has been suggested that some ergot alkaloids might inhibit uptake of noradrenaline (Pacha and Salzmann, 1970). Our experiments with noradrenaline and ergometrine in vitro produced no evidence that ergometrine might prevent re-uptake of noradrenaline. Potentiation of noradrenaline was not seen with any concentration of ergometrine. Very high concentrations of ergometrine had some antagonist action and since this action was more effective against noradrenaline than potassium, ergometrine may have some alpha-blocking actions in addition to non-specific depressant actions at these concentrations. This would explain the maximum response to ergometrine being lower than that produced by noradrenaline and the slight diminution of maximum response to ergometrine seen in the phentolamine experiments.

The in-vivo experiments suggested that the pressor response to ergometrine was mediated via the alpha-adrenoceptor. The pA₂ value for phentolamine against ergometrine on the portal vein in vitro was 8.3 ± 0.14. This indicates that ergometrine is a fairly
specific alpha agonist since the pA for phentolamine against noradrenaline on this tissue was found to be 8.15 ± 0.07 (Kelly, 1971).

In summary our results have shown that the vasoconstrictor effects of ergometrine are mediated by a direct action on alpha-adrenoceptors. In vivo, preparations with high autonomic function appear to be particularly sensitive to ergometrine. However the experiments in vitro have failed to determine the mechanism for this action, although they have shown that uptake blocking actions, or release of noradrenaline from nerve terminals are unlikely to be important factors.

Although direct comparisons between the animal and human situation are unwise, our results support the views of Brooke and Robinson (1970) and Johnstone (1972) that ergometrine is a more potent pressor agent than is commonly thought and that there are particular dangers to its use in patients with high autonomic tone.

REFERENCES


