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Investigation into the cardioregulatory properties of the α_1-adrenoceptor blocker indoramin

Vanessa Pierce[1], N.B. Shepperson, M.H. Todd[2] & J.F. Waterfall[3]

Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire, SL6 0PH

1 The cardioregulatory properties of the α_1-adrenoceptor blocker indoramin have been compared with those of prazosin in the anaesthetized rat. The effects of autonomic blockade on heart rate responses evoked by these two agents and their effects on blood pressure and heart rate after peripheral or central administration have been compared.

2 Cumulative administration of indoramin (0.8–25.6 mg kg^{-1} i.v.) evoked significant decreases in arterial blood pressure and a concomitant bradycardia. Pithing or autonomic blockade, by pretreatment with a combination of practolol and bilateral vagotomy, prevented the bradycardia evoked by indoramin (0.8–3.2 mg kg^{-1} i.v.). Atropine sulphate pretreatment abolished the bradycardia until a cumulative dose of 25.6 mg kg^{-1} (i.v.) of indoramin had been reached. Bilateral vagotomy, intravenous administration of atropine methylnitrate or practolol pretreatment attenuated the bradycardia.

3 Prazosin (0.02–0.64 mg kg^{-1} i.v.) evoked a fall in arterial blood pressure of similar magnitude to that observed following indoramin. A bradycardia was evoked only at a relatively high dose (0.64 mg kg^{-1} i.v.).

4 Intracisternal injection of indoramin or prazosin evoked bradycardia and hypotension at a dose which had no effect after intravenous injection (25 μg). Intracerebroventricular injection of indoramin (25 μg) had no significant effect on heart rate or blood pressure compared to control values, whereas prazosin (25 μg) evoked a significant tachycardia and hypotension.

5 It is concluded that the bradycardia evoked by indoramin in the rat is not due to a direct action on the heart except possibly at high doses. Central α_1-adrenoceptor blockade, possibly in the brainstem region, results in a bradycardia and this may explain the lack of reflex tachycardia following the administration of indoramin.

Introduction

Lowering blood pressure by the administration of vasodilators frequently evokes a reflex increase in heart rate (DuCharme & Zins, 1980; Kreye, 1980; Taylor, 1980). In contrast to the non-selective α-adrenoceptor blockers phentolamine and phenoxybenzamine, the vasodilatation evoked by the selective α_1-adrenoceptor blocker indoramin is not accompanied by a tachycardia in either animals or man (Baum *et al.*, 1973; Carballo *et al.*, 1974; Antani *et al.*, 1983).

It has been suggested that the lack of tachycardia following the administration of indoramin may be attributed to a direct action on cardiac muscle as the result of membrane stabilizing properties (Algate *et al.*, 1981; Nichols *et al.*, 1983). This hypothesis is based upon a number of experimental findings. For example, indoramin has been found to cause a concentration-related ($10^{-6} - 2 \times 10^{-5}$ M) reduction in the force and rate of contraction of the rabbit isolated heart (Alps *et al.*, 1970). In addition indoramin was shown to have membrane stabilizing properties in the guinea-pig weal test (Alps *et al.*, 1971).

Algate *et al.* (1981) have shown that indoramin (0.8–25.6 mg kg^{-1} i.v.) evokes a bradycardia in anaesthetized and anaesthetized/pithed rats. These authors also demonstrated that, in the pithed rat, indoramin and the local anaesthetic agents lignocaine and procaine reduced the positive chronotropic responses evoked by electrical stimulation, whereas other α-adrenoceptor blockers had no effect.

More recently the lack of tachycardia following the

[1] To whom all correspondence should be addressed at Wyeth Laboratories. [2] Present address: I.C.I. Pharmaceuticals division, Bioscience 2, Alderley Park, Macclesfield, Cheshire, SK10 4TJ. [3] Present address: Roche Products Ltd. P.O. Box 8, Welwyn Garden City, Herts, AL7 3AY.

administration of indoramin has been investigated in the anaesthetized dog (Harron *et al.*, 1984a). It was concluded that the absence of tachycardia does not result from a myocardial membrane-stabilizing action of indoramin or from alterations in sympathetic and parasympathetic activity. Harron *et al.* (1984b) have demonstrated that indoramin (6 mg kg^{-1} i.v.) exerts Class III anti-arrhythmic activity in the anaesthetized cat, and suggest that this property is responsible for the induction of bradycardia by this drug.

However, other experiments in anaesthetized cats, have shown that, following the administration of indoramin or prazosin, sympathetic nerve activity is reduced with a concomitant decrease in blood pressure and heart rate (Baum & Shropshire, 1975; McCall & Humphrey, 1981; Ramage, 1984). These results suggest that indoramin and prazosin have centrally mediated properties which could explain why a tachycardia does not accompany their hypotensive effects.

We have now investigated the cardioregulatory action of the selective α_1-adrenoceptor blocker indoramin in the anaesthetized rat and compared its effects with those of prazosin. In addition, the effects of indoramin and prazosin on blood pressure and heart rate have been compared following central administration, in order to determine whether a peripheral or central site of action is involved.

Methods

Female Sprague-Dawley rats (230–270 g) were anaesthetized with a combination of α-chloralose (80 mg kg^{-1} i.p.) and pentobarbitone sodium (6 mg kg^{-1} i.p.). The trachea was intubated and the rat allowed to breathe room air. Blood pressure was monitored via a cannula introduced into the left femoral artery and recorded using a Statham p231D pressure transducer connected to a Grass 7D Polygraph. Heart rate was derived from the pulse pressure signal using a Grass 7P4 model tachograph. Drugs were administered peripherally via a cannula into the left femoral vein. Rectal temperature was monitored and maintained (37 ± 0.5°C) using a thermostatically controlled heating blanket.

The preparations were allowed to stabilize for at least 15 min before experimental procedures were carried out.

The effects of α_1-adrenoceptor blockers on heart rate before and after autonomic effector blockade

Groups of 5 rats were anaesthetized as described above and cumulative doses of indoramin (0.8–25.6 mg kg^{-1} i.v.), prazosin (0.02–0.64 mg kg^{-1} i.v.) or vehicle (1 ml kg^{-1} i.v.) were administered at 15 min intervals. In a further series of experiments separate groups of rats were prepared using one of the following treatments: (a) pithing with a stainless steel rod (artificially ventilated with room air, 60 strokes min^{-1}, 1 ml 100 g^{-1}); (b) bilateral vagotomy; (c) atropine sulphate (1 mg kg^{-1} i.v.); (d) atropine methylnitrate (1 mg kg^{-1} i.v.); (e) practolol (3 mg kg^{-1} i.v.); or (f) practolol (3 mg kg^{-1} i.v.) in addition to bilateral vagotomy. The animals were given their treatments 15 min before the administration of indoramin (0.8–25.6 mg kg^{-1}) or vehicle (distilled water and a further dilution of 1 part distilled water added to 9 parts saline).

The effects of peripheral versus central administration of α_1-adrenoceptor blockers on heart rate and blood pressure

Groups of four rats were anaesthetized as described above. Drugs were administered by intravenous injection (i.v.) via the left femoral vein or centrally by injection into the lateral cerebral ventricles (i.c.v.) or the cisterna magna (i.c.). For i.c.v. injection the skull was exposed by a midline incision and the periosteum scraped away. A hole was drilled in the skull 1 mm lateral and 1 mm posterior to the bregma. Drugs were administered at a depth of 4 mm from the surface of the skull. The injection site was verified by post mortem examination of the location of staining following the administration of 10 µl of ink. For i.c. injection the head was flexed and the skin incised in the neck region to expose the external occipital protuberance. The atlanto-occipital membrane was located and drugs were injected into the cisterna magna using a 25 g needle.

Preliminary experiments were carried out to determine the largest dose of indoramin that could be administered intravenously without significantly affecting blood pressure or heart rate. This dose was found to be 25 µg. A dose of 25 µg of either indoramin or prazosin was then administered centrally (i.c.v. or i.c.) in a volume of 10 µl. Distilled water was administered centrally (10 µl) or peripherally (1 ml kg^{-1}) as a vehicle control. Blood pressure and heart rate readings were taken immediately before the administration of drug and at 15, 30 and 45 min after injection.

Analysis of data

All statistical comparisons were made using the raw data. Values were compared within groups using a 2 way analysis of variance. Analysis between groups, for example the effects of indoramin alone compared to its effects following various pretreatments, was carried out using a nested analysis of variance. A t ratio was then derived from the analysis. A value of $P < 0.05$ was taken to be significant. If a statistically significant

change in the data was noted following vehicle administration during the control experiments, drug-treated groups were then compared with the vehicle group using a nested analysis of variance.

Drugs and solutions

The following drugs were used: indoramin hydrochloride (Wyeth); prazosin hydrochloride (Pfizer); atropine sulphate (Sigma); atropine methylnitrate (Sigma); and practolol, supplied as the base, (I.C.I.). Indoramin and prazosin were dissolved in distilled water and then diluted in 0.9% w/v NaCl solution (saline) (1 part distilled water added to 9 parts of saline). All other drugs were dissolved in saline.

Results

The effects of α_1-adrenoceptor blockers on blood pressure

Doses of indoramin within the range 0.8–25.6 mg kg^{-1} (i.v.) were used in this study as they have previously been shown to evoke significant falls in blood pressure (Algate *et al.*, 1981). Our data confirmed this finding (Figure 1a). Doses of prazosin which evoked a similar hypotensive response to indoramin were then chosen (Figure 1a).

The effect of indoramin on heart rate

In control experiments the administration of vehicle had no significant effect on heart rate except following pithing where heart rate rose significantly ($P < 0.05$) during the latter half of the experiment. None of the pretreatments had a statistically significant effect on heart rate before the administration of indoramin or vehicle with the exception of one group. This group received vehicle following a combination of practolol and bilateral vagotomy; and there was a significant ($P < 0.01$) increase in heart rate compared to the predose value of the group receiving indoramin alone.

Practolol was used to provide β-adrenoceptor blockade in this study because, as a result of its intrinsic sympathomimetic activity (Vickers, 1980), it had no significant net effect on heart rate, the loss of neurogenic stimulation being balanced by the agonist action of practolol. This was considered desirable since a reduction in heart rate *per se*, such as that observed following propranolol in this model (unpublished observation), might alter the response to indoramin.

Indoramin evoked a significant decrease in heart rate of 70 beats min^{-1} following a dose of 0.8 mg kg^{-1} (i.v.). Increasing the dose of indoramin did not evoke a further significant decrease in heart rate (Figure 1b). In contrast, following pithing, indoramin did not significantly decrease heart rate over the dose range 0.8–3.2 mg kg^{-1} (i.v.) (Figure 2a). Although the predose heart rate was lower in pithed animals than in the non-pithed preparations, the values following indoramin (0.8–3.2 mg kg^{-1} i.v.) in the pithed animals were significantly higher ($P < 0.05$) than those of the non-pithed group. Higher doses of indoramin (6.4–25.6 mg kg^{-1} i.v.) evoked a significant bradycardia in pithed rats (Figure 2a).

Preliminary experiments in anaesthetized rats deter-

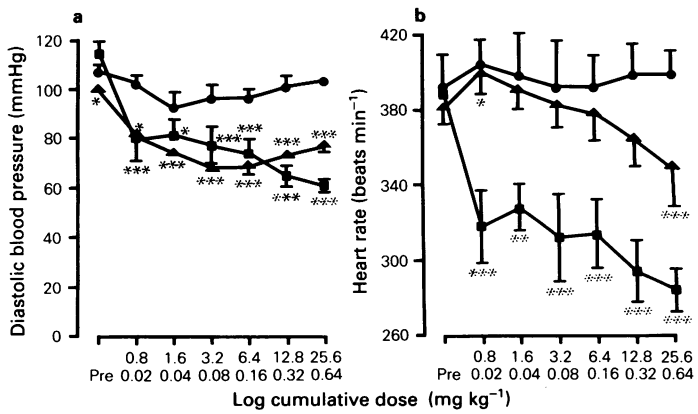

Figure 1 The effect of cumulative intravenous doses of vehicle, 1 ml kg^{-1} each time (●), indoramin, 0.8–25.6 mg kg^{-1} (■) or prazosin, 0.02–0.64 mg kg^{-1} (▲) on (a) diastolic blood pressure (mmHg) and (b) heart rate (beats min^{-1}) of anaesthetized rats. Each point represents the mean, and vertical lines s.e.mean, of 5 experiments. Pre- indicates the heart rate or blood pressure prior to dosing. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ indicates levels of significance of values, in (a) after comparison with vehicle controls (nested analysis of variance) and (b) after comparison with predose readings (2-way analysis of variance).

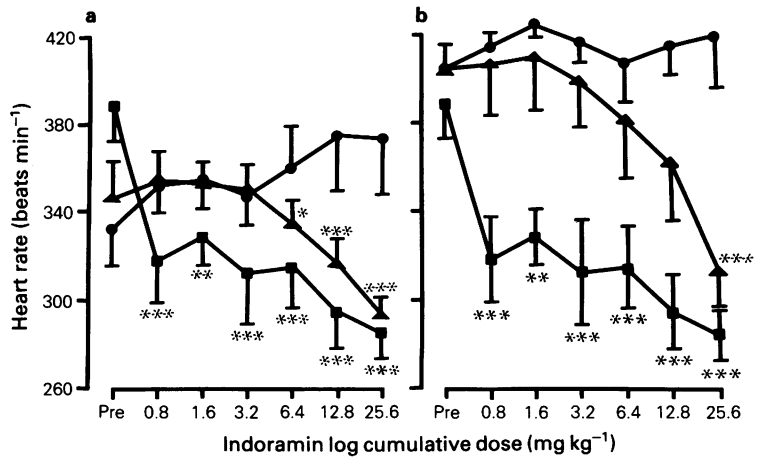

Figure 2 The effect of cumulative intravenous doses of indoramin (mg kg^{-1}) or vehicle (1 ml kg^{-1} each time) on the heart rate (beats min^{-1}) of anaesthetized rats after various pretreatments: (a) vehicle after pithing (●); indoramin after pithing (▲) or indoramin after vehicle (■), (b) vehicle after 1 mg kg^{-1} atropine (●); indoramin after 1 mg kg^{-1} atropine (▲) or indoramin after vehicle (■). Each point represents the mean, and vertical lines s.e.mean, of 5 experiments. Pre- indicates the heart rate 15 min after each pretreatment. $*P<0.05$, $**P<0.01$, $***P<0.001$ indicates levels of significance of values when compared with pretreatment values (2-way analysis of variance) except in pithed animals where the drug-treated group was compared with the pithed/vehicle-treated group (nested analysis of variance).

mined that a dose of 1 mg kg^{-1} of atropine sulphate or atropine methylnitrate blocked entirely the bradycardia induced by methacholine (10 μg kg^{-1} i.v.) and 3 mg kg^{-1} practolol completely blocked an isoprenaline (30–300 ng kg^{-1} i.v.)-induced tachycardia, for the duration of the experiments (1.75 h, data not shown). After atropine pretreatment, indoramin did not produce a significant decrease in heart rate until a cumulative dose of 25.6 mg kg^{-1} (i.v.) (Figure 2b). Following the administration of indoramin (0.8–12.8 mg kg^{-1} i.v.) the heart rates of atropine pretreated rats were significantly higher ($P<0.001$) than those of rats receiving indoramin alone. After bilateral vagotomy or the intravenous administration of atropine methylnitrate, indoramin did not evoke a significant bradycardia until a cumulative dose of either 3.2 mg kg^{-1} (i.v.) or 1.6 mg kg^{-1} (i.v.) respectively (Figure 3a,b). Heart rates of vagotomized rats were significantly higher ($P<0.01$) than those in rats receiving indoramin alone following doses of indoramin of 0.8–3.2 mg kg^{-1}. However, after methylatropine pretreatment heart rates were only significantly higher ($P<0.01$) following a dose of 0.8 mg kg^{-1} of indoramin. Comparisons of heart rates were made, at each dose of indoramin, between atropine pretreated animals and vagotomized or atropine methylnitrate pretreated animals (compare Figure 2b with Figure 3a,b): significant differences ($P<0.05$) were found at doses of 3.2–12.8 mg kg^{-1} and 1.6–25.6 mg kg^{-1}, respectively, but not in the absence of indoramin. Therefore, atropine antagonized the bradycardia induced by indoramin to a greater extent than did either vagotomy or atropine methylnitrate.

Following practolol pretreatment the heart rate decreased significantly after a cumulative dose of 3.2 mg kg^{-1} indoramin (Figure 3c). The bradycardia was significantly ($P<0.01$) attenuated over the dose range of 3.2–12.8 mg kg^{-1} (i.v.). Indoramin did not evoke a significant bradycardia in rats pretreated with a combination of practolol and bilateral vagotomy, until a cumulative dose of 6.4 mg kg^{-1} (i.v.) was administered (Figure 3d). The heart rates of this group of rats were significantly higher ($P<0.001$) following all doses of indoramin compared to the group receiving no pretreatment.

The effect of prazosin on heart rate

In contrast to the bradycardia induced by indoramin, the first dose of prazosin (0.02 mg kg^{-1} i.v.) evoked a small but significant ($P<0.05$) rise in heart rate in comparison with predose values (Figure 1b). The increase in heart rate, however, was not significant when compared to the changes occurring in the vehicle-treated group. A significant ($P<0.001$) bradycardia was evoked by prazosin following a cumulative dose of 0.64 mg kg^{-1} (i.v.) (Figure 1b).

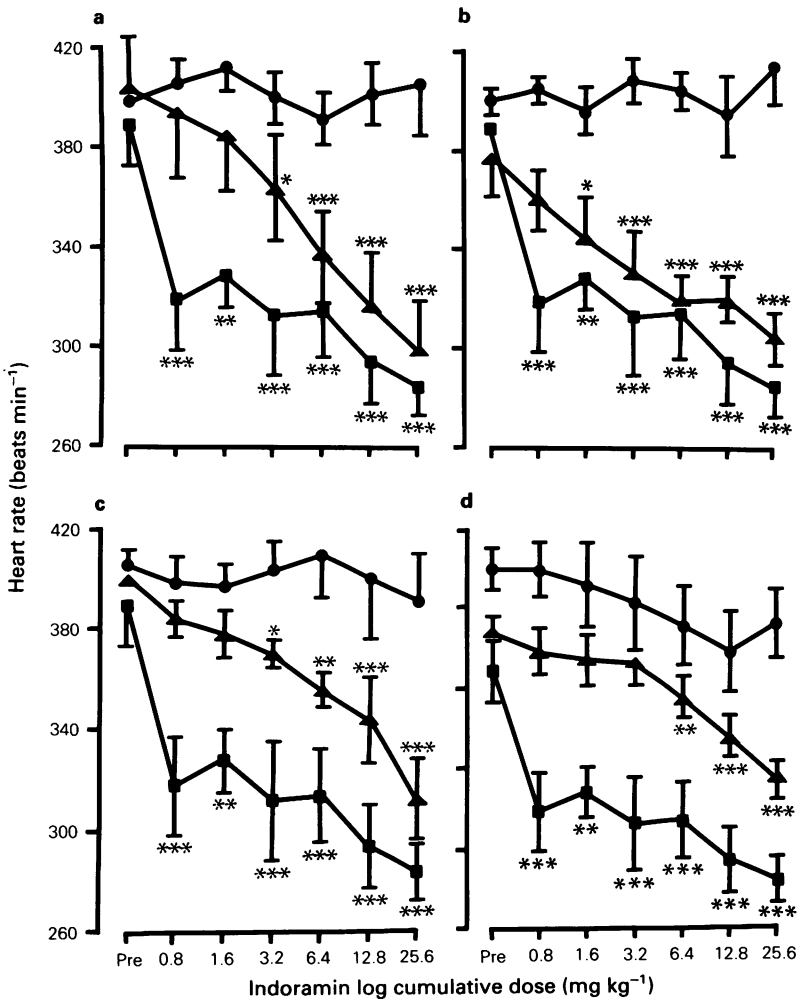

Figure 3 The effect of cumulative intravenous doses of indoramin (mg kg^{-1}) or vehicle (1 ml kg^{-1} at each time point) on the heart rate of anaesthetized rats after various pretreatments: (a) vehicle after bilateral vagotomy (●), indoramin after vehicle (■), indoramin after bilateral vagotomy (▲); (b) vehicle after atropine methylnitrate, 1 mg kg^{-1} (●), indoramin after vehicle (■), indoramin after atropine methylnitrate, 1 mg kg^{-1} (▲); (c) vehicle after practolol, 3 mg kg^{-1} (●), indoramin after vehicle (■), indoramin after practolol, 3 mg kg^{-1} (▲); (d) vehicle after a combination of practolol, 3 mg kg^{-1} and bilateral vagotomy (●), indoramin after vehicle (■), indoramin after a combination of practolol 3 mg kg^{-1} and bilateral vagotomy (▲). Each point represents the mean, and vertical lines s.e.mean, of 5 experiments. Pre- indicates heart rate 15 min after each pretreatment. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ indicate levels of significance of values when compared with pretreatment values (2-way analysis of variance).

The effect of peripheral and central administration of α_1-adrenoceptor blockers

Intravenous injection of the distilled water vehicle (1 ml kg^{-1}), indoramin (25 μg) or prazosin (25 μg) had no significant effect on heart rate (Figures 4a and 5a).

Small but significant ($P < 0.05$) decreases in blood pressure were noted 30 and 45 min after i.v. administration of vehicle. Neither indoramin (25 μg) nor prazosin (25 μg) evoked significant falls in blood pressure following intravenous administration compared to the vehicle data (Figures 4b and 5b).

Following i.c. administration of vehicle there was no significant change in heart rate over the 45 min time interval. Intracisternal injection of either indoramin (25 μg) or prazosin (25 μg) evoked significant decreases in heart rate (37 ± 10 ($n = 4$) and 44 ± 13 ($n = 4$) beats min^{-1} respectively) 15 min after injection

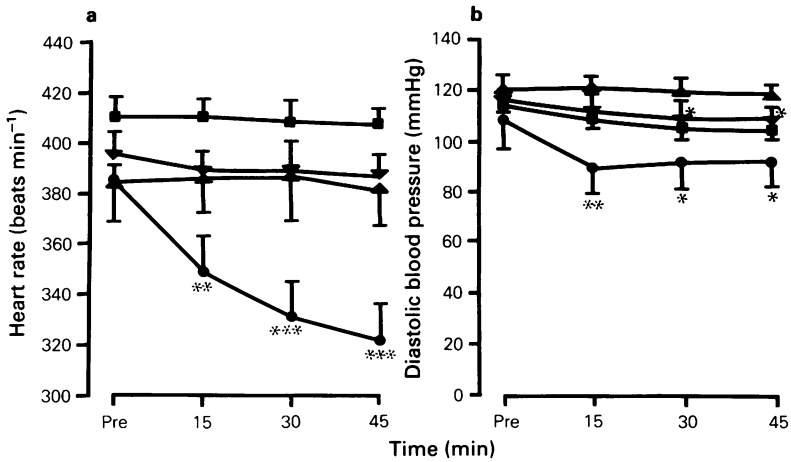

Figure 4 The effect of injection of vehicle, 10 μl i.c. (▲); indoramin 25 μg i.c. (●); vehicle 1 ml kg^{-1} i.v. (▼); or indoramin 25 μg i.v. (■) on (a) heart rate and (b) diastolic blood pressure, 15, 30 and 45 min after administration to anaesthetized rats. Each point represents the mean, with vertical lines showing s.e.mean, of 4 experiments. Pre- indicates predose values. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ indicates levels of significance of values in comparison with predose values (2-way analysis of variance). Blood pressure data after intravenous indoramin were compared with vehicle controls and showed no significant difference (nested analysis of variance).

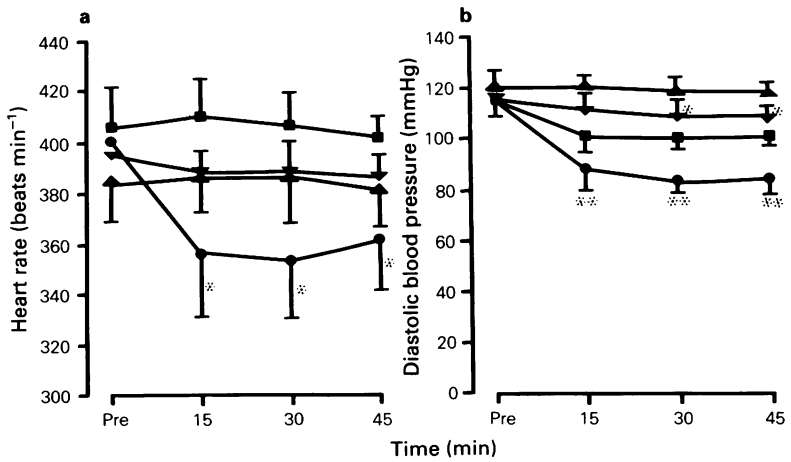

Figure 5 The effect of injections of vehicle, 10 μl i.c. (▲); prazosin 25 μg i.c. (●); vehicle 1 ml kg^{-1} i.v. (▼); or prazosin, 25 μg i.v. (■) on (a) heart rate and (b) diastolic blood pressure, 15, 30 and 45 min after administration to anaesthetized rats. Each point represents the mean, with vertical lines showing s.e.mean, of 4 experiments. Pre- indicates predose values. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ indicates levels of significance of values in comparison with predose values (2-way analysis of variance). Blood pressure data after intravenous prazosin were compared with vehicle controls and showed no significant difference (nested analysis of variance).

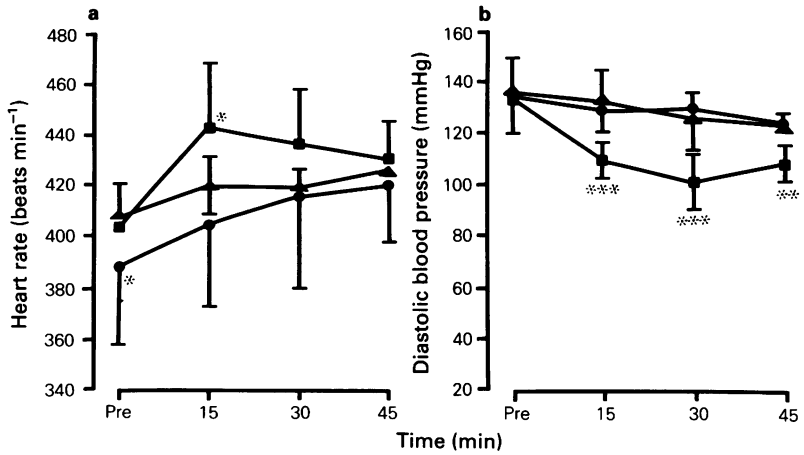

Figure 6 The effect of i.c.v. injection of vehicle, 10 μl (▲); i.c.v. indoramin, 25 μg (●) or i.c.v. prazosin, 25 μg (■) on (a) heart rate and (b) diastolic blood pressure, 15, 30 and 45 min after administration to anaesthetized rats. Each point represents the mean, with vertical lines showing s.e.mean, of 4 experiments. Pre- indicates predose values. $*P<0.05$, $**P<0.01$, $***P<0.001$ indicates levels of significance of values in comparison with vehicle controls (nested analysis of variance).

(Figures 4a and 5a). Heart rate continued to fall in the indoramin group, the decrease being 64 ± 9 beats min^{-1} ($n = 4$) after 45 min, whereas the fall in heart rate following prazosin administration was maximal after 15 min.

Administration of vehicle (10 μl i.c.) had no significant effect on blood pressure. Intracisternal administration of either indoramin (25 μg i.c.) or prazosin (25 μg i.c.) evoked small but significant decreases in blood pressure, 15 min after injection, which were sustained for 45 min (Figures 4b and 5b).

Following i.c.v. administration of vehicle (10 μl) there was a significant ($P<0.01$) increase in heart rate 45 min after injection compared to the predose level. Administration of indoramin (25 μg i.c.v.) had no significant effect upon heart rate compared to the vehicle group. Prazosin (25 μg i.c.v.), however, evoked a significant ($P<0.05$) tachycardia 15 min after injection (Figure 6a).

There was a significant decrease in blood pressure ($P<0.001$) 30 and 45 min after i.c.v. injection of vehicle. After the injection of indoramin (25 μg i.c.v.) there was no significant decrease in blood pressure compared to the control group. In contrast, prazosin (25 μg i.c.v.), evoked a significant decrease in blood pressure which was sustained for 45 min (Figure 6b).

Discussion

The selective α_1-adrenoceptor blocking agents indoramin and prazosin, evoke hypotension, usually without inducing a reflex tachycardia (Scriabine, 1980; Archibald, 1980). Several reasons for this have been suggested. For example their failure to block presynaptic α_2-adrenoceptors would allow negative feedback inhibition of noradrenaline release from cardiac sympathetic nerves to continue (Langer *et al.*, 1980; Scriabine, 1980). It is unlikely, however, that this is a sufficient explanation as vasodilators, such as sodium nitroprusside, which also do not block presynaptic α_2-adrenoceptors, evoke reflex tachycardia (Kreye, 1980). It has also been suggested that blockade of myocardial postsynaptic α_1-adrenoceptors may produce a negative chronotropic response (Benfey, 1980; Flavahan & McGrath, 1981). In the case of indoramin a widely accepted view is that the lack of tachycardia is due to a direct action on cardiac muscle as the result of membrane stabilizing properties (Algate *et al.*, 1981; Nichols *et al.*, 1983).

In anaesthetized rats we have found that, although a reflex tachycardia can be evoked following the administration of sodium nitroprusside (unpublished observation), under the same experimental conditions hypotensive doses of indoramin (0.8–3.2 mg kg^{-1} i.v.) evoke a concomitant bradycardia. This bradycardia can be abolished by pithing, combined pretreatment with practolol and vagotomy, or pretreatment with atropine. The bradycardia was attenuated following vagotomy or peripheral blockade by atropine methylnitrate (Herz *et al.*, 1965), and following β-adrenoceptor blockade by practolol. These results are not consistent with the hypothesis that the bradycardia evoked by indoramin at low doses is due to a direct

action on the heart, as autonomic blockade would not be expected to abolish the response. It would appear in fact that the bradycardia observed at these low doses is mediated via both an increase in vagal tone and a decrease in sympathetic nerve activity, as peripheral blockade of either arm of the autonomic nervous system attenuated the response. Higher doses of indoramin (6.4–25.6 mg kg^{-1}) evoked a bradycardia in pithed rats which could therefore be attributed to a direct action on the heart.

Intravenously administered atropine abolished the bradycardia evoked by indoramin whereas peripheral cholinergic blockade by atropine methylnitrate or bilateral vagotomy attenuated the bradycardia. It is likely, therefore, that some of the action of atropine was within the CNS, and the data suggest that at least part of the effect of indoramin is mediated via a central cholinergic mechanism. It has been shown by others that central cholinergic pathways are involved in cardiovascular control; for example in both conscious and anaesthetized rats the central administration of atropine can block a carbachol-induced rise in blood pressure and decrease in heart rate (Brezenoff & Giuliano, 1982).

In our experiments prazosin evoked a small but significant tachycardia following the initial dose of 0.02 mg kg^{-1} (i.v.). However, the tachycardia was not sustained, nor was it significant compared to changes seen in the vehicle control group. The highest dose of prazosin administered (0.64 mg kg^{-1} i.v.) evoked a significant bradycardia. We suggest that the bradycardia evoked by both indoramin and prazosin is a centrally mediated effect and that prazosin does not evoke a bradycardia until a relatively high α_1-adrenoceptor blocking dose, compared to indoramin, because of a difference in CNS penetration between the two compounds. By use of high performance liquid chromotography, prazosin and indoramin were found to have octanol:water distribution coefficients, at pH 7.4, of 17 and 275 respectively (C.L. Garner personal communication). These distribution coefficients indicate that prazosin has a lower lipophilicity than indoramin which may hinder its penetration into the CNS.

We have investigated the hypothesis that indoramin exerts a central action by comparing the effects of central and peripheral administration of the α_1-adrenoceptor blockers. Both indoramin and prazosin evoked a significant bradycardia in anaesthetized rats following intracisternal (i.c.) injection of a dose (25 μg) that had no significant effect following intravenous administration. In contrast, indoramin had no significant effect on blood pressure or heart rate following i.c.v. injection whereas prazosin evoked hypotension and transient tachycardia. Although prazosin can pass rapidly from the cerebrospinal fluid into the systemic circulation (Roach *et al.*, 1978), the dose of prazosin administered in these experiments had no significant effect on blood pressure or heart rate after peripheral administration. This suggests that the effects of prazosin on blood pressure and heart rate after i.c.v. injection are due to a central mechanism of action.

Since injection into the cisterna magna (i.c.) allows substances to be localized in the region of the brainstem, our results suggest that blockade of central α_1-adrenoceptors in this region evokes a reduction in heart rate in the anaesthetized rat. Higher regions of the CNS such as the hypothalamus, limbic system and cortex are unlikely to be involved in this action as i.c.v. injection did not evoke a bradycardia. In a comparative study Ramage (1984) found that indoramin and prazosin reduced peripheral sympathetic nerve activity in anaesthetized cats at threshold doses of approximately 0.5 mg kg^{-1} (i.v.) and 0.16 mg kg^{-1} (i.v.), respectively (authors' calculation from graphical data of Ramage, 1984). Prazosin has also been found to inhibit sympathetic discharge in the spontaneously hypertensive rat (Persson *et al.*, 1981). These results support the hypothesis that at relatively low doses these agents have central effects, which could explain why a tachycardia does not usually accompany their hypotensive effects.

The involvement of receptors other than α_1-adrenoceptors cannot be ruled out on the basis of the effects of indoramin alone, as it is known that this compound also blocks histamine and 5-hydroxytryptamine (5-HT) receptors (Alps *et al.*, 1972). However, the similarity of the results obtained with prazosin, a drug which lacks histamine and 5-HT blocking properties (Scriabine, 1980), suggests a major role for the α_1-adrenoceptor.

Both indoramin and prazosin have been shown to decrease sympathetic nerve discharge in the splanchnic nerve of anaesthetized cats (Baum & Shropshire, 1975; McCall & Humphrey, 1981). In our experiments indoramin and prazosin evoked significant decreases in blood pressure following i.c. administration, whereas the same doses had no effect in the periphery. These results tentatively suggest a central hypotensive action may participate in addition to peripheral α_1-adrenoceptor blockade if the compounds are able to penetrate the CNS.

In conclusion, our results suggest that central α_1-adrenoceptor blockade, possibly in the region of the brainstem, may prevent the occurrence of a reflex tachycardia following administration of the antihypertensive agent indoramin.

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