Br. J. Pharmacol. (1994), **112**, 214–218

The renal functional responses to 5-HT_{1A} receptor agonist, flesinoxan, in anaesthetized, normotensive rat

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1 The present study was designed to examine the effects of a centrally acting 5-HT_{1A} receptor agonist, flesinoxan, on the cardiovascular system and renal haemodynamics and excretory function.

2 In chloralose-urethane anaesthetized Wistar rats, i.v. administration of bolus doses of flesinoxan, at 30, 100, 300 and 1000 $\mu g\,kg^{-1}$, caused significant, dose-dependent decreases in mean arterial pressure, of 33 ± 2 mmHg ($P<0.001$) and heart rate of 57 ± 9 beats min^{-1} ($P<0.001$) at the highest dose used. Despite this substantial fall in perfusion pressure there were no meaningful changes in the renal excretion of water and sodium. In a second group of rats, reduction of renal perfusion pressure mechanically to the same values as observed in rats given flesinoxan (i.e. 100, 92, 84 and 76 mmHg) produced reductions in urine flow, absolute and fractional sodium excretions reaching a maximum of 74, 86 and 84% respectively (all $P<0.001$) at the lowest pressure. These reductions were significantly larger than those seen in the previous group of animals.

3 In the group of rats subjected to renal denervation, flesinoxan produced changes in blood pressure and heart rate which were not different from those observed in intact animals. However, the reduction in pressure was accompanied by significant decreases in urine flow of 71%, absolute sodium excretion of 68% and fractional sodium excretion of 67% (all $P<0.001$) at the highest dose, which were all significantly greater than the changes seen in the innervated animals but were not different from those observed when renal perfusion pressure was reduced mechanically.

4 The findings of this investigation showed that flesinoxan was effective in lowering blood pressure and heart rate in the anaesthetized rat, which was probably due to decreased sympathetic nerve activity. Renal excretion of water and sodium was well preserved in the face of the flesinoxan-induced hypotension. The maintenance of fluid excretion with flesinoxan appeared to be mediated via changes in renal nerve activity, since it did not occur when the kidney was denervated.

Keywords: 5-HT_{1A} receptor agonist; flesinoxan; renal function

Introduction

In recent years evidence has accumulated to show that central neural pathways utilising 5-hydroxytryptamine (5-HT) contribute towards the control of the sympathetic nervous system. Application of 5-HT to lateral ventricles of the cat brain was found to cause a fall in blood pressure, to reduce heart rate and inhibit efferent sympathetic nerve activity (Baum & Shropshire, 1975). In later studies several subtypes of receptors for 5-HT were identified in the brain (Peroutka, 1988) of which the 5-HT_{1A} subtype appeared to mediate the reduction in sympathetic outflow as a result of centrally applied 5-HT (Göthert & Schlicker, 1990). Subsequently specific agonists of this receptor site were developed, such as 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) (Peroutka *et al.*, 1990), and used to determine the effects of 5-HT_{1A} receptor stimulation on the degree of activation of the sympathetic nervous system and thereby the status of the cardiovascular system. There have been a number of reports in which agonists of this receptor site have been shown to reduce blood pressure and heart rate after intravenous (Gradin *et al.*, 1985; Dreteler *et al.*, 1990), intra-arterial (Dreteler *et al.*, 1991) and intracisternal administration (Wouters *et al.*, 1988). These responses appeared to be mediated by receptors located in dorsal raphe nucleus of the brain (Laubie *et al.*, 1989; Connor & Higgins, 1990). More recently Ramage and co-workers have provided evidence in the cat that centrally acting 5-HT_{1A} receptor agonists produce peripheral sympatho-inhibition, with efferent renal nerve activity being most sensitive (Ramage *et al.*, 1988; Ramage & Wilkinson, 1989).

The kidney is very richly innervated with the renal sympathetic nerves supplying the renal vasculature, tubules and juxtaglomerular apparatus (Barajas *et al.*, 1992). It has been shown, both in studies utilising direct renal nerve stimulation as well as in denervation experiments, that the renal nerves can influence renal haemodynamics, tubular sodium reabsorption and renin release from juxtaglomerular cells (DiBona *et al.*, 1988; Johns, 1991). In terms of function, the electrical activity in the renal sympathetic nerves has been shown to change in response to such physiological stimuli as variations in arterial blood pressure (Deka-Starosta *et al.*, 1989) and intravascular volume (DiBona *et al.*, 1988) which consequently determines the level of renal haemodynamics and fluid excretion.

Given the important influence of the renal nerves upon sodium and water excretion and existing evidence that stimulation of central 5-HT_{1A} receptors can decrease efferent renal sympathetic nerve activity, the aim of the present investigation was to examine the effects of the specific 5-HT_{1A} agonist, flesinoxan, on the cardiovascular system and renal nerve-dependent change in renal haemodynamics and water and sodium excretion in anaesthetized, normotensive rats. A preliminary account of this work was presented to the Pharmacological Society meeting at Bradford in September 1993 (Chamienia & Johns, 1993).

Methods

The experiments were performed on male Wistar rats (mean body weight 300 g) which had been fasted overnight. The animals were initially anaesthetized with 4% halothane in oxygen/nitrous oxide. A cannula was inserted into the right

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femoral vein and a bolus dose of α-chloralose/urethane mixture was given i.v. (initial dose 17.5 mg chloralose, 0.3 g urethane) and an infusion of 3 ml h^{-1} normal saline started. The anaesthesia was maintained throughout the experiment with bolus doses of the same mixture as required and the animals breathed spontaneously throughout. After the induction of anaesthesia, tracheostomy was performed and catheters placed in the right carotid artery, for systemic pressure monitoring, and in the right femoral artery to allow measurements of renal perfusion pressure and arterial blood sampling. Both kidneys were approached retroperitoneally and their ureters cannulated. The left renal artery was then carefully cleared using a dissecting microscope and an electromagnetic flow probe (Carolina EP100 series, internal circumference 2–2.5 mm) placed around it for measuring renal blood flow. Silver wire electrodes were applied to the coeliac/aortico-renal ganglia and pulses of 15 V, 10 Hz, 0.2 ms were delivered for 10 s which caused a transient blanching of the kidney. If blanching did not occur, the kidney was treated as denervated and not included in the study. Both arterial catheters were connected to pressure transducers (Statham P23 I) and the signal fed to a custom built amplifier (Grayden, Birmingham). The flow meter probe was connected to a square wave electromagnetic flowmeter (Model FM501, Carolina Medical Instruments, U.S.A.). Blood pressure and renal blood flow signals were then fed via an I/O card to an Apple Macintosh computer running custom software written in LabVIEW (National Instruments, Austin, TX, U.S.A.) and displayed on the screen. Heart rate was derived from the carotid pressure wave signal on-line. Mean values for all variables were calculated for every 2 s and then averaged over each of 15 min clearance periods. Data were stored on the hard disk for later off-line analysis. On completion of the surgery, a priming dose of 2 ml inulin in saline (1.5 g 100 ml^{-1}) was given i.v. and isotonic saline infusion replaced by one containing inulin (1.5 g 100 ml^{-1}). Animals were then allowed 2 h to stabilize and reach equilibrium before starting the experiment.

Experimental protocols

In this study, urine was collected from the ureters over 15 min and this was termed a clearance period. Five pairs of 15 min clearance periods were performed, with approximately 15 min intervals between each pair which allowed for blood sampling and for any drug to be flushed into the circulation via the venous cannula. Arterial blood samples (300 μl each) were taken before the first and then after the end of each pair of clearances. The blood samples were immediately centrifuged and plasma obtained, the red cells were resuspended in an equivalent volume of heparinized saline and reinfused into the animal within 5 min. Urine was collected in preweighed microcentrifuge capped tubes. Three groups of animals were studied:

Group 1 ($n = 8$). The first pair of clearance periods provided basal values. The rats then received flesinoxan as a bolus i.v. dose 10 min before the start of remaining pairs of clearances at doses of 30, 100, 300 and 1000 μg kg^{-1} in a cumulative fashion. Flesinoxan was injected slowly over 30 s in 300 μl of normal saline.

Group 2 ($n = 6$). In this group of rats, a loop of surgical thread was placed around the aorta, between the renal arteries, and attached to a screw device to allow reduction of left kidney perfusion pressure when tightened. The first two clearances were completed at prevailing pressure and then the perfusion pressure was lowered in steps to the same values as observed in the Group 1 animals at each dose of flesinoxan, and 10 min later the next pair of clearances begun. The levels of perfusion pressure achieved were 100, 92, 84 and 76 mmHg respectively. Only left kidney function was studied in this group.

Group 3 ($n = 6$). In this group of animals, in addition to the surgery described above, the left renal sympathetic nerves were identified, carefully dissected and cut. Only left kidney function was studied in this group. Rats received flesinoxan at the same doses as in group 1.

Chemical assays

Urinary and plasma electrolyte concentrations were measured by flame photometry (Ciba Corning 410C). Plasma and urine samples inulin was measured as described previously (Chamienia & Johns, 1991).

Drugs and chemicals

Flesinoxan was a gift from Solvay-Duphar B.V., Weesp, The Netherlands. Inulin and all other chemicals were purchased from Sigma, Poole, Dorset.

Statistical analysis

All values are presented as means ± s.e.mean. The mean values of all variables were calculated for each pair of clearances. Statistical analysis was performed with repeated measures analysis of variance (using an Apple Macintosh computer and SuperANOVA software, Abbacus Concept, Berkeley, CA, U.S.A.). The effects were taken to be significant when $P < 0.05$.

Results

Figure 1 presents the mean arterial pressure, renal perfusion pressure and heart rate in the three groups of experiments. In the first group, flesinoxan caused dose-dependent falls in both mean arterial pressure and renal perfusion pressure, of 33 ± 2 and 34 ± 2 mmHg respectively at the highest dose (both $P < 0.001$). This was accompanied by a progressive decrease in heart rate reaching some 57 ± 9 beats min^{-1} ($P < 0.001$) at the highest dose of the drug. Renal blood flow (RBF) and glomerular filtration rate (GFR) did not change significantly throughout the experiment. Despite the profound fall in perfusion pressure, the left kidney urine flow (UV), urinary sodium excretion ($U_{Na}V$) and fractional sodium excretion (FE_{Na}) fell only slightly but not significantly by 28, 29 and 16% respectively, at the highest dose of drug. At the same time, right kidney UV, $U_{Na}V$ and FE_{Na} were slightly, but not significantly, raised by 13, 14 and 11% respectively (Figure 2).

In the second group of animals, mean arterial pressure increased slightly by 8 ± 6 mmHg during stepwise reduction in left renal perfusion pressure. Levels of perfusion pressure obtained by applying aortic constriction were very similar to those observed in the animals in group 1 (Figure 1). Heart rate did not change at any time throughout the experiment in this group of rats, which was significantly different from the dose-related decreases in heart rate observed in the group 1 rats given flesinoxan ($P < 0.001$). RBF and GFR in this group were not different from those seen in group 1 and remained unchanged during the experiment. Urine flow decreased significantly (by 74% at the lowest pressure; $P < 0.001$), which was significantly less than the values observed for the right kidney in the previous group ($P < 0.05$). Absolute and fractional sodium excretions also decreased significantly (both $P < 0.001$) by 86 and 84%, respectively, at the lowest pressure. These falls in $U_{Na}V$ and FE_{Na} were significantly different from the changes seen in group 1 ($U_{Na}V$: $P < 0.02$ and $P < 0.01$; FE_{Na}: $P < 0.02$ and $P < 0.001$ vs left and right kidneys of group 1 animals, respectively).

In the last group of animals, flesinoxan caused dose-dependent decreases in mean arterial pressure of 29 ± 4 mmHg, renal perfusion pressure of 30 ± 4 mmHg and heart rate of 47 ± 14 beats min^{-1} (all $P < 0.001$) which were not

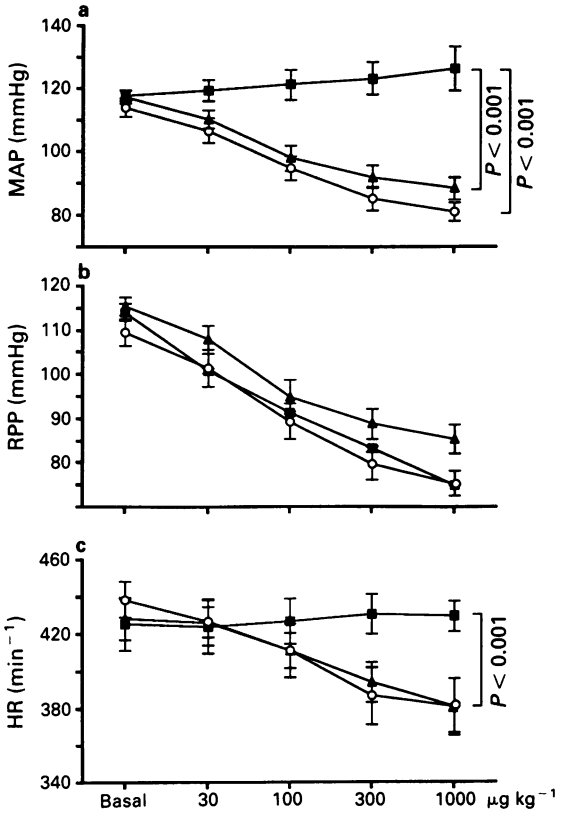

Figure 1 This shows the mean arterial pressure (MAP) (a), renal perfusion pressure (RPP) (b) and heart rate (HR) (c) in three groups of animals. Each point represents the average value of the two 15 min clearance periods. Groups 1 (○) and 3 (▲) received flesinoxan; in Group 2 (■) left renal perfusion pressure was reduced by aortic constriction. The *P* values are generated in the comparison between the group 1 data and that of groups 2 or 3 using repeated measures ANOVA.

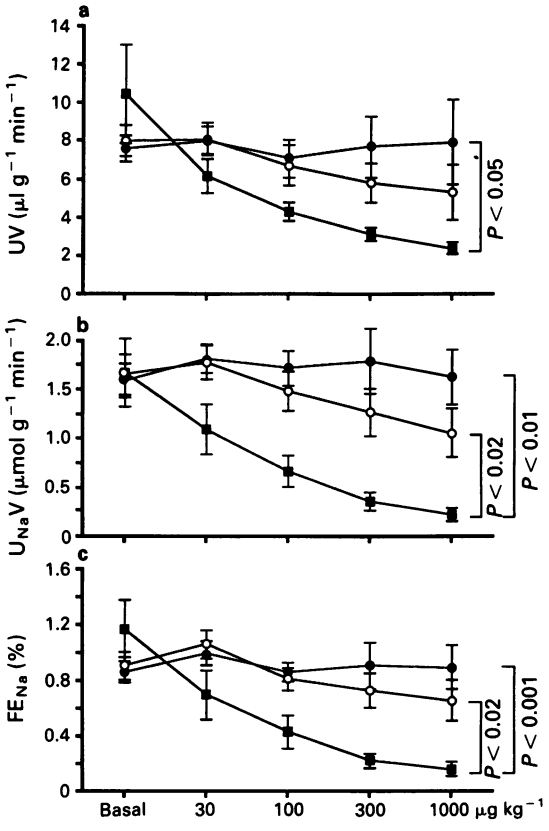

Figure 2 This shows the urine flow (UV) (a), urinary sodium excretion ($U_{Na}V$) (b) and fractional sodium excretion (FE_{Na}) (c) of animals in group 1 left kidney (○), right kidney (●) and group 2 (■). The results for both kidneys of animals in group 1 are shown. Each point represents the average value of the two 15 min clearance periods. The *P* values are generated in the comparison between the group 1 data and that of group 2 or 3 using repeated measures ANOVA.

different from those observed in group 1. RBF fell slightly but not significantly and GFR did not change. Urine flow, absolute and fractional sodium excretions decreased significantly with increasing dose of flesinoxan (all $P<0.001$). These falls reached 71, 68 and 67% respectively at the highest dose and were not significantly different from those observed in the group 2, when perfusion pressure was reduced. However, these reductions in urine and sodium excretion in the denervated kidney were significantly different from those observed in group 1 (UV; $P<0.005$ and $P<0.001$; $U_{Na}V$: $P<0.05$ and $P<0.001$; FE_{Na}: $P<0.02$ and $P<0.001$ vs. left and right kidneys of animals in group 1 respectively). The urine and sodium excretions in this group of animals are presented graphically in Figure 3.

Discussion

The purpose of the present study was to investigate the renal functional responses to 5-HT_{1A} receptor stimulation by a specific agonist and to determine the role, if any, of the renal sympathetic nerves. The results from the normotensive Wistar rats showed that intravenous administration of flesinoxan caused dose-dependent decreases in blood pressure which were accompanied by falls in heart rate. This was in agreement with previously published results of studies in cats (Dreteler *et al.*, 1989) and rats (Dreteler *et al.*, 1990). It has been suggested that the hypotension induced by 5-HT_{1A} receptor stimulation depends on inhibition of peripheral sympathetic tone with a resultant decrease in total vascular resistance. Dreteler *et al.* observed a reduction in vascular resistance in renal and cerebral circulations, but no change in cardiac output after flesinoxan administration in cats (Dreteler *et al.*, 1989) and spontaneously hypertensive rats (Dreteler *et al.*, 1991). An increase in vagal tone appears to contribute to the bradycardia since this effect was reported to be abolished by atropine and vagotomy in the cat (Ramage *et al.*, 1988).

In our experiments flesinoxan had little effect on glomerular filtration rate (GFR) or renal blood flow (RBF). This demonstrates that over this range of perfusion pressure both RBF and GFR were effectively autoregulated. However, despite the profound fall in blood pressure, renal excretion of urine and sodium was well preserved. This response was intriguing as it has been shown previously, that urine and sodium excretions depend critically on the level of renal perfusion pressure (pressure-natriuresis) (Roman & Cowley, 1985; Roman *et al.*, 1988) and therefore it might have been anticipated that urinary volume and sodium excretion would decrease in parallel with the hypotension. Indeed, in the study in which renal perfusion pressure was lowered by the means of aortic constriction to levels similar to those observed with flesinoxan, urine flow, absolute and fractional sodium excretions all fell significantly along with perfusion pressure. The mechanism by which renal excretory function was preserved in the presence of flesinoxan is not clear. Baum & Shropshire (1975) in early experiments were able to show an inhibition of efferent renal sympathetic nerve activity (ERSNA) due to a central action of 5-HT. More recently, Stein *et al.* (1987) and Montes & Johnson (1990) have shown

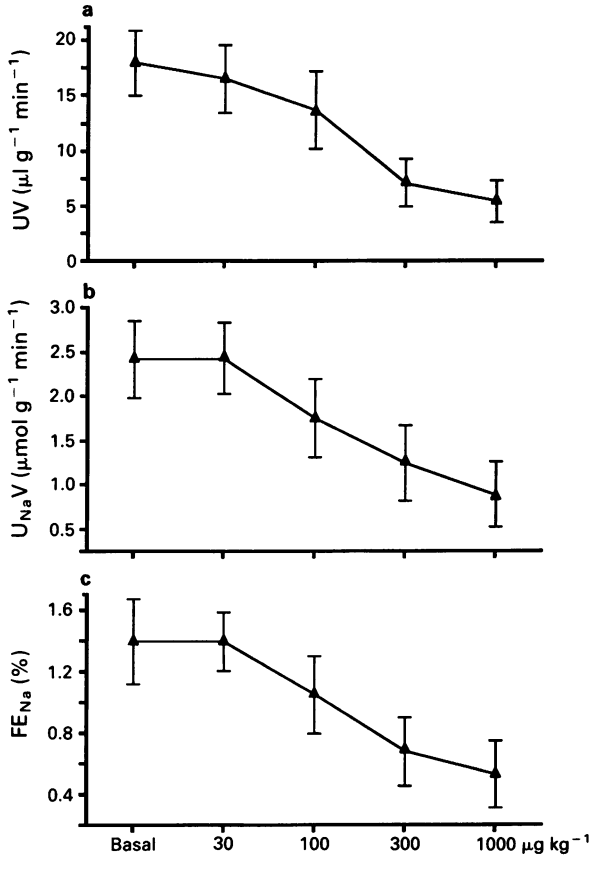

Figure 3 This shows the urine flow (UV) (a), urinary sodium excretion ($U_{Na}V$) (b) and fractional sodium excretion (FE_{Na}) (c) of animals in group 3. Rats in this group had the kidney surgically denervated. Each point represents the average value of the two 15 min clearance periods. The *P* values are generated in the comparison between the group 1 data and those of group 2 or 3, using repeated measures ANOVA.

increased water and electrolyte excretion following intraventricular application of 5-HT in hydrated, conscious rats. The latter authors additionally found ERSNA to decrease after central administration of 5-HT. Clearly 5-HT will be acting on a range of different 5-HT receptors each having its own specific function but there is a recognition that activation of 5-HT_{1A} receptors results in inhibition of sympathetic outflow. Ramage *et al.* (1988) and Ramage & Wilkinson (1989) have reported that intravenous and intraventricular injections of specific agonists of 5-HT_{1A} receptor subtype, such as 8-OH-DPAT and flesinoxan, led to decreases in sympathetic activity recorded in cardiac and renal sympathetic nerves, furthermore, they found that these 5-HT_{1A} agonists preferentially inhibited renal nerve activity in the anaesthetized cat.

The renal sympathetic nerves may influence renal haemodynamics under certain circumstances, like hard exercise, psychological stress or haemorrhage, but under normal conditions renal nerve activity is low, having minimal haemodynamic effect. Moreover, low levels of direct renal nerve stimulation have been shown to influence tubular water and sodium reabsorptions without any detectable changes in renal blood flow or glomerular filtration (DiBona, 1989). This view has been supported by experiments which showed that renal denervation could enhance excretion of water and sodium without changes in renal haemodynamics (Pelayo *et al.*, 1983; Bencsath *et al.*, 1985). Furthermore, such physiological stimuli as variations in arterial blood pressure (Deka-Starosta *et al.*, 1989) and intravascular volume (DiBona *et al.*, 1988) have been shown to cause reflex changes of ESRNA and renal nerve-dependent changes in water and sodium excretion. Consequently, in a physiological situation, a fall in blood pressure produces a reflex increase in ESRNA and increases the reabsorption of water and sodium. An increase in intravascular volume or blood pressure, on the other hand, results in a decrease in ESRNA, which in turn promotes water and sodium excretion.

Thus, one of the most likely explanations of our findings would be that flesinoxan via its action on central 5-HT_{1A} receptors causes inhibition of ESRNA, which contributes to unchanged excretion of water and sodium. Although a decrease in ESRNA in itself could have been expected to cause a diuresis and natriuresis, a concomitant large fall in renal perfusion pressure was present, which would have an opposite effect. Hence the net result would be an unchanged excretion of urine and sodium in face of falling perfusion pressure. The data obtained in the last group of animals lend further support to the role of renal nerves. In those rats with denervated kidneys, i.v. flesinoxan caused a similar reduction in perfusion pressure to that observed in intact animals. However, when perfusion pressure decreased there were corresponding reductions in urine and sodium excretions, indeed in a manner similar to that present in animals of group 2. Taken together these results clearly support the role of renal nerves in the changes in renal excretory function induced by systemic administration of flesinoxan.

In contrast to the results reported by Stein *et al.* (1987) and Montes & Johnson (1990), we did not observe a positive diuresis or natriuresis. It is possible that the different routes of administration and different specificity of the agonist used may partly explain this discrepancy. It should also be noted that in both studies only minor falls in perfusion pressures (approx. 10 mmHg) were observed. Furthermore, both studies utilized conscious animals, while we used anaesthetized rats in our investigation. In addition, the animals in both reports cited above were hydrated with intravenous infusion of 6–12 ml h^{-1} of fluid, which most probably induced a diuretic state.

Although the effects of flesinoxan in our study appear to be mediated via a central mechanism it is of interest that 5-HT_{1A} receptors have recently been found in rat and human kidneys. Those receptors appear to be present on the basolateral membranes of the cells in medullary and cortical thick ascending limbs, distal convoluted tubules and initial portion of collecting tubules (Raymond *et al.*, 1993). The role of those receptors in the regulation of the renal function is not clear at the present time. However it is unlikely that they contributed to the responses observed in the present study as they would have been equally activated in both the innervated and denervated kidneys.

This study attempted to assess the effects of a novel 5-HT_{1A} receptor agonist, flesinoxan, on renal function. We confirmed the findings in earlier reports that flesinoxan is effective in lowering blood pressure and heart rate in anaesthetized rat. Moreover we were able to establish that the renal excretion of urine and sodium is well preserved during flesinoxan-induced hypotension and this is a function of the renal nerves. It is likely that it reflects an inhibition of renal sympathetic outflow by flesinoxan leading to a partial denervation diuresis and natriuresis. This finding may suggest a potential role for this drug in the treatment of hypertension.

The generous gift of flesinoxan by Solvay-Duphar B.V. is greatly appreciated. The work presented in this manuscript was supported by a grant from the British Heart Foundation.

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(Received August 26, 1993
Revised November 16, 1993
Accepted January 10, 1994)