J. Pharm. Pharmacol. 1980, 32: 272–277 Received July 3, 1979

Cardiovascular withdrawal effects of clonidine and tiamenidine on abrupt cessation of oral treatment in conscious cats

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In conscious renal hypertensive cats prepared with permanent indwelling arterial catheters oral administration of clonidine (0·05 mg × 3 daily) clonidine (0·0125 mg × 3 daily), or tiamenidine (0·25 mg × 3 daily) induced hypotension and bradycardia during 6 days of treatment, although these responses were not well sustained. A pronounced tachycardia was demonstrated in all cats, 16–20 h after cessation of treatment with the higher dose of clonidine, however, only two cats in this group showed increased blood pressures above pre-dose levels at this time; these 'withdrawal' effects were absent 44 h after the final dose. No evidence of tachycardia, or blood pressure overshoot was seen up to 44 h after cessation of the low clonidine treatment regime, providing evidence for a dose-withdrawal effect relationship. Significant tachycardia was demonstrated in all cats 15–19 h after cessation of treatment with tiamenidine with no evidence of blood pressure elevation; the tachycardia was absent 48 h after the final dose. In four of these same cats clonidine (0·1 mg × 2 daily), in a long-acting, sustained release formulation (LA clonidine), elicited prolonged falls in blood pressure and heart rate over a 10 day period. No evidence of withdrawal effects were obtained 14–48 h after cessation of this treatment.

Clonidine is an effective antihypertensive agent which is considered to act mainly in the central nervous system (for reviews see Haeusler 1973; Van Zwieten 1973). Reports of 'rebound' rises in blood pressure in man, if the drug is withdrawn abruptly (Hansson et al 1973; Hunyor et al 1973; Cairns & Marshall 1976; Goldberg et al 1977; Reid et al 1977) have, however, questioned the usefulness of imidazolines in antihypertensive therapy.

The clinical picture of the imidazoline withdrawal syndrome incorporates symptoms of sympathetic nervous system overactivity such as sweating, flushing, apprehension and tachycardia. Increased circulating and urinary excretion of catecholamines have also been demonstrated after withdrawal of guanfacine (BS 100–141) in controlled clinical studies (Zamboulis et al 1978) without concomitant increases in blood pressure.

Several reports of withdrawal phenomena in rats have also been made (Dix & Johnson 1977; Atkinson et al 1978a; Oates et al 1978a, b; Prop 1978; Salzmann 1979). Most of these have demonstrated withdrawal effects on blood pressure after cessation of imidazoline treatment, although only in a few has the heart rate response been measured and in many cases pretreatment data have proved insufficient to allow satisfactory interpretation of post-treatment data.

The present study examines the cardiovascular changes which occur during and after oral treatment with different doses of clonidine, or another imidazoline, tiamenidine (Linder & Kaiser 1974), in the same conscious cats, in which both the responsiveness to clonidine treatment and the progression of hypertension have been established.

Preliminary evidence for withdrawal effects on blood pressure after termination of clonidine treatment, has been found in cats and dogs (Cavero et al 1977; Finch et al 1978).

METHODS

Cats of either sex (2·0–3·0 kg) were used.

Conscious renal hypertensive cats

Cats were anaesthetized with sodium pentobarbitone (30 $mgkg^{-1}$; i.p.) and were made hypertensive by wrapping one kidney in Cellophane, together with contralateral nephrectomy. At an earlier operation, a cannula was placed down the right carotid artery and its tip located in the thoracic aorta. The cannula was exteriorized at the base of the neck and attached to a one-way valve secured to the neck muscle (Finch 1974).

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Cardiovascular measurement

Blood pressure and heart rate recordings were carried out in trained cats 1–2 weeks after recovery from the operations. Blood pressure was measured on a Grass 7 polygraph using Statham P23 pressure transducers and all readings were taken between 0900–1700 h. Mean blood pressure was expressed as: Diastolic b.p. + $\frac{1}{3}$ pulse pressure. Heart rate was recorded from the blood pressure trace.

Experimental procedure

In trained cats with established hypertension the blood pressure and heart rate were recorded until constant daily readings were obtained. Pretreatment data were assessed on three consecutive days before drug administration. Cardiovascular parameters were evaluated at the following times on each day: 10.30, 12.00 and 15.30 h and pre-dose values expressed as average blood pressure or heart rate. During drug administration, blood pressure and heart rate were monitored continually on each day of recording and values were assessed at these times throughout treatment as percentage changes from pre-dose values. During the withdrawal phase, blood pressure and heart rate were measured at 1 h intervals between 0900 and 1700 h on two consecutive post-treatment days.

Dosing protocol

All treatments were by the oral route in tablet or capsule form. Standard formulation of clonidine (SF clonidine), tiamenidine or placebo were administered three times daily at 10.30, 15.30 and 20.00 h on each day. LA clonidine was administered twice daily for 10 days at 10.30 and 20.00 h on each day. Twice daily administration of LA clonidine was employed since this resulted in long-lasting hypotension and bradycardia. Each drug treatment was administered to the same group of cats (n = 5) over 12 weeks, n = 4 for LA clonidine. A recovery period of one week was allowed between treatments (Table 1).

In a separate study, 7 renal hypertensive cats were treated with empty gelatin capsules using the same dosing protocol.

Drugs

Clonidine hydrochloride as Dixarit (Boehringer Ingelheim): was used because each tablet contains 0·025 mg clonidine, an effective antihypertensive dose after oral administration in cats. There is no evidence of cardiovascular withdrawal effects in man after cessation of treatment with this preparation, tiamenidine (Hoechst); sustained release preparation of clonidine, LA clonidine (Boehringer Ingelheim).

Statistical analysis

Statistical evaluation of heart rate data was made using Student's *t*-test, between pre-dose data, placebo data and data obtained during withdrawal of clonidine or tiamenidine. No statistical assessment of blood pressure was made, since only two cats in this study demonstrated blood pressure-withdrawal effects at these times. Significance was accepted when $P < 0{\cdot}05$.

RESULTS

Oral administration of clonidine

Oral administration of SF clonidine (0·05 mg × 3 daily or 0·0125 mg × 3 daily) for 6 days elicited hypotension and bradycardia (Fig. 1). These effects were not sustained between days, thus the blood pressure and heart rate at 10.30 h on each day during dosing was not different from pre-dose levels (Fig. 1).

Table 1. Blood pressure and heart rate measurements in conscious cats before (Group 1 only) and 3–12 weeks after contralateral nephrectomy and renal wrapping. These readings are the average blood pressure or heart rate measured during 5 h daily recordings on at least 3 consecutive days, before the drug treatments indicated.

		Weeks after nephrectomy				
Group I (n = 5)	Normo-tensive	3–4	6	8–9	11–12 (n = 4)	Group II (n = 7) 3
Blood pressure (mmHg)	88 ± 8 / 62 ± 6	126 ± 7 / 86 ± 7	140 ± 6 / 92 ± 5	125 ± 9 / 85 ± 5	130 ± 6 / 89 ± 4	139 ± 3 / 94 ± 2
MAP (mm Hg)	70 ± 4	98 ± 4	108 ± 4	97 ± 5	102 ± 5	109 ± 5
Heart rate (b min^{-1})	144 ± 10	134 ± 12 SF clon (0·05 mg × 3)	131 ± 8 SF clon (0·0125 mg × 3)	169 ± 9 tiamen (0·25 mg × 3)	154 ± 5 LA clon (0·1 mg × 2)	160 ± 8 Placebo

± s.e.m.

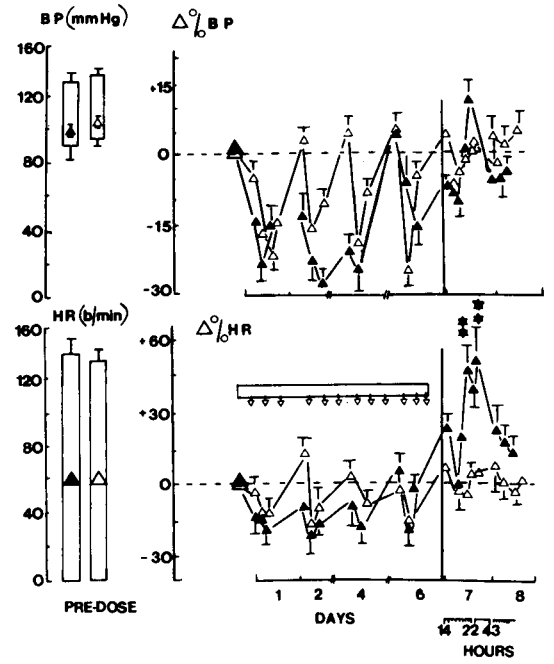

Fig. 1

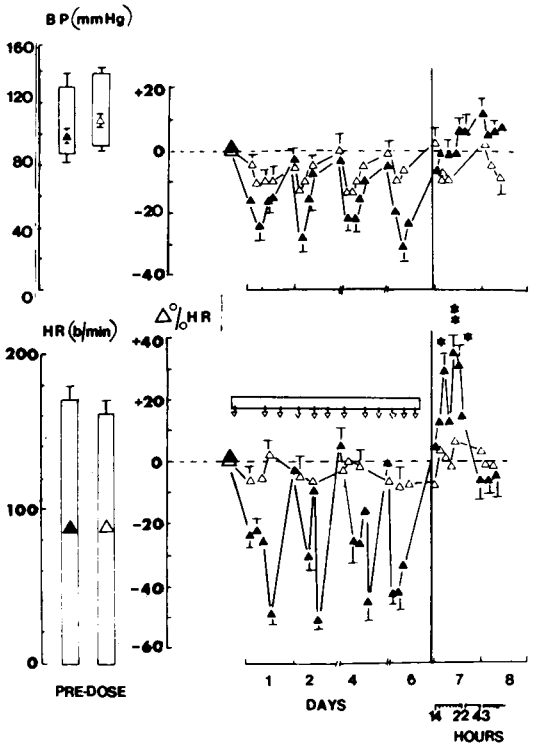

Fig. 2

FIG. 1. Conscious renal hypertensive cats. The average blood pressure (mm Hg) and heart rate (b min^{-1}) measured during 5 h daily recordings on three consecutive days (pre-dose), before oral administration of clonidine in the same group of cats (n = 5) during independent studies. △% in blood pressure (BP) or heart rate (HR) measured during six days (1–6) of treatment with either clonidine (0·05 mg × 3 daily; ▲—▲) or clonidine (0·0125 mg × 3 daily; △—△). Measurements were recorded at 10.30, 12.00 and 15.30 h on days 1, 2, 4 and 6. No recordings were made on days 3 or 5. On days 7 and 8, BP and HR readings were recorded at 1 h intervals (14–22 and 43–46 h after the last dose of clonidine) vertical bars indicate s.e.m., * $P < 0·05$, ** $P < 0·01$, compared with pre-dose data. Horizontal bar indicates duration of clonidine treatment, ↓ indicates incidence of dosing.

FIG. 2. Conscious renal hypertensive cats. The average blood pressure (mm Hg) and heart rate (b min^{-1}) measured during 5 h daily recordings on three consecutive days (pre-dose) before oral administration of a long acting formulation of clonidine (LA clonidine). %△ in blood pressure (BP) or heart rate (HR) during 10 days (1–10) of treatment with LA clonidine (0·1 mg × 2 daily; ▲—▲). Measurements were recorded at 10.30, 12.00 and 15.30 h on days 1, 2, 3, 4, 7, 8, 9, and 10. Animals were dosed on days 5 and 6, but no recordings were made. On days 11 or 12, BP and HR readings were recorded at 1 h intervals (14–22 and 43–46 h after the last dose of LA clonidine). Vertical bars indicate s.e.m.; n = 4). Horizontal bar indicates duration of dosing, ↓ indicates incidence of dosing.

This dosing regime with clonidine induced sedation in all animals and marked aphagia for the duration of treatment. The mean heart rate of the higher dose-treated group was significantly ($P < 0·01$) elevated above pre-dose control levels on day 7 (day 1 of withdrawal) between 13.00–16.00 h, (17–20 h after the last dose of clonidine) (Fig. 1) and significantly different from the low dose clonidine treated cats at these times ($P < 0·01$, Fig. 1). On day 8 the mean heart rate of this group was not significantly different from pre-dose levels at any time (Fig. 1). No evidence of overshoot was obtained after cessation of clonidine (0·0125 mg × 3) treatment (Fig. 1). Two cats only in the clonidine (0·05 mg) treated group demonstrated elevated blood pressure on day 7 of the study (16–22 h after the final dose). The blood pressure of these cats remained persistently higher than during predose control periods at these times (Changes in mean b.p. of +20–+35 mmHg).

Cats which demonstrated cardiovascular effects in response to cessation of clonidine also showed behavioural effects during this time, in that they often appeared restless and would not exhibit the normal lying and sleeping postures adopted by

clonidine-treated, or non-treated animals. Piloerection was also evident during the 'crisis' period.

Oral administration of LA clonidine (0·01 mg × 2 daily) administered to 4 of the previously used cats elicited long-lasting hypotension with marked bradycardia (Fig. 2). All cats exhibited normal feeding behaviour throughout treatment with this preparation, in contrast the aphagia induced by the high dose of SF clonidine which precluded a longer period of dosing. No significant elevation in blood pressure, nor heart rate occurred following abrupt cessation of LA clonidine in any of these cats (Fig. 2).

Oral administration of tiamenidine

In the same 5 conscious cats, tiamenidine (0·25 mg × 3 daily) induced marked hypotension and bradycardia 1–2 h after dosing, despite emesis which occurred in all cats within 15–25 min of dosing. Sedation was marked throughout and aphagia prominent in all cats.

Significant tachycardia ($P < 0·001$) was elicited 15–19 h after cessation of tiamenidine treatment (Fig. 3), although no significant elevation in blood pressure was observed in any of the cats at any time during the withdrawal phase. At 1600 h on day 7, the heart rate of this group of cats was not significantly different from either pre-dose control levels at the same time of the day, or from placebo treated animals (Fig. 3).

In 7 hypertensive cats, the effects of placebo administration was studied using the same dosing proctocol (3 × daily); this treatment resulted in a slight fall in blood pressure (10%) on each day of dosing (Fig. 3). No significant elevation in either blood pressure or heart rate was observed above pre-

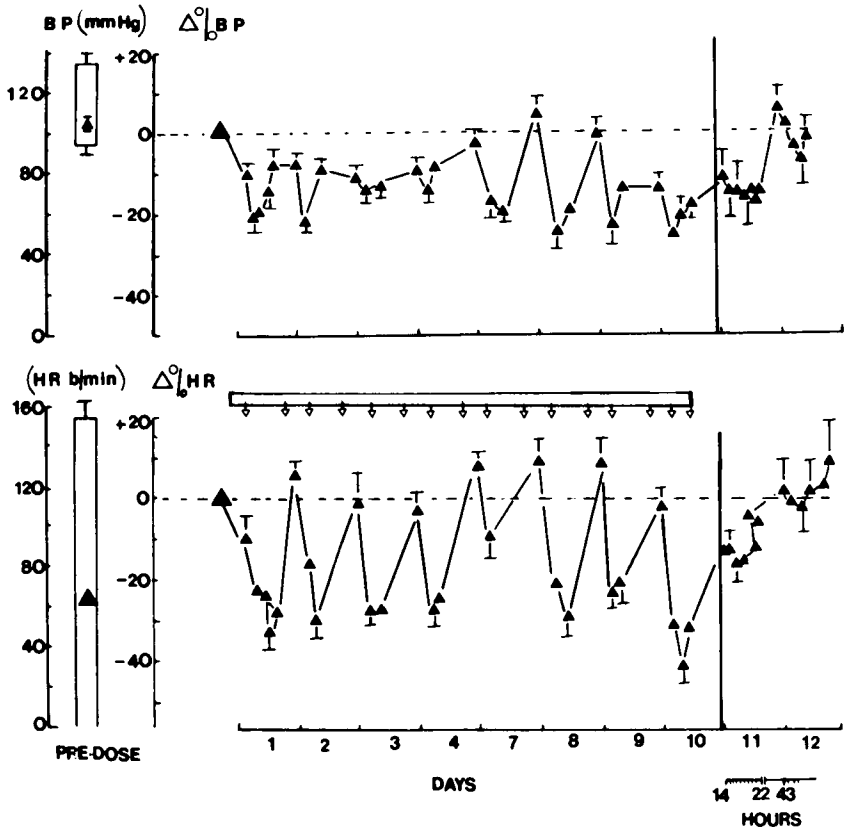

FIG. 3. Conscious renal hypertensive cats. The average blood pressure (mm Hg) and heart rate (b min^{-1}) measured during 5 h daily recordings on three consecutive days (pre-dose), before oral administration of either tiamenidine (n = 5) or placebo (n = 7) in two groups of cats. Δ% in blood pressure (BP) or heart rate (HR) measured during 6 days (1–6) of treatment with either tiamenidine (0·25 mg × 3 daily; ▲—▲), or placebo (×3 daily; △—△). Measurements were recorded at 10.30, 12.00 and 15.30 h on days 1, 2, 4, 6, no recordings were made on days 3 or 5. On days 7 and 8, BP and HR readings were recorded at 1 h intervals (14–22 and 43–46 h after the last dose). Vertical bars indicate s.e.m. * $P < 0·05$; ** $P < 0·01$ compared with placebo, or pre-dose data. Horizontal bar indicates duration of treatment, ↓ indicates incidence of dosing.

dose levels in any cats on either days 7 or 8 after cessation of placebo treatment (Fig. 3).

DISCUSSION

A study of the cardiovascular effects induced after cessation of chronic oral treatment with clonidine or tiamenidine has been described in the conscious hypertensive cat. Significant and long-lasting tachycardia commencing 14–16 h after the final dose of either clonidine (0·05 mg × 3 daily) or tiamenidine (0·25 mg × 3 daily) was elicited in all cats studied. Equi-effective hypotension and bradycarida was elicited by both clonidine and tiamenidine during treatment, however, the morning (10.30) readings of blood pressure and heart rate were not significantly reduced from pre-dose data, indicating a fluctuation in these parameters over a 24 h period. Overshoot hypertension was only observed in two out of five cats under the conditions of this experiment with no evidence of overshoot after cessation of LA clonidine treatment in the same cats.

Our data indicate that imidazoline withdrawal syndrome in cats is mainly and consistently associated with overshoot tachycardia. Similar evidence has been presented in normotensive rats (Dix & Johnson 1977). While data such as catecholamine concentrations, or heart rate may provide useful indices of 'rebound' and withdrawal phenomena, the most important clinical parameter remains the rapid and potentially dangerous elevation in blood pressure elicited after abrupt cessation of imidazoline therapy. Zamboulis et al (1978) demonstrated an increase in plasma catecholamine concentrations, after cessation of treatment with guanfacine in man, without observing increases in either blood pressure or heart rate. In the present study, no evidence of blood pressure overshoot was observed after cessation of tiamenidine treatment, although significant overshoot tachycardia was demonstrated. Therefore extrapolation of these data to man, in order to predict the possibility of cardiovascular withdrawal phenomena should only be made with caution.

When the same cats were treated with a lower dose regime of clonidine followed by abrupt cessation of treatment, no overshoot in blood pressure or heart rate was seen, thus providing some evidence of a dose-effect relationship for withdrawal effects in cats. Reid et al (1977) found one incidence when a lower dose of clonidine in man failed to induce withdrawal effects on cessation of treatment, however, Hunyor et al (1973) failed to note any correlation between clonidine dose and overshoot severity in man. Similarly no evidence of a dose-effect relationship for withdrawal syndrome was demonstrated in rats (Oates et al 1978b). That a withdrawal phenomenon is repeatable is suggested by the observation of overshoot tachycardia after cessation of tiamenidine treatment in the same animals, which previously gave a positive overhsoot upon cessation of clonidine treatment.

The data indicate that clonidine prepared in a long acting formulation may not induce overshoot in either blood pressure or heart rate up to 44 h after cessation of treatment in contrast to the results obtained with SF clonidine. It has been suggested that after cessation of SF clonidine a gradual withdrawal of clonidine treatment in patients would be an effective means of preventing overshoot (Pettinger 1975), although incidences of overshoot have been reported after gradual withdrawal of clonidine treatment (Cairns & Marshall 1976; Van Holder et al 1977). The possibility that the rate of elimination of clonidine, rather than critical plasma concentration, is a determining factor of the incidence of withdrawal phenomenon has yet to be studied. The preparation of LA clonidine used was an experimental formulation (Boehringer Ingelheim), which has since been modified for inclusion in clinical studies.

Treatment with LA clonidine was continued for 10 days rather than the 6 day treatment with SF clonidine, or tiamenidine. Although the total daily dose of LA clonidine was greater (0·1 mg × 2 daily) than SF clonidine (0·05 mg × 3 daily), LA clonidine did not influence food intake. Marked aphagia was demonstrated in all cats treated with SF clonidine, or tiamenidine and precluded longer periods of dosing with these agents. Clonidine has been shown to reduce fluid and food intake after peripheral treatment in rats (Atkinson et al 1978b), whereas after direct central administration the opposite effects of stimulated eating behaviour have been observed (Leibowitz 1970; Broekkamp & van Rossum 1972). It is unclear at this time why longer term treatment with LA clonidine in the present study failed to alter food intake, although similar effects have recently been observed in dogs (Finch and Hicks: unpublished observations).

Though evidence is available in rats, particularly the hypertensive models, of a syndrome that resembles the clinical picture of imidazoline withdrawal, further animal models are required to study the effects induced by cessation of antihypertensive drugs. More accurate, long term measurements of pre-dose data are essential and consideration of factors, such as lability of blood pressure, some-

times seen in hypertensive animals, and the circadian rhythm are also important.

This paper provides evidence that the cat may also be a useful model in which to study some aspects of the imidazoline withdrawal phenomena, it is, however, clear that not all animals in any one group may respond positively on withdrawal of treatment. Furthermore, administration of clonidine in a three times daily schedule resulted in daily fluctuations, rather than sustained falls, in blood pressure or heart rate.

At equieffective hypotensive and bradycardic doses, both SF clonidine or tiamenidine induced sustained overshoot tachycardia that commenced within a defined time after abrupt cessation of treatment. No evidence of cardiovascular withdrawal effects were obtained on cessation of treatment with either a low dose of SF clonidine or with LA clonidine in the same cats.

Acknowledgements

The authors wish to express their gratitude to Hoechst Pharmaceuticals for gifts of tiamenidine, also to Boehringer Ingelheim for their financial support.

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