J. Pharm. Pharmacol. 1982, 34: 188–190
Communicated September 25, 1981

0022–3573/82/030188–03 $02.50/0


# The effects of captopril on blood pressure and fluid and electrolyte balance in rats made hypertensive by isolation

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Currently, there is widespread interest in the use of angiotensin converting enzyme inhibitors (CEI) for the treatment of arterial hypertension. The orally active CEI captopril (D-3-mercapto-2-methyl-propranoyl-L-proline; SQ14225) lowers blood pressure (BP) in hypertensive man and in several animal models of hypertension (Heel et al 1980), although the mechanism of action remains to be determined.

We have shown that housing rats individually in glass metabolism cages causes systolic arterial hypertension (Gardiner & Bennett 1977). Earlier (Bennett & Gardiner 1979), we suggested that isolation-induced hypertension in rats may be a useful animal model for human hypertension since it is susceptible to treatment with the clinically effective β-adrenoceptor antagonists—a phenomenon not consistently seen in other animal models.

In the present work we have studied the effects of captopril on BP in rats made hypertensive by short-term isolation. In addition, fluid and electrolyte balances were monitored to determine whether any effects of captopril on BP could be explained by a change in the renal handling of salt and water.

## *Methods*

Ten male Wistar rats (230–260 g) were given free access to food (Heygates diet 41B; sodium; 0·26 mmol $g^{-1}$; potassium; 0·20 mmol $g^{-1}$) and water throughout the experiment. Room temperature was maintained between 20 and 24 °C; lights were on from 07.00 h to 19.00 h. All measurements were made between 07.00 h and 09.30 h.

Rats were randomly allocated to either a control group (n = 5) or a captopril-treated group (n = 5). The experiment was performed on a single blind basis such that the person measuring BP was unaware of the groupings.

*Blood pressure.* Systolic BP was measured daily in conscious rats by the tail-cuff method (W & W Electronics BP recorder 8005). Four consecutive cycles were performed on each animal and the mean of the last three recordings was taken as systolic BP. Measurements were made for a week whilst the animals were housed in groups and the recordings made on the last 5 days were noted. Rats were then transferred to individual glass metabolism cages (Metabowl, Jencons) and left undisturbed for 5 days; this is referred to as *continuous* isolation. Thereafter, the animals were housed in isolation except for a short period each day when they were grouped and handled for the measurement of BP; this is referred to as *intermittent* isolation. In the text the days have been numbered, day 0 being the first day of individual housing.

*Fluid and electrolyte balances.* Measurements of fluid and electrolyte intakes and outputs began 3 days before drug administration (day 10) and continued for 3 days after the last drug administration (day 27). Details of the methods used for measuring sodium, potassium and water balances have been described by Bennett & Gardiner (1978).

*Drug administration.* Captopril was administered in the drinking water between days 12 and 24. Its concentration was adjusted daily according to the water intake such that each rat received a dose of approximately 25 mg $kg^{-1}$ $day^{-1}$. Control animals received tap water.

*Statistical analysis.* Results are expressed as the mean value ±1 standard error of the mean (s.e.m.); n is the number of animals. Results were analysed for statistical significance using Student's paired or unpaired *t*-test as appropriate.

## *Results*

*Blood pressure.* Five days of continuous isolation in a glass metabolism cage caused a significant systolic arterial hypertension in both groups (Fig. 1) and BP remained high during the following 7 days of intermittent isolation ($P < 0.05$ on each day).

When captopril was introduced into the drinking water there was a reduction in BP which was significant ($0.01 > P > 0.001$) by the second day of drug administration (Fig. 1) and BP continued to fall on the following two

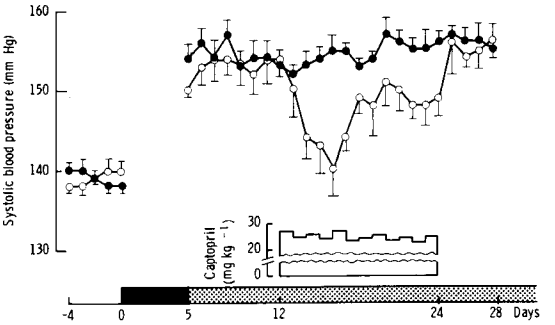


FIG. 1. Systolic blood pressure (mean ± s.e.m.) of rats made hypertensive by 5 days of continuous isolation (■) and subsequently given a captopril solution (0; n = 5) to drink whilst being housed in intermittent isolation (▨); the daily captopril intake by each animal was noted and the mean values are recorded.

* Correspondence.

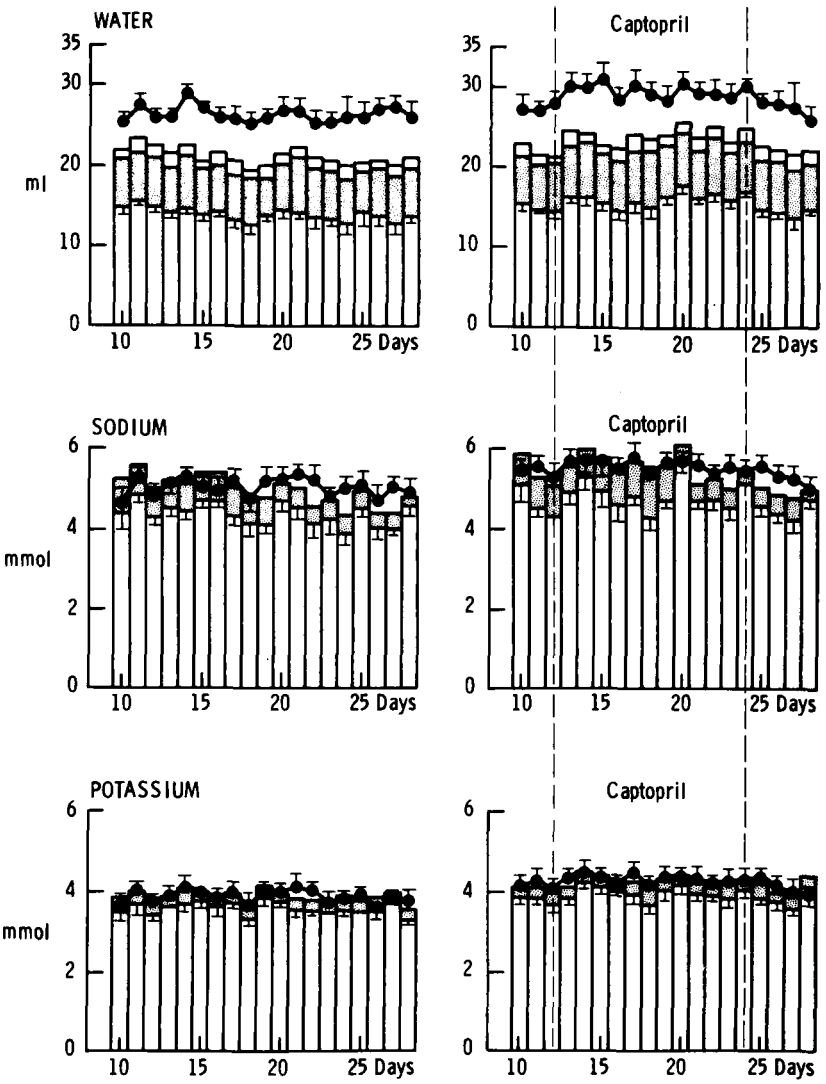


FIG. 2. Intakes and measured outputs (mean ± s.e.m.) of water, sodium and potassium by control rats (left hand column; n = 5) and rats given a captopril solution to drink (right hand column; n = 5). In each case the filled circles represent intake from the food and water combined. The total block of the histogram represents output which comprises: urinary output—open section (lowermost), faecal output–stippled. The third component of the water output (uppermost open section) represents the weight loss incurred during the period of heating prior to the measurement of blood pressure. There were no significant changes in the intakes or measured outputs of sodium, potassium or water throughout the experiment.

days of treatment. However BP then began to increase, despite continued drug administration, and reached a plateau which, although still significantly lower than the pre-treatment value ($P < 0{\cdot}05$), was higher than the value at the nadir of the pressure change (Fig. 1). When the treatment was stopped there was a prompt rise of BP back to a level not significantly different from the pre-treatment value (Fig. 1).

Blood pressure remained high in the control animals throughout the period of isolation (Fig. 1).

*Fluid and electrolyte balances.* There were no significant differences between the intakes or measured outputs of sodium, potassium or water in the 2 groups throughout the experiment (Fig. 2).

*Discussion*

We have shown that in rats made hypertensive by short-term isolation, captopril lowers BP without any accompanying change in the renal handling of salt and water. Systolic BP gradually fell on the first 4 days of treatment to

become not significantly different from the pre-isolation value. However, during subsequent days, BP rose to become significantly higher than before isolation but still less than the pre-treatment value, although this difference was small.

In most reports on the effects of captopril on BP the antihypertensive effect persists for as long as the treatment is continued (see Bengis et al 1978; Heel et al 1980). However, Clappison et al (1980) infused captopril into normotensive rats and measured a fall in BP on the first two days but observed that it returned to resting levels whilst the treatment was continued, and Saragoca et al (1979) reported a progressive loss of effectiveness of captopril in hypertensive man; the reason for this transient response is unclear.

The mechanisms responsible for the effects of captopril on BP are confusing, since converting enzyme inhibition not only reduces circulating angiotensin II (AII) levels but also potentiates the kallikrein-kinin system by inhibiting kininase (Heel et al 1980). Elevated blood or renal kinins may stimulate renal prostaglandin synthesis, particularly if the background activity of the renin-angiotensin system is low (Barr et al 1980). It is likely, therefore, that the antihypertensive effect of captopril is mediated by different mechanisms depending on the aetiology of the hypertension.

A reduction in circulating AII, an accumulation of plasma kinins and an increase in prostaglandin synthesis could all lower BP by a number of different processes affecting the peripheral vasculature and/or renal function. Bengis et al (1978) studied the effects of captopril on BP and fluid and electrolyte balance in normal rats and in rats with different forms of renal hypertension in which plasma renin activity was high, normal or low. They described two components to the effects of captopril; firstly a rapid fall in BP which was present only in the high renin states and which they attributed to inhibition of the vasoconstrictor influence of AII; secondly, a slower reduction in BP which occurred over a period of days, and which was accompanied by a diuresis and natriuresis. The natriuresis could have resulted from either a reduction in AII or an increase in kinins or prostaglandins (Bengis et al 1978). But in spontaneously hypertensive rats, in which there is no consistent finding of increased plasma renin activity, the antihypertensive effect of captopril is not accompanied by a diuresis or natriuresis (Muirhead et al 1978); in those animals the reduction in BP is attributable to a fall in total peripheral resistance.

Our findings resemble those of Muirhead et al (1978) since we observed a reduction in BP in response to captopril with no change in renal salt and water handling; we also have no evidence for activation of the renin-angiotensin system in isolation-induced hypertension (Bennett & Gardiner 1979). It is possible, therefore, that BP may have been lowered by a peripheral vasodilatation in our isolated rats.

The mechanisms responsible for the effects of captopril on peripheral resistance are still speculative. Under some conditions it is likely that the renin-angiotensin system, although not hyperactive, still supports the BP through the vasoconstrictor effect of AII. However bradykinin and prostaglandins are both vasodilators and could therefore mediate the vascular response to captopril. Recently Antonaccio & Kerwin (1980) have shown that treatment with captopril causes a prejunctional inhibition of noradrenaline release due to a reduction in the formation of AII in the vasculature; this provides another possible explanation for the effects of captopril on the peripheral vasculature.

We wish to thank the Squibb Institute for Medical Research, Princeton, New Jersey, for the generous donation of captopril.

This work was supported by grants from the British Heart Foundation (S.M.G.) and Science Research Council (K.E.M.) which are gratefully acknowledged.

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