British Journal of Pharmacology (1995) 116, 2161-2165 

# Ramipril-induced decrease in renal lithium excretion in the rat

[1]Mariette Barthelmebs, Michèle Grima & Jean-Louis Imbs

Institut de Pharmacologie (CNRS), Faculté de Médecine, Université Louis Pasteur, 11 rue Humann, 67000 Strasbourg, and Service d'Hypertension et Maladies vasculaires, Hôpitaux Universitaires de Strasbourg, France

**1** The interaction of ramipril, an inhibitor of angiotensin I converting enzyme, with renal lithium handling was analysed in conscious normotensive Wistar rats and compared with the known increase in renal tubular lithium reabsorption induced by the non-steroidal anti-inflammatory drug, indomethacin.

**2** The rats were treated for five days with ramipril (1 mg $kg^{-1}$ $day^{-1}$ orally), indomethacin (2.5 mg $kg^{-1}$ $day^{-1}$ intramuscularly) or their solvents. Lithium chloride (16.7 mg $kg^{-1}$ intraperitonealy) was given as a single dose on the fifth day and renal functions were measured.

**3** Ramipril induced a decrease in renal lithium clearance which was correlated with the decrease in the quantity of filtered lithium and the increase in the tubular fractional reabsorption of the metal. Ramipril also reduced the systolic blood pressure of the rats by about 15 mmHg.

**4** In the absence of any effect on creatinine clearance or systolic blood pressure, indomethacin increased renal fractional lithium reabsorption and led to an increase in plasma lithium levels, as previously reported by our group.

**5** In conclusion, our results indicate that ramipril decreases renal lithium excretion in Wistar rats, when given orally at a dose of 1 mg $kg^{-1}$ $day^{-1}$ over five days.

**Keywords:** Ramipril; lithium renal excretion; indomethacin

## Introduction

Lithium is an effective therapy for manic-depressive illness but its prescription can pose problems, on account of its narrow therapeutic index. The pharmacokinetics of lithium are highly dependent on renal excretion, a decrease of which can lead to toxic plasma concentrations of lithium.

In recent years, several clinical observations have reported signs of lithium intoxication following antihypertensive treatment with angiotensin I converting enzyme (ACE) inhibitors, in patients who had previously been well stabilized under lithium therapy. An increase in lithium plasma concentration has been reported with enalapril (Simon *et al.*, 1983; Douste-Blazy *et al.*, 1986; Mahieu *et al.*, 1988; Drouet & Bouvet, 1990; Correa & Eiser, 1992), captopril (Pulik & Lida, 1987) and lisinopril (Baldwin & Safferman, 1990; Griffin & Hahn, 1991; Correa & Eiser, 1992). Toxic effects have been seen after varying duration of treatments, ranging from 10 days to over 2 months. The mechanism of the interaction of ACE inhibitors with lithium handling is not known. A mechanism similar to that of diuretics has been suggested: the natriuresis induced by ACE inhibitors could have led to sodium depletion which increased lithium tubular reabsorption (Atherton *et al.*, 1990).

The aim of the present work was to evaluate in rats the interaction of ACE inhibitors with renal lithium excretion, suggested by clinical reports. The study was carried out in conscious Wistar rats, according to a protocol previously used in our laboratory for the study of the interaction of non-steroidal anti-inflammatory drugs (NSAIDs) with renal lithium handling (Imbs *et al.*, 1980; Barthelmebs *et al.*, 1992). The effects of a 5 day-treatment with an ACE inhibitor, ramipril, on renal lithium clearance were compared with those of indomethacin, included as a reference treatment. In a parallel study, we found no effect of losartan, a non-peptide specific $AT_1$ antagonist (Wong *et al.*, 1990), on the renal handling of lithium (Barthelmebs *et al.*, 1995).

[1] Author for correspondence.

## Methods

Male Wistar rats (Janvier, Le Genest-St-Isle, France), with a mean weight of 253 ± 2 g (mean ± s.e.mean), were randomized into four groups of 18 animals: one group was treated with indomethacin (2.5 mg $kg^{-1}$ $day^{-1}$ intramuscularly), another group received ramipril (1 mg $kg^{-1}$ $day^{-1}$ by gavage) and two control groups were treated with the respective solvents. Complete data could not be obtained in four animals (one treated by indomethacin and three animals receiving indomethacin-solvent).

### *Experimental protocol*

The experimental protocol was similar to that described previously (Imbs *et al.*, 1980) and also used in our study with losartan (Barthelmebs *et al.*, 1995). Briefly, the rats were given their daily treatment between 08 h 00 min and 10 h 00 min for 5 days. Until the morning of the 5th day, they had free access to drinking water and normal sodium standard food (AO4 pellets, $Na^+$ content = 0.4%, UAR, Villemoisson/Orge, France). On the 3rd day, 3 h after drug administration, systolic blood pressure was measured in conscious animals by tail plethysmography (Physiograph Desk Model DMP 4A, Narco Bio System Inc., Houston, Texas, U.S.A.) and the heart rate was calculated from this recording. In the evening of the 4th day, the animals were placed in individual metabolic cages (Iffa Credo, L'Arbresle, France) for a 14 h adaptation period. Renal functions were measured on the 5th day, using a 2 h urine collection. In addition to their daily treatment on day 5 (at T0), the animals were given an intraperitoneal injection of lithium chloride (16.4 mg $kg^{-1}$ at T0) and two subcutaneous injections of distilled water (16 ml $kg^{-1}$ at T0 and 8 ml $kg^{-1}$ at T0 + 2h). Urine was collected between T0 + 2h and T0 + 4h. Care was taken to ensure that the bladder was empty at the beginning and the end of the clearance period. Blood samples were drawn from the tail vein before and after the urine collection period for plasma lithium assays. At the end of the clearance period, blood was drawn by cardiac puncture under ether anaesthesia to measure plasma creatinine, sodium and potassium concentrations together with plasma renin activity (PRA) and ACE activity. The urinary lithium, creatinine, sodium, potassium and phosphate concentrations were also determined.

The entire experimental protocol was conducted in a room with controlled temperature (21 ± 1°C), relative humidity (49 ± 5%) and a 12h/12h day-night cycle.

### *Measurements, analytical methods and calculations*

Urine volume was recorded. The following measurements were carried out on the plasma and urine: lithium by atomic emission spectrophotometry (Pye Unicam SP9, Philips, Bobigny, France), creatinine by Jaffé's method (Autoanalysor II, Technicon, Domont, France), sodium and potassium by indirect potentiometry (Synchron EL-ISE, Beckman, Gagny, France). The urinary phosphate concentration was determined after complexing with ammonium molybdate (Beckman Clinical System 700). The renal excretions, clearances and fractional reabsorptions of electrolytes were calculated according to the standard formulae. Endogenous creatinine clearance was used as a measure of glomerular filtration rate. PRA was assayed by incubation of plasma at 37°C for 30 min (kit SBREN II TP6, CIS Bio International, Gif/Yvette, France) and expressed in ng of angiotensin I (AI) formed per ml of plasma per h. AI was measured by radioimmunoassay using [$^{125}$I]-AI (NEN, Du Pont de Nemours, Les Ulis, France) and a specific antibody provided by Dr J. Nussberger (Lausanne, Switzerland). Plasma ACE activity was determined according to the method of Unger *et al.* (1982) with the modifications of Welsch *et al.* (1989).

### *Drugs*

Ramipril (Laboratoires Hoechst, Paris, France) was administered by gavage at a dose of 1 mg kg$^{-1}$ day$^{-1}$ in 2 ml distilled water. Indomethacin (Merck, Sharp & Dohme-Chibret, Paris, France) was administered by intramuscular injection at a dose of 2.5 mg kg$^{-1}$ day$^{-1}$ in 2 ml kg$^{-1}$ distilled water, in the form of the N-methyl-D-glucamine salt (1.36 mg kg$^{-1}$, final pH of the solution = 6).

Ramipril solvent (2 ml distilled water kg$^{-1}$ day$^{-1}$) was administered by gavage. Indomethacin solvent, a solution of N-methyl-D-glucamine (Fluka, Buchs, Switzerland) at 1.36 mg kg$^{-1}$ in 2 ml distilled water (pH adjusted to 6), was administered by intramuscular injection.

### *Statistics*

The results are expressed as the mean ± s.e.mean. Statistical differences between groups were identified by Student's *t* test adapted according to Bonferroni for multiple comparisons. The Pearson correlation coefficient and partial correlation coefficients were calculated when appropriate. The analyses were performed with BMDP statistical software (BMDP Statistical Software Ltd, Cork, Ireland). A value of $P < 0.05$ was considered to be significant.

## Results

The ramipril and indomethacin effects were evaluated by comparison with the group receiving the corresponding solvent. There were no significant differences between the two solvent groups for any parameter (Tables 1 to 3).

**Table 1** Effects of ramipril and indomethacin on creatinine clearance and renal handling of lithium measured after five days of treatment

| *Treatment* | *Indomethacin* (17) | *Indomethacin solvent* (15) | *Ramipril* (18) | *Ramipril solvent* (18) |
|---|---|---|---|---|
| Creatinine clearance (μl min$^{-1}$ 100 g$^{-1}$) | 423 ± 27 | 479 ± 32 | 382 ± 25** | 502 ± 21 |
| Lithium filtered (nmol min$^{-1}$ 100 g$^{-1}$) | 140 ± 10 | 144 ± 10 | 127 ± 9 | 149 ± 7 |
| Lithium clearance (μl min$^{-1}$ 100 g$^{-1}$) | 53 ± 6*** | 114 ± 11 | 72 ± 8*** | 129 ± 8 |
| Lithium reabsorption (%) | 86.87 ± 1.08*** | 75.14 ± 1.44 | 79.72 ± 1.77** | 73.01 ± 1.32 |
| Lithium excretion (nmol min$^{-1}$ 100 g$^{-1}$) | 18.0 ± 1.7*** | 36.0 ± 3.3 | 25.3 ± 2.8*** | 40.0 ± 2.4 |

The results are expressed as mean ± s.e.mean and were compared by Student's *t* test adapted by Bonferroni for multiple comparisons. **$P < 0.01$, ***$P < 0.001$ compared to corresponding solvent group; the number of animals in each group is given in parentheses.

**Table 2** Effects of ramipril and indomethacin on other urinary parameters measured after five days of treatment

| *Treatment* | *Indomethacin* (17) | *Indomethacin solvent* (15) | *Ramipril* (18) | *Ramipril solvent* (18) |
|---|---|---|---|---|
| Sodium filtered (μmol min$^{-1}$ 100 g$^{-1}$) | 62 ± 4 | 71 ± 5 | 56 ± 4** | 75 ± 3 |
| Sodium reabsorption (%) | 99.88 ± 0.01** | 99.71 ± 0.04 | 99.80 ± 0.03 | 99.74 ± 0.04 |
| Sodium excretion (μmol min$^{-1}$ 100 g$^{-1}$) | 0.07 ± 0.01*** | 0.21 ± 0.033 | 0.12 ± 0.015* | 0.20 ± 0.03 |
| Potassium excretion (μmol min$^{-1}$ 100 g$^{-1}$) | 0.38 ± 0.03* | 0.55 ± 0.05 | 0.47 ± 0.04** | 0.65 ± 0.04 |
| Phosphate excretion (nmol min$^{-1}$ 100 g$^{-1}$) | 34 ± 10(*) | 76 ± 19 | 37 ± 9* | 87 ± 16 |
| Diuresis (μl min$^{-1}$ 100 g$^{-1}$) | 5.50 ± 0.82 | 8.36 ± 0.85 | 4.42 ± 0.82*** | 8.65 ± 0.78 |

The results are expressed as mean ± s.e.mean and were compared by Student's *t* test adapted by Bonferroni for multiple comparisons. (*)$P < 0.10$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared to corresponding solvent group; the number of animals in each group is given in parentheses.

**Table 3** Effects of ramipril and indomethacin on the plasma parameters

| Treatment | Indomethacin (17) | Indomethacin solvent (15) | Ramipril (18) | Ramipril solvent (18) |
|---|---|---|---|---|
| Plasma creatinine ($\mu$M) | 42.1 ± 1.2 | 41.7 ± 1.4 | 40.6 ± 1.1 | 43.1 ± 1.0 |
| Plasma sodium (mM) | 152 ± 1.3 | 153.7 ± 1.5 | 153.6 ± 1.5 | 154.8 ± 1.5 |
| Plasma potassium (mM) | 4.74 ± 0.20 | 4.88 ± 0.26 | 4.88 ± 0.20 | 4.55 ± 0.14 |
| Plasma lithium (mM) | 0.350 ± 0.013* | 0.319 ± 0.009 | 0.348 ± 0.008* | 0.315 ± 0.013 |
| Plasma renin activity (ng AI $ml^{-1}$ $h^{-1}$) | 78.2 ± 10 | 72.3 ± 5.5 | 197.7 ± 12.5*** | 94.6 ± 9.6 |
| Plasma ACE activity (nmol His-Leu $min^{-1}$ $mg^{-1}$) | 4.30 ± 0.34 | 4.12 ± 0.36 | 5.31 ± 0.49(*) | 4.22 ± 0.31 |

The results are expressed as mean ± s.e.mean and were compared by Student's $t$ test adapated by Bonferroni for multiple comparisons. (*)$P<0.10$, *$P<0.05$, ***$P<0.001$ compared to corresponding solvent group; results for plasma lithium were analysed by a one-tailed test; the number of animals in each group is given in parentheses.

### *Effects of ramipril*

A 5 day-treatment with ramipril (1 mg $kg^{-1}$ $day^{-1}$) decreased the urinary excretion and renal clearance of lithium by about 40% (Table 1). These effects were accompanied by an increase in the fractional tubular reabsorption of lithium and an increase in plasma lithium concentration (Table 3). Ramipril also decreased creatinine clearance by about 25%. Lithium clearance correlated strongly and independently (partial correlations) with creatinine clearance ($r=0.761$, $P<0.001$, ramipril and corresponding solvent-treated groups, $n=36$), filtered lithium ($r=0.499$, $P<0.002$) and tubular lithium reabsorption ($r=-0.766$, $P<0.001$). The variations in tubular reabsorption of lithium accounted for more than half ($R^2=0.59$) of the variations in lithium clearance while the non-significant changes in filtered lithium contributed to a lesser degree ($R^2=0.25$). Ramipril decreased the systolic blood pressure measured on the third day of treatment (104 ± 3 versus 119 ± 3 mmHg in solvent-treated group, $P<0.01$) without any significant effect on the heart rate (424 ± 7 versus 402 ± 7 beats $min^{-1}$). Endogenous creatinine clearance measured on day 5 correlated with systolic blood pressure on day 3 ($r=0.490$, $P<0.01$). In an additional experiment using a similar protocol, we evaluated the effects of ramipril on blood pressure on the fifth day of treatment and found a similar significant decrease in the systolic blood pressure (91 ± 4 versus 112 ± 4 mmHg in the solvent-treated group, $n=12$ per group, $P<0.005$).

The urinary excretions of sodium, potassium and phosphate were all reduced significantly by the ACE inhibitor, as was urine output (Table 2). The excretion of lithium correlated with those of sodium ($r=0.631$, $P<0.001$), potassium ($r=0.816$, $P<0.001$) and phosphate ($r=0.537$, $P<0.001$).

PRA activity doubled and plasma ACE activity tended to increase on the 5th day of treatment with ramipril when compared to corresponding solvent-treated group (Table 3).

### *Effects of indomethacin*

Indomethacin affected the renal excretion of lithium in a manner similar to previous results from our laboratory (Imbs *et al.*, 1980): indomethacin decreased the lithium urinary excretion and renal clearance by increasing the tubular reabsorption of the metal (Table 1). The excretions of sodium, potassium and phosphate were also decreased (Table 2). The plasma lithium concentration was increased (Table 3). However, unlike ramipril, indomethacin had no effect on either the systolic blood pressure (115 ± 3 versus 115 ± 5 mmHg in the solvent-treated group) measured in conscious animals on the third day of treatment or on the creatinine clearance (Table 1). Heart rate was also unchanged (410 ± 7 versus 393 ± 7 beats $min^{-1}$).

## Discussion

Our results demonstrate that the ACE inhibitor, ramipril, is able to decrease the renal lithium clearance in rats and subsequently increase the plasma lithium concentration. This result confirms the interaction suggested by clinical case reports, in which antihypertensive treatment with ACE inhibitors has led to lithium intoxication in patients previously well stabilized under lithium therapy (Douste-Blazy *et al.*, 1986; Pulik & Lida, 1987; Griffin & Hahn, 1991; Correa & Eiser, 1992). Since toxic effects of lithium have been reported with several ACE inhibitors (enalapril, captopril, lisinopril) but not with other antihypertensive treatments such as nifedipine (Douste-Blazy *et al.*,1986; Drouet & Bouvet, 1990), betaxolol (Mahieu *et al.*, 1988) or clonidine (Baldwin & Safferman, 1990), the interaction seems to be specific for the therapeutic class rather than linked to the antihypertensive effect. Present data indicate that the ramipril-induced decrease in the renal lithium clearance results from two mechanisms: a rise in the tubular lithium reabsorption together with a decrease in glomerular filtration rate reducing the amount of filtered lithium. The first mechanism seems to be the more important.

The ramipril-lithium interaction probably takes place in the proximal tubule, since lithium reabsorption mainly occurs in this tubular segment and is considered as a valid indicator of proximal tubular sodium reabsorption (Leyssac, 1990; Koomans & Dorhout Mees, 1990). Permeability to lithium has been shown in more distal parts of the nephron, but the contribution to overall lithium reabsorption is small when sodium intake is normal (Greger, 1990). The strong correlation we found between lithium and phosphate excretions strengthens the case for a predominantly proximal tubular site for ramipril-induced rises in lithium reabsorption, since phosphate reabsorption mainly occurs in the proximal tubule (Knox *et al.*, 1973). A ramipril-induced increase in proximal tubular sodium reabsorption would be expected to decrease the distal sodium load and subsequent potassium excretion, as found in the present study.

These results with ramipril differ from those obtained with losartan, a non-peptide antagonist of $AT_1$ receptors (Wong *et al.*, 1990), after a 5 day-treatment in a similar experimental protocol (Barthelmebs *et al.*, 1995), since losartan did not modify the renal lithium excretion in normotensive rats. This difference cannot be due to a difference in the inhibition of the renin-angiotensin system (RAS), since the doses of ramipril and losartan were chosen to inhibit the RAS throughout 24 h periods. This was the case with ramipril at 1 mg $kg^{-1}$ $day^{-1}$, which still reduced the plasma AII/AI ratio by 85% 24 h after the final dose was administered (Grima *et al.*, 1993). Four hours after ramipril treatment, we found no inhibition of the plasma ACE activity but rather an increase. This result is in line with the induction in plasma and lung ACE reported after chronic treatment with ACE inhibitors and linked to an increase in enzyme concentration (Fyhrquist *et al.*, 1980). This

induction makes it difficult to estimate *in vivo* ACE inhibition by *in vitro* measurement of its activity (Michel *et al.*, 1993). The *in vivo* inhibition of the RAS by ramipril was however evident in our study from the increase in PRA, linked to a decrease in the negative feedback of AII on renin release. A similar increase in PRA has been seen after losartan treatment (Barthelmebs *et al.*, 1995).

It is unlikely that the direct inhibition of the intra-renal tubular effects of AII could explain the increase in proximal tubular reabsorption of lithium and sodium. AII increases sodium reabsorption via proximal tubular $AT_1$ receptors (Cogan *et al.*, 1991) and ACE inhibitors induce an acute natriuretic effect in rats (Sakamoto *et al.*, 1994) and man (Sanchez *et al.*, 1985). This could lead to sodium depletion during chronic treatment. A negative sodium balance is known to increase lithium reabsorption, as documented with diuretics (Atherton *et al.*, 1990). A similar mechanism could be involved in ramipril-induced increase in lithium reabsorption in the present study. However, the same effect was not seen with losartan (Barthelmebs *et al.*, 1995). ACE inhibitors not only reduce conversion of AI to AII but also inhibit bradykinin breakdown (Ehlers & Riordan, 1990). The increase in renal bradykinin-(1–9) level (Campbell *et al.*, 1994) contributes then to a more marked acute natriuresis after ramipril when compared to losartan (Sakamoto *et al.*, 1994), and possibly to a more pronounced chronic negative sodium balance. The influence of salt depletion in the first days after the beginning of ramipril treatment remains to be confirmed in our experimental conditions as well as the contribution of bradykinin to these effects.

A potentiation of endogenous bradykinin can also be involved in the lowering of blood pressure which is observed in ramipril- but not in losartan-treated normotensive rats. A specific bradykinin $B_2$-receptor antagonist was shown to attenuate the antihypertensive action of ramipril (Bao *et al.*, 1992). Since the RAS participates in the autoregulation of renal haemodynamics (Hall *et al.*, 1977; Brunner *et al.*, 1987), a progressive decrease in glomerular filtration rate can be expected when the inhibition of the RAS is associated with a fall in renal perfusion pressure. This is consistent with the correlation we found between ramipril-induced decrease in creatinine clearance and systolic blood pressure. An alteration in glomerular function participates in the ramipril-induced decrease in lithium clearance in our study. A similar mechanism seems to play a role in the patients with toxic interaction of ACE inhibitors with lithium. A decrease in glomerular filtration rate has been reported in these patients, often slight (Douste-Blazy *et al.*, 1986; Mahieu *et al.*, 1988; Drouet & Bouvet, 1990), but sometimes larger (Simon *et al.*, 1983; Correa & Eiser, 1992).

In conclusion, a 5 day-treatment with ramipril, decreases the renal lithium clearance in normotensive rats mainly through an increase in the tubular reabsorption of lithium and also via a decrease in the glomerular filtration rate. Since losartan did not modify renal lithium excretion in a previous study, the role of ramipril-induced potentiation of bradykinin in the difference in the two drugs' behaviour with regard to renal lithium handling, remains to be elucidated.

The authors are grateful to Dr Wybren de Jong for fruitful discussion and to Christian Fontaine, Antoine Jund and Catherine Coquard for skilful technical assistance. They also gratefully acknowledge the gift of ramipril from Hoechst (Paris, France) and that of indomethacin from Merck Sharp & Dohme Chibret (Paris, France).

## References

ATHERTON, J.C., GREEN, R., HIGGINS, A., LARGE, A., MCNICHOLAS, C., PARKER, D., PEMPKOWIAK, L., RAJANI, K. & SMITH, J. (1990). Lithium clearance in healthy humans: effects of sodium intake and diuretics. *Kidney Int.*, **37**, (suppl. 28), S36–S38.

BALDWIN, C.M. & SAFFERMAN, A.Z. (1990). A case of lisinopril-induced lithium toxicity. *DICP Ann. Pharmacother.*, **24**, 946–947.

BAO, G., GOHLKE, P., QADRI, F. & UNGER, T. (1992). Chronic kinin receptor blockade attenuates the antihypertensive effect of ramipril. *Hypertension*, **20**, 74–90.

BARTHELMEBS, M., DECKER, N., DANION, J.M., STEPHAN, D., WELSCH, M. & IMBS, J.L. (1992). The effects of sulindac and its active metabolite, desoxysulindac, on renal lithium excretion in the rat. *Lithium.*, **3**, 35–42.

BARTHELMEBS, M., ALT-TEBACHER, M., MADONNA, O., GRIMA, M. & IMBS, J.L. (1995). Absence of a Rosartan interaction renal lithium excretion in the rat. *Br. J. Pharmacol.*,

BRUNNER, H.R., WAEBER, B. & NUSSBERGER, J. (1987). Renal effects of converting enzyme inhibition. *J. Cardiovasc. Pharmacol.*, **9** (suppl 3), S6–S14.

CAMPBELL, D.J., KLADIS, A. & DUNCAN, A.M. (1994). Effects of converting enzyme inhibitors on angiotensin and bradykinin peptides. *Hypertension*, **23**, 439–449.

COGAN, M.G., LIU, F.Y., WONG, P.C. & TIMMERMANS, P.B.M.W.M. (1991). Comparison of inhibitory potency by nonpeptide angiotensin II receptor antagonists PD 123177 and DuP 753 on proximal nephron and renal transport. *J. Pharmacol. Exp. Ther.*, **259**, 687–691.

CORREA, F.J. & EISER, A.R. (1992). Angiotensin-converting enzyme inhibitors and lithium toxicity. *Am. J. Med.*, **93**, 108–109.

DOUSTE-BLAZY, P., ROSTIN, M., LIVAREK, B., TORDJMAN, E., MONTASTRUC, J.L. & GALINIER, F. (1986). Angiotensin converting enzyme inhibitors and lithium treatments. *Lancet*, **i**, 1448.

DROUET, A. & BOUVET, O. (1990). Lithium et inhibiteurs de l'enzyme de conversion. *L'Encéphale*, **XVI**, 51–52.

EHLERS, M.R.W. & RIORDAN, J.F. (1990). Angiotensin-converting enzyme: biochemistry and molecular biology. In *Hypertension: Pathophysiology, Diagnosis, and Management*. ed. Laragh, J.H. & Brenner, B.M. pp. 1217–1231. New York: Raven Press.

FYHRQUIST, F., FORSLUND, T., TIKKANEN, I. & GRONHAGEN-RISKA, C. (1980). Induction of angiotensin I-converting enzyme in rat lung with captopril (SQ 14225). *Eur. J. Pharmacol.*, **67**, 473–475.

GREGER, R. (1990). Possible sites of lithium transport in the nephron. *Kidney Int.*, **37**, (suppl. 28), S26–S30.

GRIFFIN, J.H. & HAHN, S.M. (1991). Lisinopril-induced lithium toxicity. *DICP Ann. Pharmacother.*, **25**, 101.

GRIMA, M., DANEL, V., STEPHAN, D., BARTHELMEBS, M. & IMBS, J.L. (1993). Evaluation de l'inhibition de l'enzyme de conversion par le rapport des concentrations plasmatiques de l'angiotensine II et I. *Arch. Mal. Coeur*, **86** (suppl), 62.

HALL, J.E., GUYTON, A.C., JACKSON, T.E., COLEMAN, T.G., LOHMEIER, T.E. & TRIPPODO, N.C. (1977). Control of glomerular filtration rate by renin-angiotensin system. *Am. J. Physiol.*, **233**, F366–372.

IMBS, J.L., SINGER, L., DANION, J.M., SCHMIDT, M. & ZAWISLAK, R. (1980). Effects of indomethacin and methylprednisolone on renal elimination of lithium in the rat. *Int. Pharmacopsychiatry*, **15**, 143–149.

KNOX, F.G., SCHNEIDER, E.G., WILLIS, L.R., STRANDHOY, J.W. & OTT, C.E. (1973). Site and control of phosphate reabsorption by the kidney. *Kidney Int.*, **3**, 347–353.

KOOMANS, H.A. & DORHOUT MEES, E.J. (1990). Lithium in renal physiology: post-conference discussion and consensus. *Kidney Int.*, **37** (suppl. 28), S78–S79.

LEYSSAC, P.P. (1990). Validity of the lithium clearance concept assessed with micropuncture studies. *Kidney Int.*, **37** (suppl. 28), S17–S21.

MAHIEU, M., HOUVENAGEL, E., LEDUC, J.J. & CHOTEAU, Ph. (1988). Lithium-inhibiteurs de l'enzyme de conversion: une association à éviter? *La Presse Médicale*, **17**, 281.

MICHEL, B., STEPHAN, D., GRIMA, M., BARTHELMEBS, M. & IMBS, J.L. (1993). Effects of one-hour and one-week treatment with ramipril on plasma and renal brush border angiotensin converting enzyme in the rat. *Eur. J. Pharmacol.*, **242**, 237–243.

PULIK, M. & LIDA, H. (1987). Captopril et lithium. *Concours Médical*, **15**, 1363.

SAKAMOTO, T., CHEN, C. & LOKHANDWALA, M.F. (1994). Contribution by bradykinin to the natriuretic response to the angiotensin converting enzyme inhibitor ramiprilat in spontaneously hypertensive rats. *Naunyn-Schmied. Arch. Pharmacol.*, **350,** 84–89.

SANCHEZ, R.A., MARCO, E., GILBERT, H.B., RAFFAELE, P., BRITO, M., GIMENEZ, M. & MOLEDO, L.I. (1985). Natriuretic effect and changes in renal haemodynamics induced by enalapril in essential hypertension. *Drugs*, **30** (suppl 1), 49–58.

SIMON, G., MORIOKA, S., SNYDER, D.K. & COHN, J.N. (1983). Increased renal plasma flow in long term enalapril treatment of hypertension. *Clin. Pharmacol. Ther.*, **34,** 459–465.

UNGER, T., SCHULL, B., RASCHER, W., LANG, R.E. & GANTEN, D. (1982). Selective activation of the converting enzyme inhibitor MK 421 and comparison of its active diacid form with captopril in different tissues of the rat. *Biochem. Pharmacol.*, **31,** 3063–3070.

WELSCH, C., GRIMA, M., GIESEN, E.M., HELWIG, J.J., BARTHELMEBS, M., COQUARD, C. & IMBS, J.L. (1989). Assay of tissue angiotensin converting enzyme. *J. Cardiovasc. Pharmacol.*, **14** (suppl 4), S26–S31.

WONG, P.C., PRICE, W.A., CHIU, A.T., DUNCIA, J.V., CARINI, D.J., WEXLER, R.R., JOHNSON, A.L. & TIMMERMANS, P.B.M.W.M. (1990). Nonpeptide angiotensin II receptor antagonist. VIII. Characterisation of functional antagonism displayed by DuP 753, an orally active antihypertensive agent. *J. Pharmacol. Exp. Ther.*, **252,** 719–720.

*(Received January 3, 1995*
*Revised June 2, 1995*
*Accepted June 9, 1995)*