Lack of effect of lithium on the renal response to DA₁-dopamine receptor stimulation by fenoldopam in normal man

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1 The effect of oral lithium (300 mg) on the renal response to the selective DA₁-dopamine receptor agonist fenoldopam was investigated in seven normal men. Lithium had no influence on sodium excretion and renal haemodynamics during fenoldopam infusion. The fenoldopam-induced rise in PRA was enhanced in the presence of lithium. We conclude that a previously described interaction between lithium and the dopamine agonist gludopa is not mediated by DA₁-dopamine receptors or is confined to higher doses of lithium.

Keywords dopamine fenoldopam renin lithium natriuresis

Introduction

There is cumulating evidence that dopamine receptors, present in the proximal tubule and responsible for direct natriuretic effects are of the DA₁-type (Felder *et al.*, 1984; MacDonald *et al.*, 1987). A recent publication (Jeffrey *et al.*, 1988) suggests that lithium interacts with dopamine at the proximal tubule.

Fenoldopam (SK & F 82526-J) is a both intravenously and orally active DA₁-dopamine receptor agonist and stimulates DA₁ receptors selectively, without any significant α - or β -adrenoceptor, or DA₂-receptor agonist activity (Hahn *et al.*, 1982).

We investigated the renal effects of intravenous fenoldopam in healthy volunteers both with and without previous lithium administration.

Methods

Seven healthy volunteers, five males and two females, age 20–57 years, mean 34 years, were studied on two occasions. Renal function was normal in all (GFR: 111 ± 9 ml min⁻¹) and none used any medication. All gave written informed consent and the study was approved by the Ethics Committee of the University Hospital of

Groningen. All volunteers were asked to abstain from animal protein containing foods on the day before and during the renal function studies and to adhere to a mildly sodium restricted diet (150 mmol sodium day⁻¹) at least 4 days before the studies. As a control, a 24 h urine sodium was checked. Throughout the renal function studies they were asked to drink at least 250 ml h⁻¹ of non-sodium containing beverages. One cup of tea and a light lunch were permitted but smoking was not allowed. The participants rested in a supine or semi-sitting position. Glomerular filtration rate (GFR) and effective renal plasma flow were measured simultaneously using ¹²⁵I-iothalamate and ¹³¹I-hippurate respectively according to the method described by Donker *et al.* (1977). Filtration fraction (FF) represents the ratio GFR/ERPF. Two renal function studies were performed, the first study day being at least 2 weeks separated from study day 2. At study day 1 and 2 after two base-line values fenoldopam was infused in ascending doses, ranging from 0.05 to 0.5 μ g kg⁻¹ min⁻¹. Each dose was given for a period of 1 h.

Nine h before renal functions tests at study day one, 300 mg lithium carbonate was taken orally and serum levels were checked at the beginning of the studies.

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At study day 2 the same procedure was followed, except that no lithium was taken.

Urine portions were examined for urinary electrolytes. Blood samples for plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were withdrawn at baseline and at the end of 1 h $0.10 \mu\text{g kg}^{-1} \text{min}^{-1}$ and $0.50 \mu\text{g kg}^{-1} \text{min}^{-1}$ of fenoldopam infusion.

Statistical analysis was performed by single comparisons using Student's *t*-test for paired data. The data for sodium excretion were analyzed by analysis of variance. Results of $P < 0.05$ were accepted as statistically significant.

Results

No side effects were encountered after lithium administration or during fenoldopam infusion. Serum lithium concentration was $0.12 \pm 0.025 \text{ mmol l}^{-1}$ at the start of the study.

The mean baseline sodium excretion demonstrated that lithium was natriuretic: $13.3 \pm 7.9 \text{ mmol h}^{-1}$ for study day 1 and $9.1 \pm 5.7 \text{ mmol h}^{-1}$ for study day 2 ($P < 0.05$). Comparison of cumulative (Figure 1) and hourly sodium excretion during fenoldopam infusion for both studies revealed no significant differences. The median percentage difference for cumulative sodium excretion was 4% between both study days. Fenoldopam-induced changes of renal haemodynamics (Figure 2) were not different in the studies with and without lithium.

PRA increased significantly from a baseline value of $1.40 \pm 1.07 \text{ nmol l}^{-1} \text{h}^{-1}$ to a maximum of $5.24 \pm 1.82 \text{ nmol l}^{-1} \text{h}^{-1}$ in the studies with lithium, and from 1.46 ± 1.71 to $3.57 \pm 2.33 \text{ nmol l}^{-1} \text{h}^{-1}$ without lithium. For the $0.50 \mu\text{g kg}^{-1} \text{min}^{-1}$ fenoldopam dose PRA levels were significantly higher in the studies with lithium.

PAC rose significantly during the first study day (with lithium) with 43%; on the second

Figure 1 Cumulative sodium excretion, 95% confidence intervals, during 4 h of fenoldopam administration with and without the presence of lithium. No significant changes are found.

Figure 2 Effects of fenoldopam on glomerular filtration rate (a), effective renal plasma flow (b) and filtration fraction (c) during fenoldopam infusion. Presence of lithium does not alter dose-response curves. *Significant difference compared with baseline values — + lithium, --- no lithium.

study day, without lithium, a non-significant rise of 27% was observed, but comparing matched data showed no significant differences between the percentage increases during both studies.

Discussion

Lithium is commonly used as a marker of proximal tubule function (Thomsen, 1984). However, a recent report by Jeffrey *et al.* (1988) suggests an interaction of lithium with dopamine receptors at the level of the renal tubule. Fenoldopam is known to affect natriuresis and renal haemodynamics by selective DA_1 -dopamine stimulation (Hughes *et al.*, 1988). The natriuretic effect is (partially) mediated by specific DA_1 receptors in the proximal tubule.

Therefore, we expected lithium induced changes in especially the natriuresis during fenoldopam administration. However, no significant changes occurred in this study with seven volunteers. In the study of Jeffrey *et al.* (1988) lithium abolished the natriuresis produced by gludopa; they used higher doses of lithium (750 mg lithium carbonate) also resulting in higher lithium levels: $0.29 \pm 0.09 \text{ mmol l}^{-1}$ vs $0.12 \pm 0.025 \text{ mmol l}^{-1}$ (after 300 mg lithium carbonate) in our report. This could suggest a dose relationship: possibly higher levels of lithium are required to interfere with dopamine induced changes in natriuresis. However, lithium interaction could also be mediated by other than DA₁-dopamine receptors, since gludopa also stimulates DA₂-dopamine and adrenergic receptors.

A stimulation of PRA by lithium has been reported in man (Shopsin *et al.*, 1973). Jeffrey *et al.* (1988) reported higher levels of PRA in the group with lithium pretreatment compared with the group without lithium pretreatment. We only found higher levels of PRA during the maximal dose of fenoldopam and no significant

differences were present during baseline values and lower doses of fenoldopam. Higher levels of PRA eventually result in sodium retention and the difference in PRA levels could explain the discrepancy between Jeffrey *et al.* (1988) and our results.

Cavero *et al.* (1987) demonstrated a rise of PRA by direct DA₁ stimulation. The extent of increase in PRA during fenoldopam infusion was influenced by the presence of lithium and suggests that lithium enhances the effects of DA₁-dopamine stimulation. Other DA₁ receptor mediated changes in renal haemodynamics remained unaffected.

Whether the interaction of dopamine and lithium is non-DA₁ receptor mediated or dose related remains a question for further investigation, bearing in mind a possible type 2 error or effects due to non randomization in our report.

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References

- Cavero, I., Thiry, C., Pratz, J. & Lawson, K. (1987). Cardiovascular characterisation of DA₁ and DA₂-dopamine receptor agonists in anaesthetized rats. *Clin. exp. Hypertension [A]*, **9**, 931-952.
- Donker, A. J. M., Hem, G. K. van der, Sluiter, W. J. & Beekhuis, H. (1977). A radioisotope method for simultaneous determination of the glomerular filtration rate and the effective renal plasma flow. *Neth. J. Med.*, **20**, 97-103.
- Felder, R. A., Blecher, M., Calgagno, P. L. & Jose, P. A. (1984). Dopamine receptors in the proximal tubule of the rabbit. *Am. J. Physiol.*, **247**, F499.
- Hahn, R. A., Wardell, J. R. & Sarau, H. M. (1982). Characterization of the peripheral and central effects of SK&F 82526, a novel dopamine agonist. *J. Pharmac. exp. Ther.*, **223**, 305-313.
- Hughes, J. M., Beck, T. R., Rose, C. E. & Carey, R. M. (1988). The effect of selective dopamine-1 receptor stimulation on renal and adrenal function in man. *J. clin. Endocrinol. Metab.*, **66**, 518-525.
- Jeffrey, R. F., MacDonald, T. M., Brown, P. W., Rae, P. W. H. & Lee, M. R. (1988). The effect of lithium on the renal response of the dopamine prodrug gludopa in normal man. *Br. J. clin. Pharmac.*, **25**, 725-732.
- MacDonald, T. M., Jeffrey, R. F., Freestone, S. & Lee, M. R. (1987). (+)-sulpiride antagonises the renal effects of gamma-L-glutamyl-L-dopa in man. *Br. J. clin. Pharmac.*, **23**, 612P-613P.
- Shopsin, B., Shathananthan, G. & Gershon, S. (1973). Plasma renin response to lithium in psychiatric patients. *Clin. Pharmac. Ther.*, **14**, 561-564.
- Thomsen, K. (Edit.) (1984). Lithium clearance: a new method for determining proximal and distal tubular reabsorption of sodium and water. *Nephron*, **37**, 217-223.

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