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Lithium and the renal response to gludopa, fenoldopam and dopamine

Schoors & Dupont (1990) provide very interesting data on the lack of effect of lithium on the renal response to dopamine, which were not published before we wrote our report (Girbes *et al.*, 1990). These data support our speculation that the interaction between lithium and the dopamine prodrug gludopa is not mediated by (proximal tubular) dopamine DA₁-receptors. However, the location and way of interaction between gludopa and lithium is not clarified by the study of Schoors & Dupont (1990). They make a very interesting speculation on a different proximal tubular response to intrarenally formed dopamine. However, the results of Schoors do not exclude a lithium dose related interaction with gludopa. Data on gludopa with different doses of lithium would therefore be of interest and will hopefully soon be provided (M. R. Lee, personal communication). Furthermore, some caution with the interpretation of the results of Schoors & Dupont (1990) is required, because they did not find any natriuretic effect of lithium alone. This is in contrast with our results and those of Jeffrey *et al.* (1988). Possibly there is a difference in salt status of the subjects studied at the beginning of the studies, which might influence the results. In fact Schoors & Dupont (1990) observe a higher sodium excretion at baseline during the study day without lithium than was observed in our (Girbes *et al.*, 1990)

and Jeffrey *et al.*'s (1988) study. Schoors & Dupont (1990) as well as Jeffrey *et al.* (1988) found higher levels of PRA in the group with lithium pretreatment, which might play a role in the abolished natriuretic response to gludopa, through increased aldosterone secretion. Some evidence, however, suggests that lithium induces a relative resistance to the action of aldosterone on the distal nephron (Singer, 1981).

We do not agree with Schoors & Dupont (1990) that fenoldopam induces a *marked* reduction in blood pressure in healthy volunteers. Schoors refers to Allison *et al.* (1987), who reported a dose-related decrease in diastolic blood pressure to a maximum of 6 mm Hg during fenoldopam infusion of 0.50 µg kg⁻¹ min⁻¹. In hypertensive patients however, a marked decrease in blood pressure is found (Glueck *et al.*, 1987; Murphy *et al.*, 1987; Ventura *et al.*, 1984). In our seven healthy subjects a significant decrease of 7 mm Hg and 8 mm Hg in median diastolic blood pressure was observed during 0.50 µg kg⁻¹ min⁻¹ fenoldopam infusion on the study day with and without lithium, respectively. No significant changes in systolic blood pressure were observed. However, we do agree with Schoors & Dupont (1990) that a compensatory reflex to the fall in blood pressure will contribute to a rise in PRA. Evidence, both *in vivo* and *in vitro*, on a direct stimulation of

renin release by fenoldopam, however, is accumulating (Antonipillai *et al.*, 1989; Kurtz *et al.*, 1988; Montier *et al.*, 1989). We therefore believe that this direct stimulation of renin secretion by fenoldopam is important and may limit its sustained use.

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Debrisoquine oxidation phenotype and susceptibility to lung cancer

We are responding to the criticisms of our recent article (Speirs *et al.*, 1990) on the question of a possible association between debrisoquine oxidation phenotype and susceptibility to lung cancer made by Dr Caporaso and Professor Idle (Caporaso & Idle, 1990). Other studies of the frequency of poor metabolisers (PM) in patients with lung cancer are not quite what Caporaso and Idle would have us believe. Two of the studies (Ayesh *et al.*, 1984; Law *et al.*, 1989) cannot be considered as independent, as drug analysis was conducted in the same laboratory. A third study (Caporaso *et al.*, 1988) is reported only as an abstract, and has not been subjected to peer review. In the fourth study (Roots *et al.*,

1988) there was no significant difference in the frequency of poor metabolisers in patients with bronchial cancer and a reference group of patients. We could add to this another large study in 153 cancer patients, and two control populations, submitted for publication by Bechtel *et al.* (personal communication), in which there was no under-representation of poor metabolisers in the lung cancer group. Thus, our own study (Speirs *et al.*, 1990) apart, there are two other independent studies which disagree with the results of Ayesh *et al.* (1984).

Caporaso & Idle (1990) are critical of much of the methodology used in our study. They state that 'determination of the DBR (debrisoquine