The acute toxic effect of the phosphodiesterase inhibitor rolipram on plasma osmolality

Rolipram (Schoering ZK 62 711) is a phosphodiesterase inhibitor which produces rises in the tissue content of cyclic AMP in a wide variety of tissues (Weishaar *et al.*, 1985; Lugnier *et al.*, 1986). Currently the use of rolipram in depression is under investigation in clinical trials (Zeller *et al.*, 1984). In view of the wide ranging functions of cyclic AMP as a second messenger, including osmoregulation, we have studied the acute and chronic effects of rolipram on plasma and urinary osmolality.

Ten healthy male volunteers aged between 20 and 40 years were studied prior to, after 24 h and after 1 week of rolipram given orally at a dosage of 1 mg three times daily. Simultaneous blood and urine samples were taken at 09.00 h on each occasion after an overnight fast. Osmolality was measured by freezing point depression. Figure 1 demonstrates the effect of rolipram on plasma and urinary osmolality. Using two way analysis of variance there is a significant fall in plasma osmolality following 24 h of rolipram ingestion with an inappropriate maintenance of urine osmolality. After 1 week of rolipram ingestion plasma osmolality had returned to normal. Plasma sodium fell from a mean (s.e. mean) $142.7 (1.1) \text{ mmol l}^{-1}$ to $130 (3.3) \text{ mmol l}^{-1}$ ($P < 0.05$) after 24 h and returned to $139 (2.1) \text{ mmol l}^{-1}$ after 1 week of rolipram ingestion. Plasma albumin underwent the same

changes falling from $44.9 (0.7) \text{ g l}^{-1}$ to $37.7 (1.1) \text{ g l}^{-1}$ ($P < 0.05$) after 24 h, confirming a rise in total body water as none of the subjects developed proteinuria.

It appears that arginine vasopressin exerts its antidiuretic effect through the activation of adenylate cyclase with a rise in the production of cyclic AMP in the renal tubule. This rise in cyclic AMP can be measured in the urine of patients with cranial diabetes insipidus who are given vasopressin (Ohzeki, 1985). The marked fall in plasma osmolality seen in our subjects may be the result of the inhibition of phosphodiesterase in the collecting tubules. We have no data on plasma vasopressin levels during rolipram ingestion, however another phosphodiesterase inhibitor, enoximone (MDL 17 043), does not have any acute effect on plasma vasopressin levels (Uretsky *et al.*, 1986). The fall in plasma sodium concentration is of concern as there is a risk of convulsions particularly at the lowest levels seen. We can find no previous reports of this type of acute effect on plasma osmolality by this group of drugs and it brings into question the safety of rolipram in the treatment of depression. We suggest that this potentially serious side effect be screened for in all trials of the newer phosphodiesterase inhibitors particularly in studies of their effectiveness in congestive cardiac failure, a situation where other sodium

Figure 1 Plasma (○) and urinary (●) osmolality changes during ingestion of rolipram. * $P < 0.001$ ($n = 10$).

lowering agents will be in use concurrently. Further studies on the exact mechanism of this effect are required.

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Lack of effect of spiramycin on cyclosporin pharmacokinetics

In a recent paper Vernillet *et al.* (1989) reported the lack of effect of spiramycin on cyclosporin pharmacokinetics. This study confirms our previously published data showing that spiramycin does not increase plasma cyclosporin concentrations in renal transplant patients (Kessler *et al.*, 1988). Our study included seven cadaveric renal transplant patients (three men and four women), aged 24 to 59 years. The mean duration of graft was 8 months (range: 1 to 14 months). All patients were treated with cyclosporin (mean $\pm$ s.d.: 3.6 ± 1.3 mg kg⁻¹ day) in association with prednisone (13.7 ± 9.4 mg day). Renal graft function was stable in all patients and their serum creatinine level averaged 181.6 ± 43.3 μ mol l⁻¹ prior to the administration of spiramycin. Plasma cyclosporin concentrations were measured using the polyclonal Sandoz RIA kit. The mean plasma cyclosporin trough concentration was 57.6 ± 24.7 ng ml⁻¹. Spiramycin was administered because of upper respiratory tract infections (four patients), dental care (two patients) and

toxoplasmosis (one patient) for a mean duration of 31 days (range 6 to 135 days). During the 30 first days of coadministration of spiramycin and cyclosporin no significant modification (paired *t*-test and T Wilcoxon test) of plasma cyclosporin concentrations or serum creatinine was detected (Table 1).

Macrolide antibiotics are prescribed for many types of infections, particularly for infections of the upper and lower respiratory tract. The potential for interactions is not the same for all of these antibiotics. Troleandomycin appears to be the most potent inhibitor of drug metabolism, erythromycin has a much weaker action (Kessler *et al.*, 1986), josamycin has seldom been involved (Kreft-Jais *et al.*, 1987) and spiramycin and midecamycin have not been shown to inhibit.

We confirm that spiramycin does not modify the metabolism of cyclosporin. Therefore, its use in transplant patients treated with cyclosporin may be recommended.