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Pharmacokinetics and safety of ciclopriolol in uraemic patients

Ciclopriolol is a β_1 -adrenoceptor partial agonist. Thus, it has a predominant agonistic effect when the sympathetic tone is low, at rest for example, and a predominant antagonistic effect when it is high, during exercise (Caffrey *et al.*, 1988; Hicks *et al.*, 1987).

In patients with anginal symptoms, ciclopriolol 50 and 100 mg once daily has potent antianginal activity and allows a significant increase in exercise performance even in presence of mild congestive heart failure (Cabanès *et al.*, 1986; Rigaud *et al.*, 1988; Silke *et al.*, 1987).

We have studied the pharmacokinetics of ciclopriolol in two groups of patients; one with normal renal function and the other with decreased renal function.

Ciclopriolol was assayed in blood and urine by h.p.l.c. with spectrofluorimetric detection (Guinebault *et al.*, 1990). The lower limits of the assay was 1 ng ml⁻¹ blood and 25 ng ml⁻¹ urine. The relative standard deviation was less than 10% and the accuracy was better than 10%.

After a single oral dose of 50 mg ciclopriolol hydrochloride to eight young healthy volunteers, peak blood drug concentrations were 121 $\pm$ 4 s.d. ng ml⁻¹ at 2.5 $\pm$ 0.1 h. Thereafter concentrations decrease monoexponentially with an elimination half-life of 10.9 $\pm$ 0.2 s.d. h. Total and renal clearances were 0.324 $\pm$ 0.013 s.d. l h⁻¹ kg⁻¹ and 0.100 $\pm$ 0.015 s.d. l h⁻¹ kg⁻¹, respectively. The urinary recovery of unchanged ciclopriolol was 27.3 $\pm$ 3.5 s.d. %. Ciclopriolol undergoes hepatic metabolism to a series of inactive metabolites, and a minor metabolite, prenalterol which has β -adrenoceptor blocking activity. However, since the urinary recovery of unchanged prenalterol is only 0.26% of the administered dose of ciclopriolol and its concentrations in blood were below the assay limit (5 ng ml⁻¹), its contribution to the activity of the parent compound is probably negligible (Dubruc *et al.*, 1987).

Eight patients with a creatinine clearance of 13 $\pm$ 3 s.d. ml min⁻¹ 1.73 m⁻² also received a single oral dose of 50 mg ciclopriolol. All patients were free of cardiac or hepatic insufficiency and were not taking drugs capable of inducing hepatic metabolism or of modifying intestinal drug absorption. In these patients, $t_{\max}$ was 2.6 h (1.8 to 3.6 h) a value similar to that observed in normal subjects, but $C_{\max}$ was significantly higher at 186 $\pm$ 21 s.d. ng

ml⁻¹. The elimination half-life was prolonged to 30 $\pm$ 2 s.d. h. Clearance was decreased (0.124 $\pm$ 0.011 s.d. l h⁻¹ kg⁻¹) and renal clearance was very low (0.015 $\pm$ 0.03 s.d. l h⁻¹ kg⁻¹). The urinary recovery of unchanged ciclopriolol ranged between 5.3 and 21.5% with a mean of 12 $\pm$ 2%.

Cardiovascular parameters remained unchanged throughout the study and, in particular, no bradycardia was observed, confirming the absence of antagonist activity at rest. No adverse event were reported.

Hydrophilic drugs are more readily excreted by the kidneys and may accumulate in patients with severe renal impairment. Ciclopriolol hydrochloride is moderately hydrophilic (pKa = 9.2, log P octanol/water at pH 7.4 = 0.4) and is comparable with atenolol, nadolol, sotalol and bisoprolol with respect to renal excretion. For these drugs, prolonged elimination half-lives have been reported in patients with severe renal insufficiency. In healthy volunteers and uraemic patients with low creatinine clearances (< 10 ml min⁻¹) the values of elimination half-life are respectively, 6–9 h and 42 h for atenolol (Hannedouche & Fillastre, 1986), 16–23 h and 45 h for nadolol (Hannedouche & Fillastre, 1986) 15–17 h and 42 h for sotalol (Hannedouche & Fillastre, 1986) and 12 and 24 h for bisoprolol (Kirch *et al.*, 1987; Payton *et al.*, 1987).

In conclusion, a three fold prolongation of the elimination half-life of ciclopriolol was observed in patients with creatinine clearances of about 10 ml min⁻¹. We suggest that in patients with very severe renal failure half the normal dose (i.e. 25 mg once a day) should be administered at the beginning of treatment. The dose should then be increased according to the clinical response.

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