Antimuscarinic and anticholinesterase activity of cimetidine and ranitidine: clinically significant?

Cimetidine and ranitidine, two potent inhibitors of gastric acid secretion, are widely used in the effective treatment of peptic ulcer disease (Weir, 1988). The pharmacological profile of the drugs is determined principally by specific inhibition of histamine H_2-receptors, although several adverse effects of the drugs (e.g. mental confusion, gynaecomastia, sexual impotence) and their ability to inhibit the cytochrome P_{450}-dependent mixed function oxidase activity cannot be attributed to H_2-receptor antagonism (see Gwee & Cheah, 1986).

More recently, however, we have shown that pharmacological doses of cimetidine and ranitidine can cause dose-dependent blockade of vagally- and methacholine-induced bradycardia in anaesthetised animals, i.e. blockade of the cardiac muscarinic receptor site (Gwee & Cheah, 1989, 1990). Thus, the tachycardia, urinary retention and blurred vision occasionally observed during therapy with these drugs (Physicians' Desk Reference, 1990; Stoelting, 1987), provide strong clinical evidence that cimetidine and ranitidine can cause blockade of muscarinic receptors in humans: such effects are typical clinical manifestations of muscarinic receptor blockade commonly associated with the use of antimuscarinic agents like atropine (Katzung, 1990).

It is now well documented that cimetidine and ranitidine also possess anticholinesterase activity (Gwee & Cheah, 1986; Lee *et al.*, 1985). It would be reasonable to suggest, therefore, that the inherent anticholinesterase activity of cimetidine and ranitidine could contribute to the 30% or so relapse rate in patients on maintenance dosage with the drugs (Misiewicz & Bradbury, 1982) and the reported decrease in their efficacy in inhibiting acid secretion during prolonged therapy (Prichard *et al.*, 1986; Sewing *et al.*, 1978), although such outcome of therapy has been attributed to the development of tachyphylaxis and an up-regulation of H_2-receptors (Jones *et al.*, 1988; Prichard *et al.*, 1986).

The anticholinesterase activity of cimetidine and ranitidine can be expected to cause accumulation of acetylcholine at cholinergic (vagal) sites within the gastric cells during prolonged therapy with the drugs. This can, therefore, result in a persistent stimulation of the three (acetylcholine, histamine, gastrin) interdependent and mutually potentiating pathways involved in the regulation of and leading to an increase in acid secretion (Soll & Berglindh, 1987; Wolfe & Soll, 1988). Thus, the anticholinesterase activity of cimetidine and ranitidine tends to oppose the inhibitory action of the drugs on gastric acid secretion which could be a plausible explanation for the relapse rate and the decreased efficacy of the drugs in some patients during long term therapy. The anticholinesterase activity of cimetidine and ranitidine can, in fact, also account for several other clinically documented effects of the drugs, including bradycardia, A-V heart block, diarrhoea, mental confusion, flushing, lacrimation and increased lower oesophageal sphincter pressure (Gwee & Cheah, 1986; Physicians' Desk Reference, 1990; Stoelting, 1987).

Thus, the inherent antimuscarinic and anticholinesterase activity of cimetidine and ranitidine, as determined from *in vitro* and *in vivo* studies in animals, seem to correlate well with the clinical manifestations of muscarinic receptor blockade and acetylcholinesterase inhibition by the drugs. Such inhibitory actions of cimetidine and ranitidine may therefore have important clinical implications in determining the toxicological profile of the compounds and in their potential to interact with drugs that also possess antimuscarinic (e.g. tricyclic antidepressants) and anticholinesterase activity.

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Pharmacokinetics and safety of cicloprolol in uraemic patients

Cicloprolol 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, cicloprolol 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 (Cabanes *et al.*, 1986; Rigaud *et al.*, 1988; Silke *et al.*, 1987).

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

Cicloprolol 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 cicloprolol hydrochloride to eight young healthy volunteers, peak blood drug concentrations were 121 ± 4 s.d. ng ml^{-1} at 2.5 ± 0.1 h. Thereafter concentrations decrease monoexponenetially with an elimination half-life of 10.9 ± 0.2 s.d. h. Total and renal clearances were 0.324 ± 0.013 s.d. l h^{-1} kg^{-1} and 0.100 ± 0.15 s.d. l h^{-1} kg^{-1}, respectively. The urinary recovery of unchanged cicloprolol was 27.3 ± 3.5 s.d. %. Cicloprolol 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 cicloprolol 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 ± 3 s.d. ml min^{-1} 1.73 m^{-2} also received a single oral dose of 50 mg cicloprolol. 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 ± 21 s.d. ng ml^{-1}. The elimination half-life was prolonged to 30 ± 2 s.d. h. Clearance was decreased (0.124 ± 0.011 s.d. l h^{-1} kg^{-1}) and renal clearance was very low (0.015 ± 0.03 s.d. 1 h^{-1} kg^{-1}). The urinary recovery of unchanged cicloprolol ranged between 5.3 and 21.5% with a mean of 12 ± 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. Cicloprolol 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.*,9 1987; Payton *et al.*, 1987).

In conclusion, a three fold prolongation of the elimination half-life of cicloprolol 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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