LETTER TO THE EDITOR

EFFECT OF ACUTE AND CHRONIC TREATMENT WITH CIMETIDINE AND RANITIDINE ON DEPRESSANT EFFECT OF DIAZEPAM

Sir,

(Received on February 16, 1983)

Cimetidine inhibits the hepatic cytochrome P–450 mixed–function oxygenase enzyme system and potentiates the effects of drugs like theophylline, propranolol, phenytoin, warfarin and diazepam (4,13,14,16,18), which are normally inactivated by these enzymes.

Ranitidine, a newer H_2–receptor antagonist closely resembles cimetidine in pharmacological profile, and has recently been introduced into clinical practice for the treatment of peptic ulcer (2). Early reports suggested that it does not affect hepatic drug metabolism and does not change the hepatic handling of drugs already shown to be influenced by cimetidine (8, 9, 10, 11, 17, 19). However, it has been recently reported that ranitidine also has the same biochemical effects as cimetidine, and like cimetidine reduces liver blood flow (3). This effect may be of therapeutic interest as reduction in liver blood flow would be expected to impair the hepatic elimination of drugs metabolised in liver (1,5,6,7,12,15,20).

In view of these controversies, we studied the effect of acute and chronic (6 days) feeding of cimetidine and ranitidine on the effect of diazepam on hexobarbitone sleeping time. It was hoped that if the H_2–blockers affect the hepatic handling of diazepam, the effect will be reflected in hexobarbitone sleeping time.

Albino mice of either sex (20 to 25 *g*) were used in groups of 10 animals each. The test compounds, cimetidine (150 *mg/kg*) or ranitidine (150 *mg/kg*) were administered orally in 1% carboxymethyl cellulose suspension every day for 6 days or once only. Control mice received the vehicle alone (0.1 *ml*/10 *g* body weight). Immediately after the last dosing (chronically treated groups) or after the single dose (single dose studies), diazepam (0.25 *mg/kg*) was given ip. Two hours after diazepam administration all groups were injected with aqueous solution of hexobarbitone sodium (75 *mg/kg*, ip). Sleeping time (interval between the loss and reappearance of righting reflex) was noted. Mean sleeping time, with standard error, was calculated for each group and the signi-

ficance of difference between the means was assessed by the Student's unpaired t–test. The level of statistical significance chosen was $P<0.05$. All experiments were carried out at ambient room temperature ($25\pm1°C$). Each animal was used once only.

Pretreatment with single dose of cimetidine, ranitidine and diazepam *per se*, had no significant effect on hexobarbitone sleeping time (Table I). When diazepam was given after single dose of cimetidine and ranitidine, the hexobarbitone sleeping time was increased. The increment, however, was significant only with cimetidine. In mice chronically treated with cimetidine or ranitidine the hexobarbitone sleeping time was increased significantly over the respective controls (Table I). When diazepam was also given to mice chronically treated with cimetidine or ranitidine the sleeping time was further significantly increased in cimetidine group, but not in ranitidine group (Table I).

TABLE I : Hexobaribitone sleeping time after diazepam alone in control mice and in mice pretreated with single or multiple doses of cimetidine and ranitidine.

Group	*Treatment*	*Route of administration and dose mg/kg*	*Mean sleeping time (mins± SE) after hexobaribitone sodium 75 mg/kg, ip*	
I	Vehicle (control)	0.1 *ml*/10 *g*	38.8±3.67	
II	Cimetidine	150 po	37.7±4.26	
III	Ranitidine	150 po	42.2±4.68	
IV	Diazepam	0.25 ip	49.4±4.59	
V	Cimetidine + Diazepam	150 po + 0.25 ip	108±9.58	a
VI	Ranitidine + Diazepam	150 po + 0 25 ip	63.7±5.40	b
VII	Cimetidine	150 po (6 days)	68.4±6.44	c
VIII	Ranitidine	150 po (6 days)	65.2±6.34	c
IX	Cimetidine + Diazepam	150 po (6 days) + 0.25 ip	147.0±13.47	d
X	Ranitidine + Diazepam	150 po (6 days) + 0.25 ip	87.0±9.14	e

a — Significantly different from group IV ($P<0.001$)

b — Not significantly different from group IV ($P>0.05$)

c — Significantly different from respective control ($P<0.01$)

d — Significantly different from group IV ($P<0.001$) and group VII ($P<0.001$)

e — Significantly different from group IV ($P<0.01$) but not from group VIII ($P>0.05$)

The central imidazole ring of cimetidine has been replaced by furan ring in ranitidine, and the side chain has also been modified. It has been suggested (8, 9, 10, 11, 17, 19) that imidazole ring facilitates binding of cimetidine to microsomal cytochrome P-450 enzyme system. Renitidine, thus may not bind significantly to cytochrome P-450 and hence may not affect the metabolism of drugs normally inactivated by these enzymes (16).

Our results clearly indicate that both single dose and chronic treatment of mice with cimetidine increases diazepam effect significantly. Ranitidine was found to differ from cimetidine in its interaction with diazepam in both acutely and chronically treated groups in not increasing diazepam effect significantly. Nonetheless, caution is required even while using ranitidine, since it may reduce liver blood flow and may still resemble cimetidine in overall effects.

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