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LETTER TO THE EDITOR

PHARMACOKINETICS OF ANTIPYRINE AND THEOPHYLLINE : UNALTERED BY MULTI-DOSE OMEPRAZOLE TREATMENT IN RABBITS

(Received on Jannuary 1, 1994)

Sir,

Omeprazole contains a benzimidazole moiety which is essential for irreversble inhibition of the gastric enzyme $H^+K^+ATPase$. Ability to selectively inhibit this enzyme makes omeprazole a potent, safe, efficacious and widely used anti-ulcer agent (1). Omeprazole is completely metabolized by hepatic mixed function oxidase (MFO) system. Cimetidine, a well known H_2-blocker also contains the benzimidazole moiety and is extensively reported to inhibit the hepatic MFO system which results in numerous clinically significant drug interactions (2).

We studied the pharmacokinetic interactions of omeprazole with two marker drugs antipyrine and theophylline which are mainly metabolized by hepatic MFO system.

Healthy male rabbits weighing between 1.5 to 2.5 kg were used in the study. A single oral dose of antipyrine (20 mg/kg) was given to each one of 16 rabbits between 0700 to 0800h. One millilitre blood samples from marginal ear vein were collected just prior to antipyrine and at 1, 2, 3, 4, 6 and 8h post-antipyrine. Plasma was separated by centrifugation and stored at -20°C till assayed spectrophotometrically for antipyrine (3). Intra-assay coefficient of variation was 4.35% and sensitivity 2 µg/ml.

These 16 rabbits were randomly divided into 2 groups (n=8). The first group received oral 4 ml 0.5% methylcellulose (vehicle) per day between 0700-0800h for 14 consecutive days while the second groups received oral omeprazole (4 µg/kg) suspended in vehicle per day between 0700-0800h for 14 consecutive days. Both groups received 1 ml of 4 mmol sodium bicarbonate just prior to vehicle/omeprazole administration to prevent acid degradation of omeprazole (4). On day 15, both groups again received on oral dose of antipyrine (20 µg/kg) at 0700-0800h. Blood samples were collected at similar time intervals as described earlier and plasma samples were assayed for antipyrine.

To a separate group of 16 rabbits, a single oral dose of theophylline (10 µg/kg) was given to each rabbit at 0700-0800h. One ml blood samples from marginal ear vein were collected just prior to theophylline and at 1, 2, 3, 4, 6 and 8h post-theophylline. Plasma was separated and assayed by HPLC technique for theophylline (5). Sensitivity and intra-assay coefficient of variation of the method were 1 µg/ml and 5.25% respectively.

These 16 rabbits were randomly divided into 2 groups (n=8). For 14 consecutive days, the first group received oral vehicle (4 ml 0.5% methylcellulose) and the second group, oral omeprazole (4 mg/kg) suspended in vehicle at 0700=0800h. Both groups also received sodium bicarbonate (1 ml or 4 mmol) just prior to vehicle/omeprazole. On day 15, both groups again received on oral dose of theophylline (10 mg/kg) at 0700-0800h. Blood samples were collected as described above and plasma was separated and assayed for theophylline (5).

The steady state kinetics of theophylline were studied in another groups of 16 rabbits. The rabbits were administered oral theophylline (10 mg/kg) thrice a day at 0700, 1500 and 2300h for 5 consecutive days. On day 6, 1 ml blood samples were collected just prior to theophylline (at 0700h) and at 1, 2, 3, 4, 6 and 8h post-theophylline. Plasma was separated and assayed for theophylline. These 16 rabbits were randomly divided into two groups (n=8). For 14 consecutive days, the first groups received vehicle and the second groups received omeprazole suspended in vehicle as described earlier. From day 10 onwards both groups also received oral

theophylline (10 mg/kg) thrice a day at 0700, 1500 and 2300 h. On day 15, blood samples were collected at similar time intervals as described earlier after 0700h administration of theophylline at a dose of 10 mg/kg. Plasma was separated from these samples and stored at –20°C until assayed for theophylline.

No significant difference was observed in Cmax, tmax, t½, AUC_0-8 and AUC_0-α of antipyrine or theophylline (single dose) before and after omeprazole and vehicle treatment (Table I). However, the AUC_0-α was significantly different for antipyrine between post and pre-omeprazole treated groups, which could possibly due to higher Kel of antipyrine in post-omeprazole treated group.

Table II shows the multi dose theophylline study. No significant difference was observed in any of the steady state pharmacokinetic parameters studied between the pre-omeprazole, vehicle and post-omeprazole treated groups of rabbits.

It has been reported that omeprazole is able to alter the drug metabolizing activity of hepatic MFO system through induction or inhibition (6). Omeprazole is reported to inhibit metabolism of diazepam and phenytoin in animal and human studies (7). Both the drugs are metabolized by MFO subfamily IIC. Omeprazole does not interact with cyclosporin, nifedipine and lignocaine (8, 9, 10) which are metabolized by MFO subfamily IIIA.

TABLE I : Single dose pharmacokinetics of antipyrine and theophylline in Rabbits.

	Cmas ($\mu g.ml^{-1}$)	*tmax* (*h*)	*t½B* (*h*)	$AUC_{0\text{-}8}$ ($\mu g.ml^{-1}.h$)	$AUC_{0\text{-}\alpha}$ ($\mu g.ml^{-1}.h$)
Antipyrine					
Pre-omeprazole (n=16)	15.62 ± 0.94	1.00 ± 0.00	7.71 ± 0.86	86.34 ± 5.99	184.53 ± 22.22
Vehicle (n=8)	16.26 ± 0.53	1.00 ± 0.00	6.33 ± 0.62	89.93 ± 4.67	164.42 ± 21.16
Post-omeprazole (n=8)	16.15 ± 0.47	1.12 ± 0.08	5.87 ± 0.37	83.50 ± 0.33	128.58 ± 10.97*
Theophylline					
Pre-omeprazole (n=16)	11.37 ± 1.40	1.12 ± 0.08	2.30 ± 0.03	32.86 ± 3.35	38.30 ± 03.29
Vehicle (n=8)	11.94 ± 1.17	1.00 ± 0.00	2.00 ± 0.04	36.68 ± 1.97	42.33 ± 03.17
Post-omeprozole (n=8)	12.43 ± 0.35	1.12 ± 0.08	2.49 ± 0.13	35.40 ± 2.31	43.49 ± 01.99

Values are expressed as Mean ± SEM
*P < 0.05 as compared to pre-omeprazole group.

TABLE II : Steady state pharmacokinetics of theophylline in Rabbits.

	C^{ss} *max* ($\mu g.ml^{-1}$)	C^{ss} *min* ($\mu g.ml^{-1}$)	$AUC_{0\text{-}8}$ ($\mu g.ml^{-1}.h$)	*tmax* (*h*)
Pre-omeprazole (n=16)	19.77 ± 0.71	5.67 ± 0.32	99.18 ± 4.34	1.00 ± 0.00
Vehicle (n=8)	18.30 ± 2.79	5.18 ± 0.30	92.64 ± 1.89	1.00 ± 0.00
Post-omeprazole (n=8)	20.11 ± 4.24	4.78 ± 0.49	97.07 ± 1.90	1.00 ± 0.00

Values are expressed as Mean ± SEM

Antipyrine and theophylline are both mainly metabolized by MFO subfamily IA. The present study suggests that omeprazole may not alter activity of subfamily IA. Therefore, theophylline which has a narow therapeutic index may not require dosage adjustment on concurrent administration with omeprazole.

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