Indian J Physiol Pharmacol 1995; 39(1) : 74-76

PHARMACODYNAMIC INTERACTIONS OF OMEPRAZOLE WITH CNS ACITVE DRUGS IN RATS

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(Received on January 1, 1994)

Abstract: A pharmacodynamic interactional study with omeprazole was undertaken in rats. Omeprazole (7 mg/kg, orally once daily for 14 days) significantly prolonged pentobarbitone (30 mg/kg, ip) induced hypnosis while it had no effect on haloperidol (1 mg/kg, ip) induced catalepsy or morphine (5 mg/kg, ip) induced analgesia models in rats. The study highlighted the fact that dynamic interaction with omeprazole was selective.

Key words: omeprazole, haloperidol, morphine, drug interaction, pentobarbitone

INTRODUCTION

Omeprazole is used widely in the treatment of peptic ulcer disease. It contains benzimidazole moiety which is essential for irreversible inhibition of the enzyme hydrogen-potassium adenosine triphosphatase (H^+-K^+ ATPase) (1). Cimetidine has a substituted benzimidazole moiety and has been known to cause large number of drug interactions of clinical relevance due to inhibition of hepatic microsomal cyochrome P-450 enzyme system (2). Therefore, omeprazole may also cause inhibition of cytochrome P-450 enzyme system of liver (3). Diazepam (4), phenytoin (4) and ^{14}C-aminopyrine (5) are reported to have significant kinetic interactions with omeprazole.

The present study was undertaken to ascertain the possibility of dynamic interactions of omeprazole with a narcotic analgesic morphine and a butyrophenone antipsychotic, haloperidol and also with pentobarbitone.

METHODS

The study was done in randomly selected healthy male rats (125-150 g body weight). They were housed four per cage and maintained in constant ambient temperature of 23 ± 2°C and a 12 h dark-light cycle (6 am to 6 pm). The rats had free access to food (Hindustan Lever pellets) and water was given *ad libitum*.

Morphine induced analgesia : The rat tail-hot wire technique of Davies et al (6) was employed. Utilizing this technique the latent period (the time interval between tail flick response and onset of heat application to the tail) was measured with a cut off point of 25s for maximun heat application to the tail.

The effect of omeprazole on morphine induced analgesia was studied by a cross over design. On day 1, the rats (n = 10) were administered morphine sulphate 5 mg/kg intraperitoneally (ip) and the latent period for tail flick response was measured at different time

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intevals i.e. 5, 10, 15, 30, 45, 60, 75, 90, 120 and 150 min after morphine administration. From day 2 to day 15 (both days inclusive), each rat received 7 mg/kg of omeprazole suspended in 1 ml of 0·5% methylcellulose solution given orally daily through an orogastric tube at 0700 h. Four mmol $NaHCO_3$ solution in 0.5 ml volume was given orally daily 5 min before omeprazole to prevent acid degradation of omeprazole. On day 16, repeat study of morphine induced analgesia was undertaken in each rat as mentioned above.

Haloperidol induced catalepsy : This experiment was done in a separate group of rats (n = 10) and haloperidol was injected at a dose of 1 mg/kg intraperitoneally to induce catalepsy. The rats were subjected to ring test (7) to assess the depth of catalepsy. The animals were observed for immobility and any movement (namely snouting and whiskering) other than the quiet respiratory excursions and typical sagging movement marked the end point of immobility. Two stop watches, having been matched and synchronized were run simultaneously. One of them recorded the total study period of 5 min while the other one recorded the duration of immobility to the nearest second possible. Finally the percent immobility was calculated for each rat which represented the depth of catalepsy. On day 1 the depth of catalepsy in the control group was ascertained with haloperidol alone. From day 2 to day 15, the rats were given 7 mg/kg of omeprazole orally (as described earlier daily at 0700 h). On day 15, haloperidol induced catalepsy test was repeated in chronically omeprazole treated rats.

Pentobarbitone induced hypnosis : This experiment was done in a cross over design in another group of rats (n = 10). On day 1, pentobarbitone sodium (dissolved in normal saline) was injected at a dose of 30 mg/kg, ip. Sleeping time was recorded as the time interval between the loss and return of righting reflex in the pentobarbitone treated rats. From day 2 to day 15, the rats were administered with omeprazole suspension, orally daily at 0700 h as mentioned above. On day 16, the study of pentobarbitone induced hypnosis was repeated.

Student's paired 't' test was used to determine statistical significance.

RESULTS

Table I shows the effect of omeprazole on morphine induced analgesia. In the control group as well as in the treated group, morphine produced significant prolongation of tail flick latency period as compared to the respective baseline values. In both the groups the onset, peak effect and duration of analgesia was noted at 10, 45 and 90 min respectively. However, omeprazole treatment for 14 days did not influence morphine induced analgesia at any tme point.

The depth of haloperidol induced catalepsy i.e., the percent immobility index ranged from 37.3 to 56.6% in the control group while it ranged from 31.3 to 60.0% in the omeprazole treated group. The mean percent immobility values did not differ significantly between the two groups.

The pentobarbitone induced sleeping time ranged from 110 to 185 min (mean, 134·9±6·5 min) in the control group. In the omeprazole treated group, the sleeping time was significantly ($P < 0·05$) prolonged and it ranged from 135 to 225 min (mean, 175±9·7 min).

DISCUSSION

No kinetic or dynamic interaction between morphine and haloperidol on one hand and omeprazole on the other is reported. In the present study omeprazole did not influence the depth of haloperidol induced catalepsy or the extent of morphine induced analgesia in rats. Pentobarbitone is metabolised extensively by cytochrome P-450 subfamily IIC and is reported to undergo slight reduction in its elimination in presence of high doses of omeprazole (8). Chronic treatment with omeprazole resulted in significant prolongation of pentobarbitone induced sleeping time in rats. Therefore, one should be cautious while administering a barbiturate drug to a patient on omeprazole, as slowing of elimination might result in the more pronounced and prolonged CNS depression. Similarly impairment

TABLE I

Morphine induced analgesia : Time (min)	*Control group*	*Omeprazole treated group*
O (baseline)	4·9 ± 0·23	4·8 ± 0·34
Post Morphine		
30	19·7 ± 0·31*	20·4 ± 0·69*
60	16·7 ± 0·71*	17·2 ± 0·63*
90	9·5 ± 0·64 *	9·6 ± 0·65*
Haloperidol induced catalepsy :		
% Immobility in control group		*% Immobility in omeprazole treated group*
43·42 ± 1·71		43·48 ± 2·68
Pentobarbitone induced hypnosis :		
	Sleeping time (min)	
Control group		*Omeprazole treated group*
134·9 ± 6·5		175·5 ± 9·7**

Data expressed as mean ± sem (n = 10)
*P < 0·05 between post morphine and baseline values in control group.
*P < 0·05 between post morphine and baseline values in omeprazole group.
**P < 0·05 between control and omeprazole group.

of clearance of another CNS depressant i.e., diazepam was earlier reported to occur in the presence of omeprazole (4).

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