INTERACTION BETWEEN PIPERAZINE AND CHLORPROMAZINE

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The interaction between piperazine and chlorpromazine has been studied in rats and mice. Piperazine administered a few hours previously potentiated the action of chlorpromazine on the central nervous system. No such interaction was found between piperazine and prochlorperazine.

Piperazine, an anthelmintic drug, only rarely produces toxic symptoms such as tremors, nausea and vomiting, incoordination and psychic disturbances (Pallister, 1955; Brown, Chan & Hussey, 1956; Combes, Damon & Gottfried, 1956). Several workers (Savage, 1967; Jakubowska, Lebensztejn, Pedich, Rudzinski & Wollna, 1968; Fünfgeld, 1969) have demonstrated alterations in the electroencephalogram (EEG) during piperazine therapy, especially when there were disorders of the kidney or neurological lesions in the central nervous system.

In 1969, Boulos & Davis reported that a child developed convulsions after receiving piperazine and then chlorpromazine, and so they investigated this phenomenon using goats and dogs. With the doses used, toxic symptoms developed when both drugs were administered but not when each was given alone. On the other hand, Armbrecht (1970) found no potentiation of the chlorpromazine action by piperazine in goats or dogs.

This paper attempts to elucidate this drug interaction in mice and rats. The interaction between piperazine and prochlorperazine was also studied as Boulos & Davis (1969) had shown that greatly exaggerated extrapyramidal effects (which are relatively common with propylalkyl piperazine phenothiazines such as prochlorperazine) occurred with piperazine and chlorpromazine together.

Methods The acute toxicities of intraperitoneally injected chlorpromazine or prochlorperazine were determined in mice alone, and then 1 h or 24 h after injection of piperazine hexahydrate at 5, 2.5 and 1 g kg^{-1} subcutaneously. LD_{50} values and their fiducial limits ($P = 0.05$) were calculated by the method of Litchfield & Wilcoxon (1949) from lethality observed within 24 h after the phenothiazine. One hour after mice received the drugs, locomotor activity was measured over a period of 5 min by counting the number of times a beam of light was interrupted, using a method similar to that described by Dews (1953).

Groups of five female rats were injected intraperitoneally with chlorpromazine or prochlorperazine. Other groups received chlorpromazine or prochlorperazine 1 h or 24 h after subcutaneous injection of piperazine at 5, 2.5 and 1 g kg^{-1}. After 4 h, determinations of abnormal posture (catatonia) were made according to the method described by Wirth, Gosswald, Hörlein, Risse & Kreiskott (1958); scores for the degree of experimental catatonia and the doses (ED_{50} values) required to produce 50% of the maximal score were calculated. EEG patterns were recorded from rats under urethane anaesthesia (1.25 g kg^{-1}, i.p.). Two stainless steel electrodes were inserted to a depth of 2 mm through the head into the cerebral cortex in the optic region. The EEG patterns were displayed on a Devices pen recorder (M2). In all experiments, solutions of piperazine hexahydrate were neutralized with hydrochloric acid before use.

Results In mice, piperazine pretreatment had no significant effect on the acute toxicity of prochlorperazine (Table 1). However, the acute toxicity of chlorpromazine was greatly increased by doses of 2.5 and 5 g kg^{-1} piperazine administered 1 h beforehand. When the time interval for pretreatment between piperazine and chlorpromazine was increased to 24 h, there was no significant alteration of the LD_{50} value (Table 1). Both chlorpromazine and prochlorperazine (1-100 mg kg^{-1}, i.p.) also reduced the locomotor activity, and piperazine in doses of 2.5 g kg^{-1} and above produced sedation accompanied by slight muscle relaxation or weakness of the hind limbs. However, in non-sedative doses, piperazine (1 g kg^{-1}), had no significant effect on the sedation produced by either chlorpromazine or prochlorperazine. Thus, in mice, pretreatment with piperazine for 1 h modifies the chlorpromazine effect only at doses above 1 g kg^{-1}.

In rats, piperazine in doses up to 5 g kg^{-1} s.c.

did not produce experimental catatonia. Chlorpromazine, up to 20 mg kg^{-1} i.p., produced no catatonia but only increased muscle tone, while at 40 mg kg^{-1} there was some slight degree of catatonia. On the other hand, prochlorperazine, at doses as low as 1 mg kg^{-1}, produced increased muscle rigidity and catatonia. Piperazine had no significant effect on the catatonia produced by prochlorperazine (Table 1) but when the rats received piperazine (1-5 g kg^{-1}) and 1 h later chlorpromazine (5-40 mg kg^{-1}), there was a marked increase in muscle tone and catatonia. However, no catatonia was produced when chlorpromazine was administered 24 h after piperazine (Table 1). On the rat EEG, piperazine at 1 g kg^{-1} and above caused a predominance of delta waves (1-3 Hz) with an amplitude of 25-100 μV and occasionally spike waves; both chlorpromazine and prochlorperazine (1-20 mg kg^{-1}) produced slow, high voltage waves (1-3 Hz) which alternated with wave trains of 8-12 Hz. However, doses of 100-500 mg kg^{-1} piperazine s.c., did not significantly alter the EEG patterns produced by chlorpromazine or prochlorperazine.

Discussion Boulos & Davis (1969) reported a drug interaction between piperazine (220 mg kg^{-1} orally) and chlorpromazine, yet Armbrecht (1970) was unable to confirm this effect. The results from these experiments in mice and rats show that there is an interaction between piperazine and chlorpromazine, but only when dose levels of piperazine greater than 1 g kg^{-1} are used, 1 h, but not 24 h, before the phenothiazine. The excretion of piperazine given orally to man begins within 30 min and is virtually complete in 24 h, with the maximal rate of excretion occurring in the first 8 h (Standen, Goodwin, Rogers & Stephenson, 1955). When there was impaired renal activity in man, serious side effects from piperazine have been reported (Combes *et al.*, 1956; Chaptal, Jean, Labauge, Bonnet & Aghai, 1960). Therefore, the excretion rate of piperazine may determine the time interval between piperazine and chlorpromazine necessary to prevent interaction between the two drugs.

Extrapyramidal symptoms such as akinesia, muscle rigidity and tremors are relatively easily produced with the propylalkylpiperazine phenothiazines. In the present experiments in rats, prochlorperazine produced marked catatonia while chlorpromazine had only a weak action. The presence of piperazine and chlorpromazine in the body at the same time caused greatly exaggerated extrapyramidal effects, similar to those seen with the piperazine phenothiazines; however, the ability of prochlorperazine to produce extrapyramidal effects was not potentiated by piperazine.

The site and mechanism of action of the drug interaction between piperazine and chlorpromazine in the present experiments is unknown; it may be metabolic or physiological. From EEG studies, Wechselberg (1956) suggested that the site of action for piperazine was the cerebrum and cerebellum. The phenothiazines are found to penetrate throughout the central nervous system, although Wase, Christensen & Polley (1956) have reported finding higher levels of chlorpromazine in the hypothalamus, thalamus, pons and cerebellum, than in the cortex. The significance of this interaction clinically is important only where high levels of piperazine are reached in the body.

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Table 1 Acute toxicities in mice and experimental catatonia in rats of chlorpromazine and prochlorperazine alone and either 1 h or 24 h after piperazine.

	Piperazine pretreatment			
Phenothiazine	*Dose (g kg^{-1})*	*Time interval (h)*	*Acute toxicity in mice (LD_{50} mg kg^{-1})*	*Experimental catatonia in rats (ED_{50} mg kg^{-1})*
Chlorpromazine	–	–	160 (114-224)	>40
	5	1	32 (19-54)	<5
	2.5	1	50 (36-70)	<5
	1	1	185 (154-222)	<5
	5	24	130 (100-169)	>40
Prochlorperazine	–	–	150 (107-210)	1.5
	5	1	115 (77-172)	1.5
	2.5	1	130 (81-208)	1.5
	1	1	150	1.5

In column 4, 95% confidence limits shown in parentheses.

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