Toxic interactions between disulfiram, and some centrally acting drugs in rats

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Recently, Smith & Shimizu (1976) have reported that, in the rat, the administration of disulfiram (350 mg kg^{-1}), 1 h before tranylcypromine stereoisomers (10 mg kg^{-1}) resulted in a toxic interaction between disulfiram and these drugs. We have observed a toxic interaction between disulfiram and morphine during a study designed to determine the influence of disulfiram, a dopamine-β-hydroxylase inhibitor (Goldstein, 1966), on the pharmacological activity of morphine.

Male Sprague-Dawley rats, 180–250 g, housed in temperature-regulated quarters (23-25°) on a 12 h light-dark cycle (lights on from 7.00 to 19.00) had free access to food and water. They were given either vehicle (0·5% carboxymethylcellulose, CMC) or disulfiram in the vehicle followed 1 h later by a drug at the dose and by the route shown in Table 1. The number of rats dying in 24 h was recorded. After morphine, death of the disulfiram-treated rats usually occurred between 4 and 6 h and seemed to be due to respiratory failure, the animals exhibiting intermittent convulsions during the 30 min preceding death.

Disulfiram also enhanced the toxicity of meperidine, (+)-amphetamine and barbitone, death in the meperidine and (+)-amphetamine groups occurring within 2 h of the drug's administration after an intense episode of convulsions that lasted about 1 h in some animals. Animals that died in the barbitone group did not regain consciousness before death. Survivors slept at least twice as long as their controls (barbitone—CMC, 163 ± 20 min; barbitone—disulfiram, more than 470 min). Stripp, Greene & Gillette (1969) observed a 3-fold increase in hexobarbitone sleeping time in rats treated with disulfiram (200 mg kg^{-1}, i.p.) 2 h before the administration of hexobarbitone.

A variety of drug-metabolizing enzymes have been shown to be impaired by disulfiram (Zemaitis & Greene, 1976a, b). However, we find it unwise to propose that impairment of biotransformation may be an underlying mechanism for these toxic interactions. Such a proposition cannot be advanced in light of the occurrence of a toxic interaction between disulfiram and barbitone, a drug that is excreted virtually unchanged in the rat (Williams, 1959).

Table 1. *Effect of pretreatment with disulfiram 400 mg kg^{-1} on the toxicity of morphine, meperidine, (+)-amphetamine and barbitone in the rat.* Disulfiram was injected intraperitoneally 1 h before the injection of drugs. *P* value was calculated by Fisher's exact probability method as described by Goldstein (1964). (+)-Amphetamine-treated rats were placed individually in meshed-wire cages 15 × 30 × 15 cm. All other rats were placed in groups (not more than 6 to a group) in round meshed-wire cages 20 cm high with a diameter of 22 cm.

Pretreatment dose mg kg^{-1}, i.p.	Treatment dose mg kg^{-1}	No. rat dead in 24 h	Mortality %
CMC 0·5% 2 ml	Morphine sulphate 100, s.c.	1/17	6·0
Disulfiram 400	Morphine sulphate 100, s.c.	9/18	50·0 $P = 0·004$
Disulfiram 400	Saline 2 ml, s.c.	0/18	0·0
Disulfiram 400	Meperidine HCl 50, i.p.	3/10	30·0 $P = 0·105$
CMC 0·5% 2 ml	Meperidine HCl 50, i.p.	0/10	0·0
Disulfiram 400	Meperidine HCl 100, i.p.	9/10	90·0 $P = 0·027$
CMC 0·5% 2 ml	Meperidine HCl 100, i.p.	4/10	40·0
Disulfiram 400	(+)-Amphetamine sulphate 80, i.p.	6/6	100·0 $P = 0·001$
CMC 0·5% 2 ml	(+)-Amphetamine sulphate 80, i.p.	0/6	0·0
Disulfiram 400	Barbitone sodium 200, i.p.	4/6	66·6 $P = 0·03$
CMC 0·5% 2 ml	Barbitone sodium 200, i.p.	0/6	0·0

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