Effect of Chlorpromazine on Cyanide Intoxication.* (25187)

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Guth and Spirtes found that chlorpromazine and other phenothiazines antagonized cyanide intoxication in pigeons, but they were unable to account for this effect by methemoglobin formation, bypass of enzymes, competition for enzyme sites, complex formation or inhibition of mitochondrial permeability(1). However, a number of drugs protect against anoxia by lowering body temperature(2). The present experiments indicate that chlorpromazine antagonism of cyanide (histotoxic anoxia) can be explained also by occurrence of hypothermia, at least in the species studied.

Methods. Hydrogen cyanide was used because the respiratory route permits control of rate of absorption and because surviving rats show brain lesions in high incidence(3,4). It was generated by passing air through 100 cc of 5% potassium cyanide solution(4). Rats (female albino, 150-250 g) or mice (female C57-leaden, 20-30 g) in weight matched pairs were exposed in gallon or pint jars (rats and mice differ in rate of heat loss under hypothermic conditions because of different surface-volume ratios). One member of each pair was pretreated with intraperitoneal chlorpromazine (50 mg/kg); the control was sham-injected or given an equal volume of saline. In some experiments (mice and rats) hydrogen cyanide was administered at rates that were varied in accordance with the condition of the animals so as to produce fatalities over a wide range of time (from a few minutes to 1½ hours); as soon as one member of each pair died the other was removed and sacrificed a few days later for histologic study. In other experiments (mice) the flow was kept at a constant rate of 0.1 liter/minute/jar and hydrogen cyanide vapor was delivered until both members of all pairs were dead (judged by cessation of respiration); the time till death was recorded.

Results. Eighteen pairs of mice were exposed to hydrogen cyanide delivered at various rates that produced fatalities over a wide range of time (5-83 minutes). In all but 2 pairs, the control died first, showing the protective effect of chlorpromazine pretreatment.

Twenty pairs of mice (in 4 groups of 5 pairs each) were exposed to hydrogen cyanide delivered at a constant rate. Two groups were kept in air, and the chlorpromazine-pretreated mice showed 2.8°C average drop in rectal temperature in the 15 minutes before exposure. In the other 2 groups, chlorpromazine-induced hypothermia was prevented by keeping the jars in 36°C water bath for 15 minutes between injection and exposure, and during entire exposure. Table I shows that chlorpromazine nearly doubled survival time in groups with lowered body temperature, while the protective effect was largely eliminated when body temperature was maintained at normal levels.

Twenty-three pairs of rats received hydrogen cyanide at rates deliberately varied so as to produce fatalities over a wide range of time (14-75 minutes). In contrast to results with mice, the outcome depended on rate of cyanide administration. The control rat died first in 13 pairs; average time was 26.2 minutes. The chlorpromazine-pretreated rat died first in 10 pairs; average time was 54.5 min-

TABLE I. Effect of Chlorpromazine on Cyanide Intoxication, with and without Preliminary Temperature Drop.

	Chlorpromazine		Control	
	△ Temp. (°C)	Survival (min.)	△ Temp. (°C)	Survival (min.)
1*	−2.1	21.0	.0	10.8
2*	−3.5	21.2	− .1	12.0
3†	+ .1	13.6	.0	11.2
4†	+1.3	14.4	+1.0	11.0

* Groups 1 and 2 in air to permit temperature drop after chlorpromazine.
† Groups 3 and 4 in 36°C water-bath to prevent temperature drop.

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TABLE II. Effect of Chlorpromazine Pretreatment on Rats Exposed to Hydrogen Cyanide.

First fatality*	Time†	First fatality*	Time†
Control	14	Control	36
CPZ	15	CPZ	39
Control	18	Control	41
Control	20	CPZ	45
Control	21	CPZ	50
Control	22	CPZ	54
Control	22	CPZ	63
Control	25	CPZ	64
Control	27	CPZ	67
Control	30	CPZ	73
Control	32	CPZ	75
Control	33		

CPZ = Chlorpromazine pretreatment.

* The exposure was discontinued after death of one rat from each pair, and the survivor was saved for histologic study.

† The hydrogen cyanide was delivered intermittently and at various rates in order to have death times over the range of 14 to 75 min.

utes. Apparently chlorpromazine failed to protect rats against slow hydrogen cyanide administration (Table II). Examination of surviving chlorpromazine-pretreated rats showed cyanide brain lesions in corpus callosum, corpus striatum, cerebral cortex, hippocampus, thalamus and substantia nigra. These lesions were similar in type and distribution to those in control rats and to those reported previously(3).

Chlorpromazine-pretreated mice and rats showed depressed respiration which disappeared with beginning of cyanide administration; they underwent the same stages of hyperpnea, automatic respiration and terminal respiratory depression as the controls.

Discussion. Antagonism of cyanide intoxication by chlorpromazine, reported by Guth and Spirtes for pigeons(1), has been confirmed for mice. The protective effect was associated with decreased body temperature, and was largely eliminated when normothermia was maintained. Chlorpromazine pretreatment of rats failed to protect against slow, protracted hydrogen cyanide exposures. The explanation may depend on 2 factors: (a) chlorpromazine produced less pre-exposure drop in body temperature in rats than in mice, probably due to larger bulk of rats, and relatively warm room temperature; (b) profound cyanide intoxication caused a drop† in body temperature(5), proportional to depth and duration of poisoning, and this tended to level off temperature differences between chlorpromazine-pre-treated and control rats as the exposure progressed.

Chlorpromazine, like cyanide, has been reported to inhibit cytochrome oxidase(7), therefore a synergistic rather than antagonistic effect might be expected. The observed antagonism shows that cytochrome oxidase inhibition does not dominate the pharmacologic action of chlorpromazine, but it may become significant when the more important hypothermic effects of the drug are reduced or eliminated.

The antagonism of cyanide intoxication by chlorpromazine, according to our interpretation, is analogous to protection against anoxic anoxia (low atmospheric pressure) by Megaphen (a phenothiazine derivative), cardiazol, pyramidon, ethyl alcohol and other drugs reported by Flacke *et al.*(2). In their experiments, as in ours, protection was lost when temperature-lowering was prevented. It is well known that hypothermia protects the brain against anoxia, and we found, for example, that cooling anesthetized rats till their temperature was 25°C enabled them to withstand up to 2 hours a flow of hydrogen cyanide that killed normal rats in 10-20 minutes.

Summary. Hydrogen cyanide intoxication is antagonized by chlorpromazine in mice and, to a lesser extent, in rats. The protective effect of chlorpromazine is due, in large part, to hypothermia induced by this drug.

† LeBlanc studied the interaction of cyanide and chlorpromazine and reported that cyanide did not affect body temperature of rats(6). The dose of cyanide was much less than the amount required for deep intoxication, therefore this finding is not in conflict with our observations and those of Dervillée *et al.*(5).

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Effect of Neomycin, Para-Aminosalicylic-Acid and Other Antibacterial Drugs on Serum Cholesterol Level of Man. (25188)

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It has been reported(1-2) that oral administration of neomycin lowered serum cholesterol concentration significantly in 10 patients. In extending this study, the effect of neomycin and other antibacterial drugs upon serum lipid levels of an additional group of patients was observed.

Methods. Twenty-five patients, 14 males and 11 females, were studied in 44 experimental periods. The average age was 54.2 years (35 to 74 years). Sixteen patients were hospitalized and 9 were followed as outpatients. Clinical diagnoses were coronary artery disease (6 patients), cerebral vascular disease (8 patients), familial hypercholesterolemia (2 patients), familial hyperlipemia with coronary artery disease (1 patient), diabetes mellitus (2 patients, including one of the CVA patients). In 7 patients there was no evidence of vascular disease or disturbance of lipid metabolism. Serum cholesterol levels were determined once a week, in the fasting state, by the method of Zak *et al.*(3). Serum phospholipid determinations were carried out by the method of Simonsen *et al.*(4) and the alpha and beta cholesterol levels by the method of Langan *et al.*(5). The control serum cholesterol levels, prior to administration of the drugs, were followed during a period of 6 weeks or longer. Hospitalized patients were maintained on regular hospital diet with the exception of the 2 diabetics, and the diet of the outpatients remained relatively constant during the study. A preparation containing 70% of neomycin sulfate (Mycifradin Sulfate,®)† was given orally to 18 patients in doses of 1.5 to 2 g daily for 4 to 20 weeks. Doses of medication in this study represent the weight of Mycifradin Sulfate. Five patients were given 60 mg of neomycin intramuscularly daily for a period of 3 weeks. This amount is equivalent to or higher than the proportion of oral dose (3%) which is absorbed from the gastrointestinal tract(6). Para-aminosalicylic-acid‡ (PAS) was given orally to 4 patients in 6 experimental periods. Four were given 6 g of PAS daily for 4 to 5 weeks. Two patients received 12 g of PAS for 9 and 4 weeks respectively. Isoniazid‡ (300 mg daily) was administered orally to 3 patients for a period of 4 weeks. Phthalylsulfathiazole§ (12 g daily) oxytetracycline‖ (1 g daily), polymyxin B sulfate‖ (150 mg daily) and novobiocin§ (1 g daily) were each given orally to 2 patients for a period of 3 weeks. Dihydrostreptomycin‖ (2 g daily) and bacitracin‖ (20,000 units daily) were each administered orally to 2 patients for a period of 2 weeks.

Results. The results of oral administration of neomycin are summarized in Table I. Mean serum cholesterol levels were lowered significantly in each patient by 17 to 29% during administration of neomycin, the average for the group being 21%. Two to 3 weeks were necessary before the concentration of serum cholesterol decreased to its low point. Cholesterol levels remained low as long as

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