— SHORT COMMUNICATIONS

ANTAGONISTIC EFFECT OF PHENOTHIAZINE DERIVATIVES ON
NICOTINE-INDUCED DEATH IN MICE

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The previous report (1) has pointed out that the drugs belonging to the so-called tranquilizer such as reserpine, chlorpromazine and perphenazine showed the strongest actions against nicotine-induced convulsion and death. On account of high effective coefficient (LD_{50}/ED_{50}) in phenothiazine derivatives, the present experiment was designed to determine the protective activity of some representatives of phenothiazine derivatives against nicotine-induced death with reference to the behavioral phenomena in mice.

Adult mice of either sex weighing 15 to 20 g were used. Phenothiazine derivatives employed were as follows: chlorpromazine hydrochloride, perphenazine dihydrochloride, levomepromazine hydrochloride, chlorprothixene hydrochloride, TX-102 (2-chloro-9-(3-dimethylamino-2-methyl-propylidene)-thioxanthene hydrochloride), Pasotomin (prochlorperazine maleate) and Psytomin (perazine benzoate), all of which were obtained from Yoshitomi Pharmaceutical Industries, Ltd. These compounds and nicotine were all injected intraperitoneally.

LD_{50} and LD_{90} of nicotine and ED_{50} of the antagonistic drugs against death induced by LD_{90} of nicotine were calculated by the method of Litchfield and Wilcoxon (2). Behavioral changes produced by the chlorpromazine related compounds were divided into three stages, i.e. sedation, hypnosis and paralysis. In the present paper these stages were referred to the following symptoms: *Sedation*; motor activity is less, but righting reflex is present and arousability is prompt, and eyes are opened or partially closed. *Hypnosis*; eyes are closed and the animals are inactive and in abdominal posture, but arousable, and righting reflex is present. *Paralysis*; righting reflex and arousability are lost.

More than 70 per cent of the animals which were given LD_{90} of nicotine were survived by all the chlorpromazine-related compounds except Psytomin. Psytomin protected less than 50 per cent.

TABLE 1. Protective action of chlorpromazine-related compounds against nicotine-induced death.

	ED_{50} (confid. limit $P < 0.05$)	Slope function
Chlorprothixene	1.9(1.5–2.5)	1.61
Perphenazine	3.0(2.4–3.4)	1.51
Levomepromazine	4.2(2.7–6.6)	2.58
Chlorpromazine	5.8(3.2–10.3)	2.51
TX-102	11.5(5.5–24.2)	3.34
Pasotomin	14.5(8.5–24.7)	2.21
Psytomin	40.0(–)	5.13

TABLE 2. ED_{50} of chlorpromazine-related compounds on sedation, hypnosis and paralysis.

	Sedation	Hypnosis	Paralysis
Chlorprothixene	0.51	1.0	—
Perphenazine	2.3	3.2	16.0
Levomepromazine	0.72	1.9	12.3
Chlorpromazine	0.74	3.0	25.0
TX-102	3.3	16.0	—
Pasotomin	7.9	15.5	31.0
Psytomin	31.0	74.0	135

As shown in Table 1, the potency of chlorprothixene was the strongest; perphenazine was second; next in order were levomepromazine, chlorpromazine, TX-102, Pasotomin and Psytomin. It was found that chlorpromazine and perphenazine were in a group in terms of slop function, and that levomepromazine, chlorpromazine, TX-102 and Pasotomin were in another one. Only Psytomin was far from both groups. From Tables 1 and 2, these antagonists showed the protective action against nicotine-induced death in hypnotic doses. The minimal protective action of these antagonists also appeared in sedative doses.

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ACCUMULATION OF ^{14}C -NICOTINE IN MOUSE BRAIN AFTER THE INTRAPERITONEAL INJECTION

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We have reported that pretreatment with small doses of reserpine (less than 0.5 mg/kg) had no effect on the level of nicotine in the brain and that of large doses decreased the level following intraperitoneal injection of convulsive dose of nicotine, though pretreatment with the small dose of reserpine inhibited nicotine-induced convulsion and that with the large dose accelerated this convulsion (1, 2). Thereafter we have examined the effect of reserpine on the accumulation of nicotine in brain particulate fractions especially in microsomes and nerve endings, but we could not find any reserpine effect on the accumulation *in vivo*.

TABLE 1. Accumulation of ^{14}C -nicotine in brain.

Time after ^{14}C -nicotine	Fractions	
	Nuclear	Soluble
5 (min)	123 (cpm)	2295
15	98	2040

FIG. 1. Accumulation of ^{14}C -nicotine in brain. MS; microsomes + myelin. NE; nerve endings. MT; mitochondria. Curves 1 and 2; 5 and 15 minutes after ^{14}C -nicotine respectively.