Technical Papers

Potentiation of Pentobarbital Anesthesia by Isonicotinic Acid Hydrazide and Related Compounds

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During the course of investigating enzymatically catalyzed exchange reactions *in vivo* and their relationship to chemotherapy (*1*), it was observed that several of the congeners of nicotinic acid employed in antitubercular studies prolonged the anesthetic action of pentobarbital in mice.

The experiments were conducted with CDBA hybrid male mice, 10 to 12 wk old, weighing 20 to 25 g. Pentobarbital (Na) was administered intraperitoneally. All other drugs were administered subcutaneously. The drugs were administered at 1 percent body weight in a saline or water vehicle. The duration of anesthesia was measured as time elapsed from the loss of righting reflex to its return (*2, 3*).

An experiment in which the pentobarbital was administered 15 min after isonicotinic acid hydrazide (INH) is summarized in Table 1. It is evident, in the combination treatment, that the extent of pentobarbital anesthesia may be increased by increasing the dose of INH as well as by increasing the dose of pentobarbital. In other experiments prolongation of pentobarbital anesthesia was noted with doses of INH as low as 50 mg/kg (with 60 mg/kg of pentobarbital).

In the dose range employed (Table 1), INH elicits acute toxicity, characterized by tremors, convulsions, tetanic spasm, and respiratory arrest, in approximately 30 to 60 min (*4–6*). Pentobarbital afforded protection against the acute toxicity of INH (Table 1), as did phenobarbital or chloral hydrate (*4*). This protective action was observed even when the pentobarbital was administered in the initial stages of convulsive seizure. At the lower doses of pentobarbital this protection was complete (Table 1). However, at the higher doses of pentobarbital, the potentiation of anesthesia was sufficiently extensive that animals succumbed without recovery, in a manner similar to that observed with an overdose of pentobarbital alone. Thus, the extent of potentiation of pentobarbital anesthesia by INH and the protection by pentobarbital against the acute toxicity of INH appear to be interrelated and to depend on the relative doses of INH and pentobarbital employed.

Table 1. Protection against INH lethal toxicity by pentobarbital and prolongation of pentobarbital anesthesia by INH. The ratio represents mice dead/total. The numbers in parentheses indicate the mean anesthetic time in minutes plus or minus (±) 1 standard error of mean.

INH (mg/kg)	Pentobarbital (Na) (mg/kg)				
	0	51.2	64	80	100
500	5/5 (0)	0/5 (> 420)	0/5 (> 420)	3/5 (> 420)	5/5
400	5/5 (0)	0/5 (322 ± 29)	0/5 (> 420)	3/5 (> 420)	5/5
320	5/5 (0)	0/5 (201 ± 42)	0/5 (401 ± 6)	0/5 (> 420)	2/5 (> 420)
256	5/5 (0)	0/5 (240 ± 24)	0/5 (397 ± 6)	0/5 (> 420)	2/5 (> 420)
0		0/5 (46 ± 2)	0/5 (67 ± 1)	0/5 (116 ± 5)	0/5 (123 ± 8)

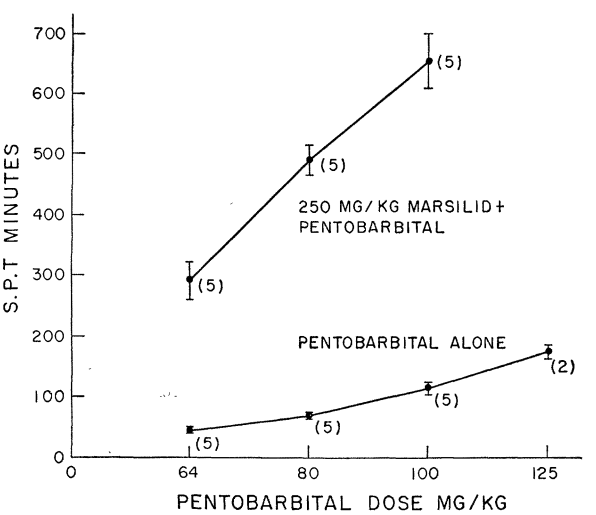

Fig. 1. Prolongation of pentobarbital anesthesia by Marsilid. "S.P.T. minutes" is the mean anesthetic time plus or minus (±) 1 standard error of mean. Five mice per group; the number in parentheses indicates the number of survivors.

Prolongation of pentobarbital anesthesia was also observed with 1-isonicotinyl-2-isopropyl hydrazine phosphate (Marsilid). Marsilid alone induced neither convulsions nor anesthesia at doses up to 1500 mg/kg. In combination with pentobarbital, Marsilid appeared to induce more extensive anesthesia than any dose of pentobarbital alone (Fig. 1).

In addition to INH or Marsilid, prolongation of pentobarbital anesthesia has been observed in our laboratory with isonicotinic acid amide, nicotinic acid hydrazide, 3-acetyl pyridine, hydrazine hydrate, and glycine. The potentiation of the duration of the action of barbiturates has been observed to occur when other types of drugs (*2, 3*) are used, and of these β-diethylaminoethyl diphenylpropylacetic acid HCl

(SKF 525-A) has been reported to be highly effective (*3*). Although no quantitative comparisons were made, the prolongation of anesthesia in mice with INH and Marsilid appeared to be of the same order as that of SKF 525-A. Dimercaprol and SKF 525-A have been reported to inhibit the rate of biotransformation of pentobarbital in the body (*2, 7*). This has not been determined with respect to the action of drugs reported here.

Although both INH and Marsilid, when administered simultaneously with or prior (4 hr) to pentobarbital, in both cases prolonged anesthesia, they do not appear to act in an entirely similar manner. Marsilid (250 mg/kg) caused a significant reduction (40 to 50 percent) in the dose of pentobarbital required to induce anesthesia in 50 percent of the animals (ED_{50}). With the same dose of INH, reduction of the ED_{50} was not significant (5 to 10 percent). This occurred even though at equivalent doses Marsilid is less toxic than INH. With a subanesthetic dose of pentobarbital (30 mg/kg), Marsilid (250 mg/kg) induced anesthesia while INH had no effect over a dose range of 50 to 400 mg/kg. Following recovery from pentobarbital (60 mg/kg) anesthesia, Marsilid (500 mg/kg) reinduced anesthesia, whereas INH (500 mg/kg) did not.

Also INH and 3-acetyl pyridine do not appear to act in an entirely parallel manner. Pentobarbital afforded protection against the toxicity of INH but did not protect against that of 3-acetyl pyridine. Nicotinamide did not protect against INH toxicity but did protect against that of 3-acetyl pyridine (*1*). The administration of nicotinamide or nicotinic acid did not result in any prolongation of anesthesia with pentobarbital.

Nicotinamide and pentobarbital do not appear to act antagonistically with respect to 3-acetyl pyridine. Protection by nicotinamide against the toxicity of 3-acetyl pyridine (*1*) did not appear to reduce the potentiating effect of the latter on pentobarbital anesthesia. Also, pentobarbital administration did not reduce the protective action of nicotinamide against 3-acetyl pyridine toxicity. However, nicotinamide metabolism has been implicated in the duration of action of barbiturates and in their metabolism (*8–10*).

Kaplan and Ciotti have observed an inhibition of diphosphopyridine nucleotidase activity by pentobarbital (*11*). The relationship of enzymatic transformations involving diphosphopyridine nucleotidases to the potentiation of barbiturate anesthesia and the observed toxicologic interrelationships is under investigation (*11*).

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Relationship of Hallucinogens to Adrenergic Cerebral Neurohumors

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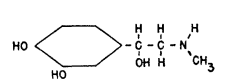
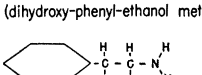
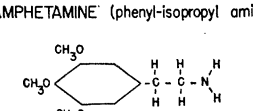
The study of cerebral synaptic transmission, by recording the postsynaptic electric response evoked by presynaptic stimulation, has demonstrated that an adrenergic synaptic transmission mechanism is present and capable of operating in the cat's brain. Marrazzi (*1*) has reviewed the evidence for this in a recent article in which he describes the use of the relatively simple transcallosal pathway connecting symmetrical points in the right and left optic cortex of the cat, thus making it possible to study one cortex when test stimuli are applied to the other. The electrocortical record so obtained indicates the activity at the terminal synapses by a surface positive wave corresponding to the inflow of impulses into the synapses and a surface negative wave indicating the outflow. In such a preparation, adrenaline, noradrenaline, and the so-called "adrenaline preservatives" cause a decrease in the surface negative wave generated by synaptic outflow without causing a change in the surface positive wave generated by the inflow—that is, a differential reduction in output or a synaptic inhibition.



ADRENALINE (dihydroxy-phenyl-ethanol methyl amine)



AMPHETAMINE (phenyl-isopropyl amine)



MESCALINE (trimethoxy-phenyl-ethyl amine)

Fig. 1. Types of phenylethyl amines producing mental effects.

Because of the structural similarity (Fig. 1) between adrenaline, which occasionally causes mental disturbances in man, amphetamine, which does so more often, and mescaline, which is a powerful hallucinogen, it was decided to compare the effects of the three on cerebral synaptic transmission. We had al-