Observations on the Pharmacology of Mephenesin Carbamate.* (19353)

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With increasing clinical experience it has become apparent that, although mephenesin may represent an important therapeutic agent in the management of spasticity and hyperkinesis, the practical usefulness of the drug is limited by its short duration of action. In order to maintain a level of beneficial effectiveness, large doses must be given at frequent intervals. The short duration of mephenesin appears to be related to the loss of activity which follows the oxidation of the terminal hydroxyl group to form β-toloxy lactic acid (1). Berger and Riley(2) studied the acid succinate of mephenesin which, after intraperitoneal administration, appeared to have a longer duration of action than mephenesin. We have confirmed this observation but we have also noted that this difference in action is not present after oral administration.

Several active compounds,† in which the terminal hydroxyl group was blocked, have been studied. Among these, 1-methoxy-2-hydroxy-3-toloxy propane showed no advantage and the 1,2-methoxy-3-toloxy propane only slight prolongation of action. The carbamate of mephenesin, 3-o-toloxy, 2-hydroxypropyl carbamate (MC 2303), however, appears to offer some promise since, possessing comparable potency, it shows in addition a significantly longer duration of action than mephenesin.

In studies on white mice weighing 16-22 g, the carbamate was found to have a mean paralyzing dose on oral administration of 3.4 mM/kg as compared to 4.17 mM/kg for mephenesin. The lethal doses were 7.67 mM/kg for MC 2303 and 10.53 mM/kg for mephenesin (Table I).

Confirmatory studies of duration of action were done, using the effectiveness of the compounds against the extensor phase of maximal electric shock pattern as a criterion. Electroshock was induced by 60 cycle square wave current of 0.5 sec. duration and 8 milliamp strength. Table II shows the results of this type of study. It is evident that MC 2303 shows longer protection and greater potency.

Pilot studies were done to ascertain whether, in animals, the mode and site of action of the compounds could be considered comparable. In mice given MC 2303 the pinna reflex disappeared before the corneal, a sign which Toman(3) has considered characteristic of mephenesin-like activity. Anticonvulsant action in mice appeared similar, using both a modification of the intravenous titration technic of Orloff *et al.*(4) and the intraperitoneal injection of twice the median lethal dose of strychnine and of metrazol. In spinal and in anesthetized cats both compounds showed a selective depression of the multisynaptic flexor reflex. Similarities were also seen in the EEG changes of intact curarized cats and mesencephalic sectioned cats. Finally, in rabbits, doses of both drugs causing a smooth reversible paralysis (150-200 mg/kg IP) caused comparable slowing in the brain wave frequency with an increase in amplitude. In studies on the depolarization of isolated frog muscle, J. Wright(5) has noted comparable effects with mephenesin and MC 2303. Although mephenesin carbamate was somewhat more potent on a molar basis, it seemed possible that its action could be related to a degradation to mephenesin. This conjecture was disproven by extracting the 24-hour urine collection of 2 dogs given either mephenesin, or mephenesin carbamate orally using a modification of the method of Riley(6). Following mephenesin, β-toloxy lactic acid was recovered in 30% yield. The appearance of this compound in the urine could not be demonstrated after the carbamate was administered. The action of MC 2303 probably is not the result of its degradation to mephenesin.

Conclusion. MC 2303 is a compound simi-

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TABLE I. Mean Paralyzing and Toxic Doses of Mephenesin and MC 2303 in mM/kg.

	Intraperitoneal		Oral	
	ED_{50}	LD_{50}	ED_{50}	LD_{50}
Mephenesin	1.08 ± 8.8%	2.83 ± 3.8%	4.17 ± 5.1%	10.53 ± 5.1%
MC 2303	1.16 ± 7.9%	2.77 ± 5.9%	3.4 ± 5 %	7.67 ± 5.4%

TABLE II. Number of Animals Protected Against Extensor Phase of Maximal Electroshock Pattern. 10 animals per group.

Drug	Dose, mM	Time in min 10	40	70	120	180
Mephenesin	3.40	10	4	1	0	—
	2.30	8	1	1	0	—
	1.54	4	1	1	0	—
	.99	6	0	—	—	—
	.66	3	0	—	—	—
MC 2303	4.20	10	10	10	5	4
	2.76	10	10	6	0	—
	1.88	10	10	6	1	2
	1.25	10	7	1	0	—
	.81	8	2	0	—	—
	.54	3	0	—	—	—

lar to mephenesin in potency and activity, and appears to have a longer duration of action.

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Thiosemicarbazide Toxicity in Mice.* (19354)

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Domagk(1) has reported that the 3-thiosemicarbazones of substituted benzaldehydes are active *in vitro* in inhibiting the growth of *Mycobacterium tuberculosis.* Promising results have been reported for a number of these compounds when tested *in vivo* in mice(2-4). However, thiosemicarbazide (TSC) itself, although active *in vitro* in low concentrations against *M. tuberculosis,* var. *bovis,* strain BCG(5) has not proven effective when tested *in vivo* because of its extreme toxicity. Indeed, Dieke(6) has suggested using TSC as a rodenticide. She found that dose levels of 10-30 mg/kg caused convulsions and death within one to 3 hours in rats, dogs, cats, guinea pigs, and monkeys.

It has been shown(7) that the ciliated protozoan, *Tetrahymena geleii,* is inhibited by TSC and that the inhibition may be reversed at the lower dose levels by small amounts of pyridoxamine. Tests to determine whether or not the toxicity of TSC to mice can also be reversed by pyridoxamine were therefore carried out.

Methods. The animals employed in these experiments were in most cases 18-20 g C57 black mice. A few experiments were performed on Swiss and A/C3H hybrid mice, the results of which were in complete accord with those using the C57 black strain. The compounds tested were administered in water solution with the concentration adjusted so that a total dose was contained in one ml. Accurate oral doses were administered by a syringe with an attached blunted, curved 15-gauge hypodermic needle, which was introduced into the esophagus. Following administration of the desired compounds the animals were observed closely for 4 hours and again at 12- and 24-hour intervals. The time of death of each animal was recorded. The great majority of deaths occurred within the first 4 hours. It was observed that striking uni-

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