Antagonism of Neuromuscular Actions of Hexamethonium by Choline Precursors

Keyphrases □ Hexamethonium—antagonism of neuromuscular actions by choline precursors without affecting hypotensive effects □ Choline precursors—used to antagonize neuromuscular actions of hexamethonium without affecting hypotensive actions □ Hypotensive agents—antagonism of neuromuscular actions of hexamethonium by choline precursors

Sir:

Hexamethonium has been classified as a ganglionic blocking agent (1) and is used as a hypotensive drug clinically. However, because of its numerous side effects, its use has been quite limited. Recently, it has been shown that hexamethonium possesses not only antinicotinic action but also hemicholinium-like action which inhibits acetylcholine synthesis to paralyze cholinergic neurons (2–5). The side effects of hexamethonium could be due primarily to this hemicholinium-like action, which can be antagonized by pretreatment of the animals with choline (6). In this study, we tried to determine whether or not the choline precursors, *e.g.*, dimethylaminoethanol plus methionine, will also prevent the hemicholinium-like action of hexamethonium.

Holtzman rats, 300–400 g, were anesthetized with 1.6 g/kg of urethan, and the jugular vein was cannulated for the injection of drugs. One carotid artery was cannulated for the determination of blood pressures using a pressure transducer and a polygraph. The sciatic nerve was exposed and passed through a pair of platinum electrodes. Interrupted tetanic stimulations were applied to the nerve with 250-Hz frequency, 0.5-msec duration, and a supramaximal voltage (4–8 v) for 0.1 sec every 10 sec. The tendon of the gastrocnemius muscle was tied with a thread and connected to an isometric force transducer for registering muscle twitches.

Table I—Effects of Choline Precursors on Neuromuscular Blockade and Hypotension Induced by Hexamethonium in Rats

Drug	Neuromuscular Blockade, %	Hypotensive Effect, %
Hexamethonium, 10 mg/kg	34 ± 5.3[a]	45 ± 4.2
Choline precursors[b] followed with hexamethonium, 10 mg/kg	9 ± 3.1[c]	46 ± 2.0

[a] Mean ± *SE*, $N = 6$. [b] Dimethylaminoethanol, 10 mg/kg, plus methionine, 5 mg/kg, administered three times in 20 min before hexamethonium injection. [c] $p < 0.005$ compared with hexamethonium alone.

When 10 mg/kg of hexamethonium chloride was injected *via* the jugular vein into the animal, there was an abrupt drop of blood pressure and a gradual inhibition of the neuromuscular transmission (Fig. 1A and Table I). On the other hand, when the animals were pretreated with 10 mg/kg dimethylaminoethanol plus 5 mg/kg methionine three times for 20 min before the administration of 10 mg/kg hexamethonium, the neuromuscular blockade was prevented while the hypotensive effect remained unaffected (Fig. 1B and Table I). These results clearly indicate that the paralysis of somatic nerves, which is one of the numerous side effects of hexamethonium when it is used to treat hypertension, can be prevented with choline precursors while the hypotensive effects of hexamethonium remain effective. This simple manipulation could make hexamethonium

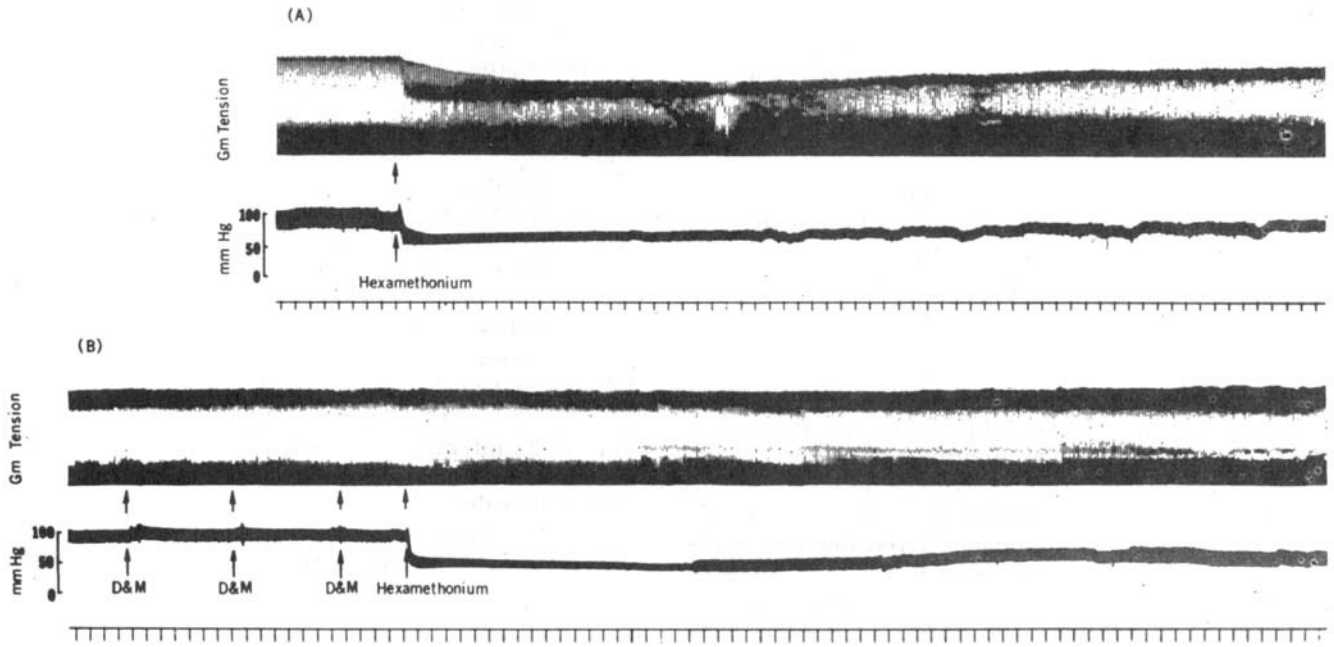

Figure 1—*Neuromuscular blockade and hypotensive effects of hexamethonium, 10 mg/kg, in rats (A) and effects of dimethylaminoethanol, 10 mg/kg, plus methionine, 5 mg/kg (D&M), on neuromuscular blockade and hypotensive effects induced by hexamethonium, 10 mg/kg, in rats (B). Each time interval represents 1 min.*

useful in treating hypertension without having side effects.

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Received August 29, 1973.
Accepted for publication November 2, 1973.
Supported in part by the National Institute of Neurological Diseases and Stroke (NS-09302-03).
The author is grateful to Mrs. Irene Schwartz for her skillful technical assistance.

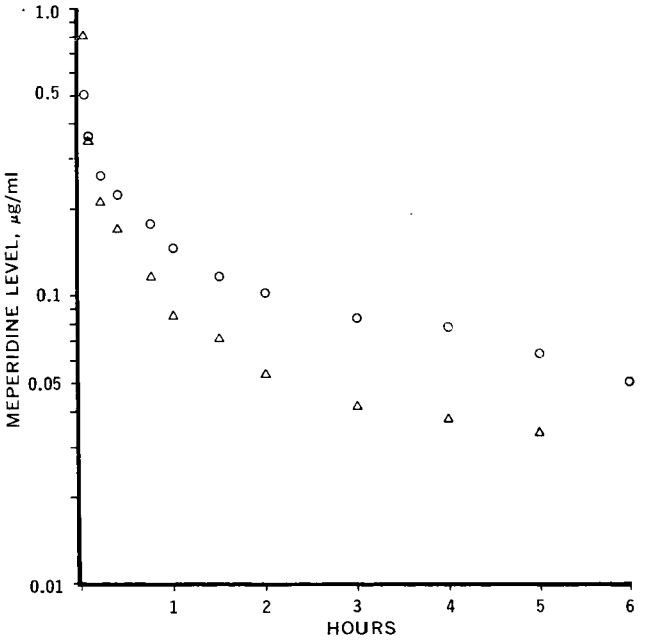

Figure 1—*Representative plasma concentration–time profiles following the intravenous injection of 50 mg meperidine hydrochloride. Key: ○, venous plasma, Subject L.M., dose corresponding to 0.74 mg/kg; and △, arterial plasma, Subject D.C., dose corresponding to 0.37 mg/kg.*

Meperidine and Other Basic Drugs: General Method for Their Determination in Plasma

Keyphrases □ Meperidine (and other basic drugs)—GLC analysis of plasma samples □ Amine drugs (basic)—GLC analysis of plasma samples □ GLC—analysis, meperidine and other basic drugs

Sir:

In a recent paper, Goehl and Davison (1) reported a GLC technique for the determination of meperidine in blood plasma. The method was used to determine plasma drug concentration *versus* time curves in dogs following administration of 15–25 mg/kg iv and yielded a limit of sensitivity of around 0.1 μg/ml.

We wish now to describe a method for the determination of meperidine, which is generally applicable to basic amine drugs. A similar procedure was reported by Hodshon *et al.* (2) for the determination of ketamine in plasma. This procedure allows the determination of clinically encountered low concentrations of meperidine for at least 6 hr following intravenous injection of 0.35–1.0 mg/kg and is currently being used to evaluate the effects of various anesthetic protocols on the kinetics of meperidine in man. Representative concentration *versus* time profiles are depicted in Fig. 1.

In the general method, the sample aliquot (usually 1.0 ml) was mixed with the internal standard solution (usually 100 μl, usually 1.0 μg), made basic with sodium hydroxide solution (100 μl, 1 *M*), extracted with ether (3 ml) in a Teflon-lined, screw-capped centrifuge tube (15 ml) by stirring on a mixer[1] (30 sec), and the phases were separated by centrifugation (2000 rpm, 2 min). Following flash freezing in an acetone–carbon dioxide bath, the organic phase was decanted into a second tube containing hydrochloric acid solution (200 μl, 1 *M*) and the phases were mixed and separated as before.

The organic phase was discarded and the aqueous phase was heated to around 60° for several minutes in a water bath to remove the residual ether. It was then cooled and transferred to a conical tube[2] with Teflon-lined screw cap (1 ml), made basic with sodium hydroxide solution (200 μl, 2 *M*), and extracted with methylene chloride (25 μl). The phases were separated as before. Aliquots (2 μl) of the organic phase were withdrawn with a microliter syringe and injected directly into the gas chromatograph[3]. The glass column, 150 cm × 3.2 mm o.d., packed with 3% OV-17 on Gas Chrom Q (100–120 mesh) was operated at 180° with helium as the carrier gas at a flow rate of 22 ml/min. For meperidine (R_T 3.8 min), the internal standard was *N*-methyl-*N*-ethyllidocaine hydrochloride[4] (R_T 5.1 min). Concentrations were calculated from a previously constructed standard curve of peak height ratio of meperidine/internal

[1] Vortex.
[2] ReactiVial, Pierce Chemical Co.
[3] Varian 1200, equipped with flame-ionization detector.
[4] 2-Methylethylamino-2′,6′-acetoxylidide hydrochloride.