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ACKNOWLEDGMENTS AND ADDRESSES

Received May 27, 1975, from the *Institute of Biological Chemistry, School of Medicine, State University, 20100 Milan, Italy.*

Accepted for publication March 16, 1976.

The authors thank Simes S.p.A. for providing Eudigox capsules and Dr. Gandolfi of Sorin S.p.A. for providing kits for digoxin radioimmunoassay.

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Cardiovascular and Neuromuscular Effects of Dimethyl Sulfoxide in Anesthetized Rabbits

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Abstract □ In rabbits anesthetized with pentobarbital, the carotid arterial blood pressure and bilateral contractions of the gastrocnemius muscles due to electrical stimulation of the sciatic nerves were recorded. Intravenous administration of up to 1 ml of dimethyl sulfoxide/kg caused profound hypotension and eventually failure of neuromuscular transmission. Caution must be used in considering dimethyl sulfoxide as a solvent for drug administration.

Keyphrases □ Dimethyl sulfoxide—intravenous administration, cardiovascular and neuromuscular effects, anesthetized rabbits □ Toxicity—dimethyl sulfoxide, intravenous administration, anesthetized rabbits □ Cardiovascular system—effects of intravenous administration of dimethyl sulfoxide, anesthetized rabbits □ Nerve impulse transmission—effects of intravenous administration of dimethyl sulfoxide, anesthetized rabbits

Previous reports demonstrated that dimethyl sulfoxide (I) has blocking activity at the neuromuscular junction *in vitro*. These studies ranged from depression of the guinea pig phrenic nerve diaphragm (1) to partial reversal of tubocurarine blockade in the frog sartorius nerve-muscle preparation (2) to a shift in the dose–response curve with acetylcholine in the chicken biventer cervicis muscular preparation (3). *In vivo* reports of the effects of I include the slow infusion of a 40% solution intravenously in unanesthetized rabbits; this dose (19.2 g/kg) resulted in a 12-mm Hg rise in arterial blood pressure and then bradycardia, which continued until death at 92 min (4). In unanesthetized cats, the LD_{50} for I was approximately 4 g/kg (5), but it was less than 0.4 g/kg in anesthetized cats (6). These findings imply that central nervous system (CNS) depression would have an appreciable effect on the toxicity caused by I.

EXPERIMENTAL

The present experiments were occasioned by the need to have a solvent for some bisquaternary ammonium water-insoluble compounds. Since the compounds were found to have sufficient solubility in I, its effect in one biological preparation to be used for the evaluation of the activity of the bisquaternary compounds was studied.

Albino rabbits, 2.2–2.5 kg, were anesthetized with pentobarbital sodium, 30 mg/kg, administered into the marginal ear vein. The right carotid artery and jugular vein were cannulated to permit the recording of the blood pressure *via* a pressure transducer and the administration of drugs, respectively. The trachea was cannulated, and the respiratory activity was monitored with a transducer connected to a polygraph. The sciatic nerve of each leg was cut proximally, and the distal stump was placed on an electrode connected to a stimulator. The Achilles tendon was cut at its insertion and attached to a transducer. The right leg was stimulated with supramaximal voltage at 1 Hz, and the left leg was stimulated at 0.1 Hz. Doses of I, 0.1, 0.5, and 1.0 ml/kg iv, were given.

RESULTS AND DISCUSSION

The lowest dose caused the diastolic blood pressure to decrease initially about 25 mm Hg. It returned to the control level within 25 min. There was an associated decrease of 50% in the force of contraction of the leg being stimulated at the faster rate. There was no appreciable change in the response occurring on the side being stimulated at the slower rate or in respiration.

When the 0.5-ml/kg dose of I was administered, there was a rapid decrease of 55 mm Hg in diastolic pressure, which returned to the control level within 1 min. Subsequently, there was a second decrease of 35 mm Hg in pressure, which was maximal at 3 min and returned to the control

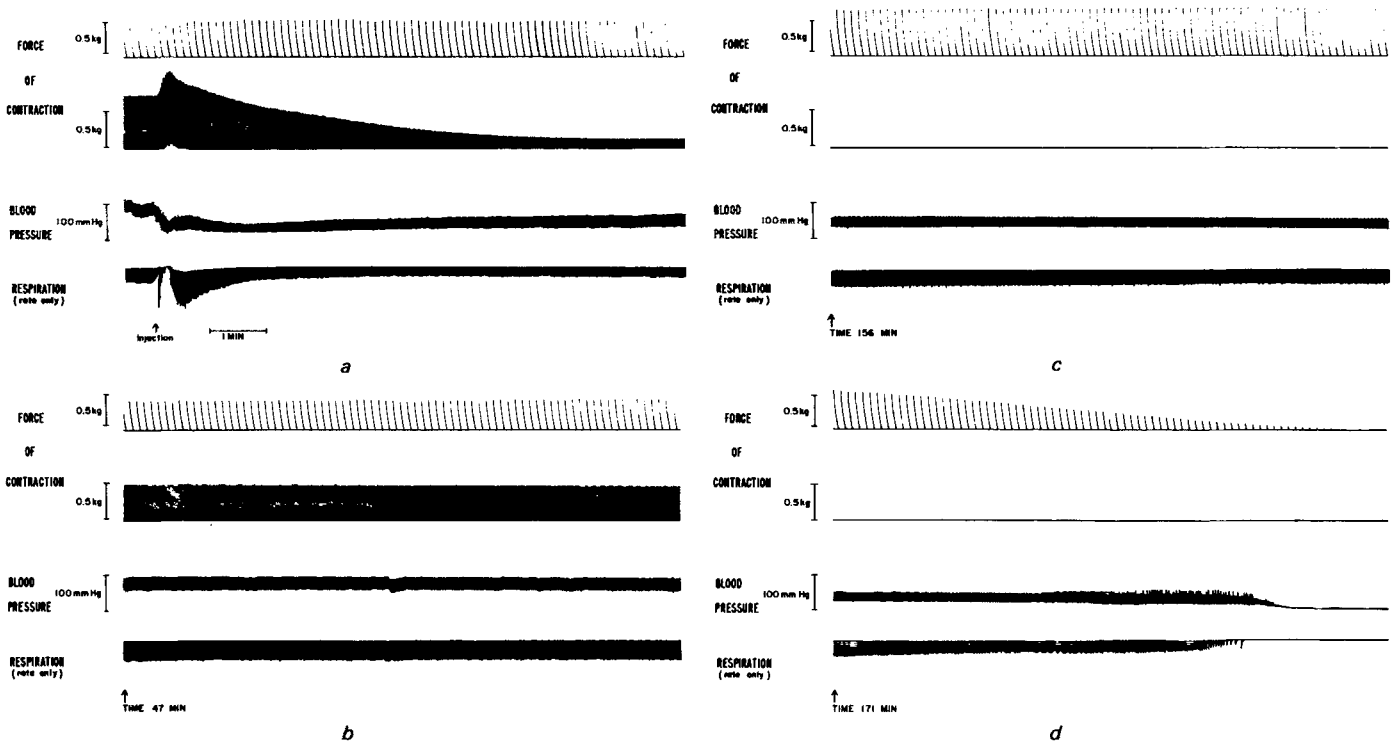

Figure 1—*Effect of dimethyl sulfoxide (1 ml/kg) on force of contraction, blood pressure, and respiration rate in anesthetized rabbits.*

level at 22 min. The leg being stimulated at the faster rate exhibited a 3–7% decrease in the force of contraction during the 1st min. After returning to the control intensity of contraction, there was a secondary decrease to a maximum of 31% at 6 min, which returned to the control level at about the same time as the blood pressure.

When the 1.0-ml/kg dose was administered, there was a rapid decrease of 55 mm Hg in diastolic pressure (Fig. 1*a*) during the 1st min. At 47 min (Fig. 1*b*), the blood pressure was still 20 mm Hg less than it had been prior to the injection. Thereafter, the blood pressure decreased progressively and the animal died at 179 min. The neuromuscular activity was initially decreased 83% at about 10 min. Subsequently, the force of contraction returned to 70% of control at 47 min (Fig. 1*b*). A secondary blockade developed, which became 100% by 156 min (Fig. 1*c*). The animal died 23 min later (Fig. 1*d*).

The profound effects upon the cardiovascular system are in agreement with a recent report (7) indicating that I caused a profound negative chronotropic effect. The effect on the force of myocardial contraction was variable and was thought to be dependent upon the efficiency of filling of the ventricles prior to each beat. The profound, sustained hypotension may have embarrassed the neuromuscular function too.

The fact that such profound effects were found in anesthetized rabbits with a total dose of 1.6 ml/kg of I is rather striking when compared to the infused dose of 19.2 g/kg required to kill unanesthetized rabbits (4). A similar enhancing effect of anesthesia on toxicity of I was found in cats (5, 6). This finding indicates that CNS depression caused by general anesthetics potentiates the toxic effects of I.

These results characterize the profound effects of I on both the cardiovascular and neuromuscular systems of the rabbit. They severely restrict its possible utility as a solvent for *in vivo* studies of poorly water-soluble compounds.

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ACKNOWLEDGMENTS AND ADDRESSES

Received January 30, 1976, from the *Department of Pharmacology, School of Medicine, Tulane University, New Orleans, LA 70112.*

Accepted for publication March 29, 1976.

Supported in part by Grant 5 R01 NS11580 from the National Institutes of Health.

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