

## EFFECTS OF BARBITURATES ON SKELETAL MUSCLE FUNCTION

R. L. BORGMAN, T. R. WALKER, M.D., C.B. PITTINGER, M.D., J. P. LONG, PH.D.

THE reported effects of barbiturates upon skeletal muscle contractions are conflicting. In usual therapeutic doses these drugs are generally considered inactive. Very high concentrations may produce blockade at the neuromuscular junction.<sup>1</sup> Positive inotropic actions have been reported for various barbiturates.<sup>2, 3</sup> The results reported in this paper concern the reinvestigation and extension of observations of barbiturate activity on skeletal muscle contractions, and suggest facilitation at the neuromuscular junction with some of these drugs.

### MATERIALS AND METHODS

The drugs investigated in this study were: barbital sodium, hexobarbital sodium (Evipal, Winthrop), methitural sodium (Neraval, Schering), pentobarbital sodium (Nembutal, Abbott), phenobarbital sodium, secobarbital sodium (Seconal, Lilly), thialbarbitone sodium (Kemithal, Imperial Chemical Industries, Ltd.), thiamylal sodium (Surital, Parke, Davis & Co.), and thiopental sodium (Pentothal, Abbott). All drugs were administered intravenously in doses of 15 mg. kg. Respiration in all experiments was assisted either manually or by a Palmer pump.

These drugs were studied in mature rabbits weighing about 1.2 kg. The rabbits were anesthetized with cyclopropane. A tracheostomy was established and an endotracheal tube inserted. Anesthesia was maintained with a to-and-fro system during the remainder of the surgical preparation. The gastrocnemius-sciatic nerve preparation was used. The sciatic nerve was severed and bipolar, silver electrodes were attached to the distal end. The animals were allowed to awaken before beginning the experiments. A Grass stimulator (Model S4-C) was used. A monophasic square

wave stimulus of 2 milliseconds duration, administered every 5 seconds, was employed for single shock experiments. Tetanic stimulation was of a frequency of 250 cycles per second and was administered for 0.2 second every 5 seconds. Voltage was supramaximal in all experiments.

The first phase of the investigation involved studies of the effects of barbiturates on muscle contractions in the following experimental situations: (a) single shock stimulation of the sciatic nerve in awake animals; (b) tetanic stimulation of the sciatic nerve in awake animals; (c) single shock stimulation of the sciatic nerve in awake animals during recovery from neuromuscular blockade produced by *d*-tubocurarine chloride; (d) single shock stimulation of the sciatic nerve in animals receiving thiopental during cyclopropane anesthesia.

The second phase of the experiment involved chronically denervated gastrocnemius muscle. The sciatic nerve was severed and 14 days allowed for nerve degeneration. Experiments were then conducted using bipolar needle electrodes placed in the tendon and belly of the gastrocnemius muscle. The muscle was stimulated directly using single shock.

### RESULTS

The effects of barbiturates on skeletal muscle contraction were observed. The results for each method will be presented individually. At least five observations were made for every barbiturate in each experimental situation.

*Indirect Single Shock Stimulation.* Thiopental, methitural, thialbarbitone, thiamylal, secobarbital and pentobarbital consistently caused an increase in the amplitude of muscle contraction with a single shock stimulus. The effect with secobarbital and pentobarbital was not as pronounced as with the other barbiturates. Increased contraction was not consistently produced by hexobarbital. No increase was seen with either phenobarbital or barbital. An illustrative record using methitural is shown in figure 1, plate 1.

Received from the Department of Pharmacology and Division of Anesthesiology, Department of Surgery, College of Medicine, State University of Iowa, Iowa City, and accepted for publication November 2, 1959. Mr. Borgman was Summer trainee fellow of the National Science Foundation.

*Direct Single Shock Stimulation.* The effects of various barbiturates on directly stimulated muscle were observed. None of the drugs used produced either an increase or decrease in the amplitude of the muscle contraction. The failure of methitural to produce an increase in contraction height is illustrated in figure 1, plate 4.

#### DISCUSSION

The augmentative effect of the barbiturates on skeletal muscle contraction using single shock indirect stimulation confirms the results that have been reported in the literature.<sup>2,3</sup> We found that the thiobarbiturates were more active than the oxybarbiturates. With indirect tetanic stimulation the barbiturates caused a decrease in the amplitude of muscle contraction. Sirnes<sup>3</sup> reported an initial increase preceding the depression of muscle contraction. This observation was not confirmed in this study. The thiobarbiturates gave the greatest decreases in contraction while the oxybarbiturates produced smaller changes.

According to Sirnes, barbiturates cause an initial stimulatory effect followed by depression in partially curarized muscle.<sup>3</sup> This phenomenon was not demonstrated by any of the barbiturates we have studied. Only thialbarbitone sodium showed antagonism of the *d*-tubocurarine block and there was no subsequent depression of muscle contraction. The other barbiturates produced only additional blockade.

Cyclopropane has been reported to increase contraction of indirectly stimulated muscle.<sup>4</sup> This observation was confirmed. Thiopental produced an additional increase.

Barbiturates produced no increase in contraction of the directly stimulated muscle. These results obtained with chronically denervated muscle do not confirm those reported

for isolated preparations.<sup>2,3</sup> The failure of barbiturates to augment muscle contractions with direct stimulation in contrast to this effect observed during indirect stimulation, seems to indicate action of the drugs at the neuromuscular junction rather than on muscle fibers.

Barbiturates are one of the few classes of compounds that either stimulate or depress the neuromuscular junction. It is evident that the type of response produced by barbiturates at this site is dependent upon frequency of stimulation. Obviously none of the parameters of stimulation used in most animal experiments are "physiological"; their action on the neuromuscular junction in man remains unknown.

#### SUMMARY

This study demonstrates that barbiturates vary in their effects on muscle contraction. Evidence has been presented that the site of action is the neuromuscular junction. The frequency of stimulation determined whether enhancement or depression of muscle contraction was produced.

This work was supported in part by a grant from the United States Public Health Service (Grant B-1396 (C-2)).

#### REFERENCES

1. Goodman, L. S., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, ed. 2. New York, Macmillan, 1956, p. 133.
2. Kraatz, C. P., and Gluckman, M. I.: Actions of barbiturates on contractions of voluntary muscle, *J. Pharmacol. & Exper. Therap.* **111**: 120, 1954.
3. Sirnes, T. B.: Some effects of barbituric acid derivatives on function of mammalian skeletal muscle, *Acta Pharmacol. et Toxicol. (Suppl. 1)* **10**: 1, 1954.
4. Watland, D. C., Long, J. P., Pittinger, C. B., and Cullen, S. C.: Neuromuscular effects of ether, cyclopropane, chloroform and Fluothane, *ANESTHESIOLOGY* **18**: 883, 1957.