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Absence of Recurarization upon Rewarming

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Anesthesiologists watch for recurarization in patients who have undergone lengthy procedures in cold operating rooms, even though neuromuscular blockade has been adequately reversed. In this experiment an attempt was made to demonstrate objective evidence of recurarization upon rewarming. Ten experiments were performed in seven mongrel dogs anesthetized with pentobarbital, iv. *d*-Tubocurarine was administered systemically. Responses to tetanic stimulation of the sciatic nerve at 40, 60, and 100 Hz were recorded from an anterior tibial tendon, with simultaneous recording of muscle temperature. Temperature changes were achieved locally with a heat-exchanging coil. Following cooling to 32 C the effect of *d*-tubocurarine was partially reversed with neostigmine such that the response to a tetanic stimulus of 40 Hz was sustained. The muscle was rapidly rewarmed to normothermia. Upon rewarming there was no evidence of fade with a tetanic stimulus that produced a sustained contraction in the hypothermic state. In the dog, when adequate reversal of neuromuscular blockade is obtained in the hypothermic state, recurarization does not occur upon rewarming. (Key words: Recurarization; Neuromuscular block; Hypothermia.)

THERE IS AMPLE EVIDENCE that the neuromuscular effect of *d*-tubocurarine is greater at normal body temperatures than during hypothermia.[1-5] Accordingly, anesthesiologists have watched for recurarization upon rewarming patients who have received *d*-tubocurarine, even though neuromuscular blockade appeared adequately reversed. There is little clinical evidence that this phenomenon occurs, and no experimental evidence.

This experiment was designed to simulate the clinical situation in the dog in an attempt to obtain objective evidence of recurarization upon rewarming.

Materials and Methods

Ten experiments were performed in seven unpremedicated mongrel dogs weighing 12 to 15 kg. The animals were anesthetized with pentobarbital, 30 mg/kg body weight, given intravenously. A tracheostomy was done and ventilation controlled using a Harvard animal respirator at volumes sufficient to maintain normal blood–gas values (P_{CO_2} 33–43 torr, pH 7.31–7.42). A carotid artery was cannulated and connected to a Statham transducer for direct monitoring of blood pressure. A jugular vein was used for intravenous infusion and administration of drugs. A sciatic nerve was exposed and transected; its distal portion was wrapped in a silver electrode and connected to a Grass S4 stimulator. The anterior tibial tendon was isolated, cut, and connected to a Statham strain gauge transducer with a 0–10-pound load accessory. A needle thermistor probe, inserted directly into the muscle, monitored muscle temperature. Blood pressure, muscular contraction and muscle temperature were recorded with a Beckman Dynograph R 411. The ipsilateral femoral artery was exposed and, following heparinization, an artery-to-artery shunt was established with a plastic coil of 25 ml capacity. The coil was used as a heat exchanger for rapid cooling and rewarming of the lower limb (fig. 1). The sciatic nerve was stimulated supramaximally with a pulse duration of 0.1 msec and a frequency of 0.4 Hz. Tetanic stimuli of 40, 60, and 100 Hz were applied for 5 seconds at five stages of the experiment: 1) control; 2) following administration of *d*-tubocurarine, 0.1 mg/kg; 3) following rapid cooling (6–8 minutes) to approximately 32 C; 4) following partial reversal with atropine, 1 mg, and neostigmine in increments of 0.5 mg such that tetanus was sustained at 40 Hz or 60 Hz but not at 100 Hz; 5) following rapid rewarming to normothermia. Rewarming was not begun until at least 5 minutes after the maximal effects of the administered dose of neostigmine had been obtained, as evidenced by stable responses to both single and tetanic stimuli.

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The shunting coil was placed in ice water to achieve efficient cooling. Rapid rewarming was accomplished in 6–8 minutes by placing the coil in tepid water and directing a heat lamp to the leg. A 50-ml syringe with a three-way stopcock was incorporated into the coil to augment blood flow and hasten temperature changes.

Results

Tetanic stimulation at the three frequencies used produced sustained ("S") muscle contractions under control conditions (table 1). After administration of *d*-tubocurarine the muscle responses showed fade ("F") in response to the same stimuli. Cooling to 32 C did not alter the fade response, although twitch height was increased (fig. 2). We intended to produce partial reversal with atropine and neostigmine so that stimulation at 100 Hz resulted in fade. After the limb was rapidly warmed we found no instance of fade with a stimulus that formerly had produced sustained contraction, namely, 40 Hz. On the contrary, in eight of ten experiments, 100-Hz current produced fade in the cold limb but a sustained contraction in the warm limb. In the other two experiments the responses to tetanic stimulation were unchanged.

Discussion

This study was performed to determine whether recurarization developed in the leg of the dog after rewarming when adequate reversal of the action of *d*-tubocurarine had been obtained in the hypothermic state. We defined "adequate reversal" as the ability to produce a sustained tetanic contraction at an indirect stimulus frequency of 40 Hz, a frequency commonly used under clinical circumstances. The dog was chosen as the experimental animal since it has a sensitivity to *d*-tubocurarine similar to that of man.[3] Pentobarbital is known to potentiate *d*-tubocurarine.[4,6] All of the data, both control and experimental, were obtained within a 20- to 30-minute period which began at least an hour after induction of anesthesia. Changes in blood and tissue levels of pentobarbital should have been minimal during the experimental

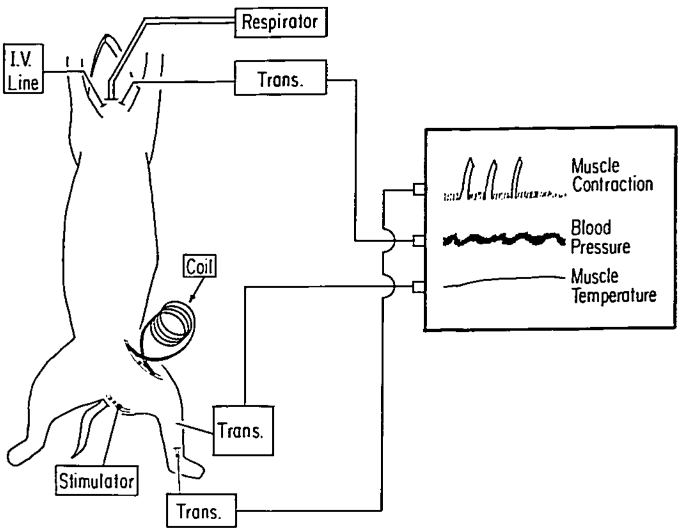

FIG. 1. Arrangement for simultaneous recording of muscle contraction, arterial blood pressure, and muscle temperature by way of appropriate transducers. Note the plastic coil which was used for rapid cooling and warming of the leg.

TABLE 1. Responses to Tetanic Stimulation at 40, 60, and 100 Hz in Each Phase of the Experiment*

	1 Warm Control			2 Warm Curarized			3 Cold Curarized			4 Cold, Reversed at 40 Hz			5 Rewarmed		
	Stimulus Frequency (Hz)			Stimulus Frequency (Hz)			Stimulus Frequency (Hz)			Stimulus Frequency (Hz)			Stimulus Frequency (Hz)		
	40	60	100	40	60	100	40	60	100	40	60	100	40	60	100
Experiment 1	S	S	—	F	F	—	S	F	F	S	S	F	S	S	F
Experiment 2	S	S	S	F	F	F	F	F	F	S	S	F	S	S	S
Experiment 3															
A	S	S	S	S	F	F	S	F	F	S	S	F	S	S	S
B	S	S	S	F	F	F	F	F	F	S	S	F	S	S	F
Experiment 4	S	S	S	F	F	F	F	F	F	S	S	F	S	S	S
Experiment 5															
A	S	S	S	F	F	F	F	F	F	S	S	F	S	S	S
B	S	S	S	F	F	F	F	F	F	S	F	F	S	S	S
Experiment 6	S	S	S	F	F	F	F	F	F	S	F	F	S	S	S
Experiment 7															
A	S	S	S	F	F	F	F	F	F	S	S	F	S	S	S
B	S	S	S	F	F	F	F	F	F	S	F	F	S	S	S

* "S" designates a sustained response; "F" connotes fade. Duplicate experiments were performed on Dogs 3, 5, and 7 after complete recovery from neuromuscular blockade.

period. The 6-C temperature range between 32 and 38 C was chosen since this is the range of unintentional hypothermia frequently seen in patients after operation.

Response to tetanic stimulus, rather than posttetanic facilitation or twitch height, was chosen as the index of neuromuscular blockade because: 1) normal uncurarized dogs often show posttetanic facilitation; 2) hypothermia itself will sometimes diminish twitch height[1] even though the response to *d*-tubocurarine is lessened by hypothermia; 3) the response to tetanic stimulation at frequencies higher than 40 Hz has been demonstrated to be capable of revealing underlying partial curarization[7,8]; 4) this index is the one most commonly used in human research to evaluate the presence of partial curarization.

The results of this study indicate that after adequate reversal of *d*-tubocurarine-induced neuromuscular blockade in the hypothermic state, recurarization does not occur during rewarming to normothermia. Previous studies have demonstrated that a given dose of *d*-tubocurarine is more effective when the animal is warm. This has usually been attributed to the effect of temperature on acetylcholinesterase activity, the enzyme being more active at higher temperatures. The effect of the temperature change in this study appears to have been overcome by the action of the cholinesterase inhibitor.

The study was designed to attempt to minimize the important effects of time and other drugs on the actions of both *d*-tubocurarine and neostigmine. Our attempts to minimize the effects of pentobarbital anesthesia are described above. Time was also allowed to permit achievement of the full action of neostigmine in the hypothermic state. Despite this and the fact that the muscle was rewarmed over a period of only 6–8 minutes, contrary to our expectation, neuromuscular conduction improved on rewarming. This improvement may have been the result of the passage of time alone. In this study, however, we have been unable to define what factor or factors might be responsible.

Walts *et al.*[9] have discussed whether the phenomenon of recurarization occurs in nor-

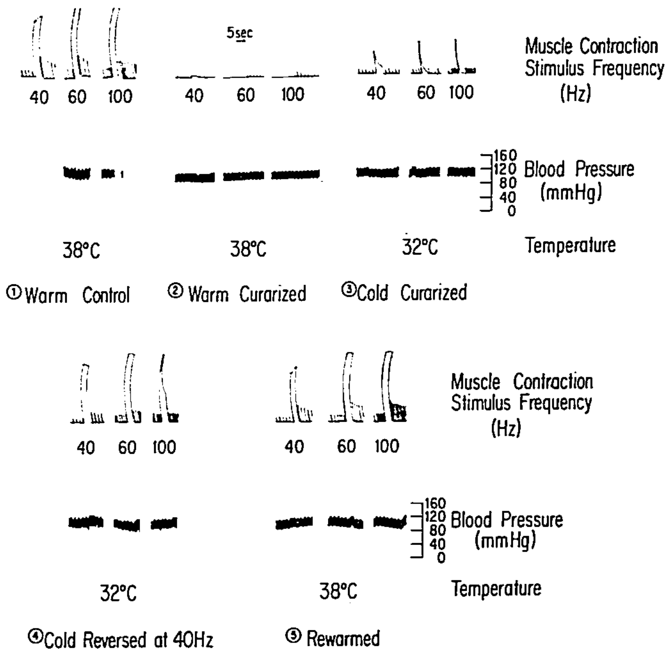

FIG. 2. Responses to tetanic stimuli of 40, 60, and 100 Hz in the five stages of the experiment.

mothermic man. It was their observation that when reversal of the effect of *d*-tubocurarine was complete, the patient did not recurarize. Our results demonstrate that in the dog, when adequate reversal is obtained in the hypothermic state, recurarization does not occur as the muscle returns to normal temperature.

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