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# *Pancuronium-induced Neuromuscular Blockade, and Its Antagonism by Neostigmine, at 29, 37, and 41 C*

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**To determine the effects of variations in temperature on the neuromuscular blockade produced by pancuronium, the drug was infused intravenously into 18 cats anesthetized with chloralose and urethane at a constant continuous rate to produce and maintain 90 per cent depression of twitch tension of the anterior tibial muscle following supramaximal stimulation of the peroneal nerve. The mean (±SE) infusion rates of pancuronium needed were 0.44 ± 0.05, 0.99 ± 0.11, and 1.05 ± 0.09 μg/kg/min (r = 0.73) at 29, 37, and 41 C, respectively. In contrast, the doses of neostigmine necessary for 50 per cent antagonism of the pancuronium-induced depression of twitch tension were not significantly different at the three temperatures. The time required to achieve peak neostigmine effect was longer at the lowest temperature. The durations of neostigmine action were longer at 29 and 37 than at 41 C. It is concluded that hypothermia augments neuromuscular blockade produced by pancuronium and prolongs the time to peak effect, and possibly the duration of action, but not the dose of neostigmine needed to antagonize the blockade. (Key words: Neuromuscular relaxants, pancuronium; Antagonists, neuromuscular relaxants, neostigmine; Temperature; Hypothermia.)**

HYPOTHERMIA supposedly lessens the neuromuscular blockade produced by pancuronium.[1] Feldman observed a decrease in twitch tension during hypothermia in man.[2] In contrast, Foldes *et al.* (unpublished data) found that hypothermia increased muscle twitch tension and augmented a pancuronium-induced blockade in the *in-vitro* rat diaphragm preparation. To re-examine this issue we determined the effects of temperature on the amount of pancuronium needed to sustain a neuromuscular block and its subsequent reversal by neostigmine.

## Methods

Eighteen cats, weighing 2.0 to 3.9 kg, were anesthetized with chloralose, 60 mg/kg, and urethane, 250 mg/kg, intraperitoneally. After performing a tracheostomy, we controlled ventilation to maintain the arterial partial pressure of carbon dioxide between 32 and 42 torr and arterial *p*H between 7.33 and 7.45. Arterial blood pressure was recorded from a cannula in the carotid artery. The anterior tibialis muscle tendon was isolated, sectioned near its point of attachment, and attached to a Grass FT .03 force-displacement transducer. Supramaximal stimuli of 0.2 Hz were applied for 0.2 msec to the peroneal nerve through shielded platinum electrodes. The resultant isometric twitch tensions were recorded on a polygraph.

Rectal and surface muscle temperatures were held constant at 29, 37, or 41 C ± 0.2 C for at least 30 minutes before injecting pancuronium. Only one temperature was studied in each cat. All temperature changes were induced by surface cooling or heating of the thorax and abdomen. All drugs were administered into a jugular vein.

Control twitch tension refers to that tension present after the desired temperature had been obtained and before pancuronium administration. After an initial dose of 40 μg/kg, pancuronium was infused continuously from an infusion pump at a rate sufficient to produce a constant 90 per cent decrease in twitch tension for at least 20 minutes before administration of neostigmine. While the infusion of pancuronium was continued an intravenous bolus of neostigmine, 5, 10, 20, 30, or 50 μg/kg, was administered. The resultant maximum antagonism of twitch depression was recorded and is presented as a percentage of the pre-existing 90 per cent depression (*e.g.*, a peak increase to 40 per cent of the pre-pancuronium twitch would be calculated as (40 − 10) 100/90, or 33 per cent antagonism). In addition, we determined the onset time for neostigmine by measuring the time lapse from neostigmine administration to peak effect and the duration of its action by measuring the time lapse from administration to 50 per cent return to the pancuronium-depressed twitch height. We have described this measurement previously in more detail.[3]

Analysis of variance and Student's range tests were used for part of the statistical analysis. Linear regression, correlation coefficient analysis, and unpaired t test were carried out for the remaining results.[4]

## Results

Hypothermia alone did not significantly alter twitch tension. Conversely, twitch tension increased 8.5 ± 2.0 per cent when temperature was increased to 41 C ($P < 0.05$). The mean infusion rate of pancuronium necessary to maintain a constant 90 per cent depression of control twitch tension was related directly to temperature (r = 0.73) (fig. 1). The required infusion rate at 29 C was approximately half of those rates needed at 37 and 41 C ($P < 0.01$). The infusion rates at 37 and 41 C were not significantly different.

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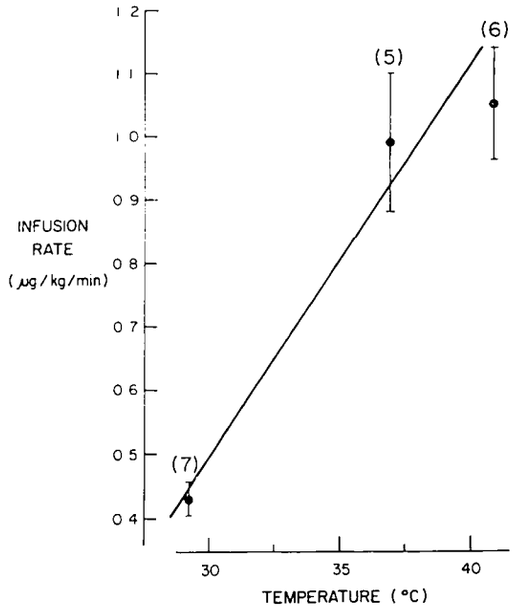


FIG. 1. Correlation between infusion rate of pancuronium necessary to maintain 90 per cent depression of twitch tension and temperature. Each dot and bracket represents the mean ± SE, respectively. The line represents analysis of linear regression. The numbers in parentheses represent the numbers of cats studied at the different temperatures.

Hypothermia did not alter the magnitude of pancuronium antagonism by neostigmine (fig. 2). Fifty per cent antagonism of the pancuronium-induced depression of twitch tension ($ED_{50}$) was produced by 11.5, 17.5, and 10.5 μg/kg neostigmine at 29, 37, and 41 C, respectively (fig. 2). These differences were not significant.

The onset time of the action of neostigmine was inversely related to temperature ($P < 0.05$), with two exceptions (fig. 3). The onset times with the 10 μg/kg dose of neostigmine were not different at 29 and 37 C, nor were the onset times significantly different with the 20 μg/kg dose at 37 and 41 C (fig. 3). The action of neostigmine persisted longer at 29 and 37 C than at 41 C ($P < 0.05$) (fig. 4). There was no difference in the durations of action of neostigmine between 29 and 37 C (fig. 4).

## Discussion

Our results suggest that a constant level of hypothermia does not significantly influence twitch tension in the steady state, but does increase the potency of pancuronium. These results are similar to those we found previously for *d*-tubocurarine.[5]

Our results do not exclude the possibility that a rapid decrease in temperature would transiently antagonize the effect of pancuronium or other nondepolarizing relaxants. This possibility may be explained as follows. Hypothermia may initially facilitate neuromuscular transmission by increasing the number of acetylcholine quanta released in response to a nerve impulse.[6,7] Hypothermia apparently has little effect on acetylcholinesterase activity or postjunctional membrane sensitivity.[6,8] The increased acetylcholine quanta release would antagonize the neuromuscular blockade from *d*-tubocurarine or pancuronium.[1,9] However, after 5 to 20 minutes this antagonism disappears and the block becomes augmented[8] because hypothermia decreases acetylcholine mobilization into readily available stores.[6] When the rat phrenic nerve–diaphragm preparation is stimulated at 400 stimuli/sec, decreasing the temperature of the bath from 38 to 30 C will decrease acetylcholine mobilization about 40 per cent.[6] Although hypothermia increases the fraction of quanta released from readily releasable stores by a nerve impulse, the decreased mobilization of acetylcholine into these stores ultimately becomes dominant.

The greater potency of pancuronium during hypothermia may relate more to relaxant elimination than to a direct effect at the myoneural junction. Elimination of pancuronium primarily depends on renal and biliary excretion.[10,11] A decrease in temperature from 37 to 29 C will decrease glomerular filtration and biliary excretion by 40 to 50 per cent.[12,13] The infusion rate of pancuronium needed was decreased by approximately this amount (fig. 1). Hypothermia probably also decreases the biotransformation of pancuronium.[10,14] Measurement of pancuronium concentrations in plasma, urine, and bile are necessary to substantiate our hypothesis that hypothermia decreases renal and biliary excretion and biotransformation of pancuronium. The effects of hypothermia on the neuromuscular junction and possibly uptake and distribution of pancuronium are consistent with our finding that less pancuronium is necessary for neuromuscular blockade during hypothermia.

Since decreasing temperature to 29 C has little effect on acetylcholinesterase activity or sensitivity of the postjunctional membrane,[6,8] hypothermia

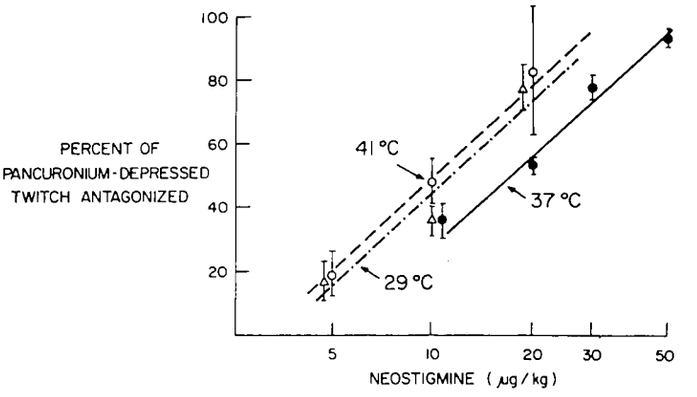


FIG. 2. Effect of temperature on the dose of neostigmine needed to antagonize pancuronium-induced depression of twitch tension. The lines represent analysis of linear regression. The dots and brackets represent mean ± SE, respectively.

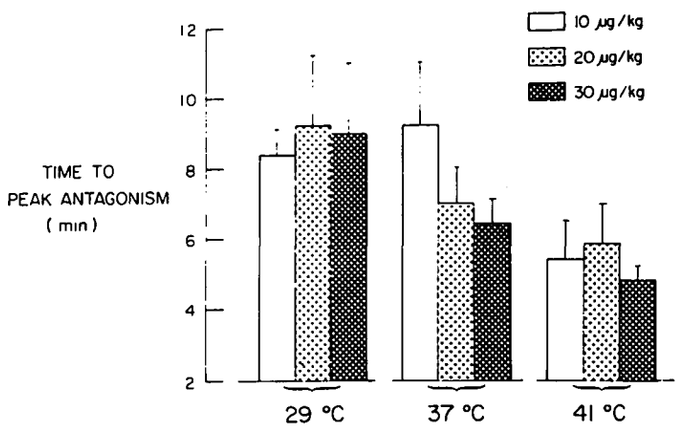


FIG. 3. Correlation between time from neostigmine administration to peak antagonism of the pancuronium-induced depression of twitch tension and temperature. The bars represent means ± SE. The times were longer with lower temperatures ($P < 0.05$), except for the 10 μg/kg dose at 29 C and the 20 μg/kg dose at 37 C.

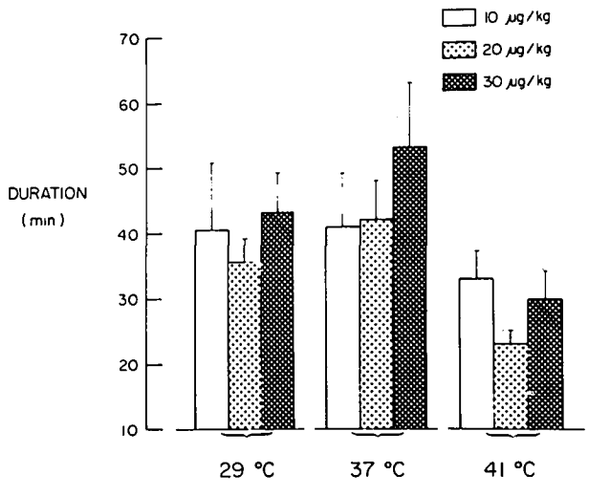


FIG. 4. Correlation between duration of neostigmine effect and temperature. These times were longer at 29 and 37 C than at 41 C. However, there was no difference between the times at 29 and 37 C.

*per se* should not alter the ability or amount of neostigmine required to antagonize a pancuronium-induced neuromuscular blockade. This is exactly what we observed (fig. 2). Time to peak effect and duration of action of neostigmine tended to be longer, which is consistent with the decreased muscle blood flow during hypothermia.[15] Hypothermia should not present any problem with antagonism of a pancuronium-induced blockade unless an excess of pancuronium is given.

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