

Disuse Atrophy with Resistance to Pancuronium

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To determine whether disuse atrophy of skeletal muscle results in resistance to pancuronium, the dose response to pancuronium was determined simultaneously in both gastrocnemius muscles of six dogs that had one hind limb immobilized in a plaster cast for one month. Muscle responses were evoked during pentobarbital-nitrous oxide anesthesia by stimulation of the exposed sciatic nerves, using the train-of-four pattern. Muscle subject to disuse atrophy was resistant to pancuronium. The ED₅₀ (dose of pancuronium which causes a 50 per cent depression of twitch tension) was 0.051 mg/kg for casted and 0.027 mg/kg for uncasted limbs for a potency ratio of 1.89. On the basis of these data the author predicts that bedridden or immobilized patients are likely to require greater doses of nondepolarizing relaxants for paralysis. (Key words: Muscle, skeletal: disuse atrophy, denervation. Neuromuscular relaxants: pancuronium. Pharmacology: dose-response curves.)

RESISTANCE TO PARALYSIS by nondepolarizing relaxants has been demonstrated in skeletal muscle of humans with upper motor neuron lesions^{1,2} and thermal trauma.³ These disparate conditions have little obvious pathology in common, except perhaps muscle disuse, the latter voluntary and due to pain and restricted movement in bed, and the former secondary to diminished activity in hyperreflexic muscles. Because muscle disuse atrophy might provide a common explanation for this resistance, I examined the effect of immobilization disuse atrophy on pancuronium-induced paralysis of the gastrocnemius muscle.

Materials and Methods

The right hind limbs of six mongrel dogs, body weight 13.4 ± 0.6 kg (SE), were immobilized with the hip, knee, and ankle each at a 90° angle in a plaster cast during anesthesia with 25 mg/kg thiopental sodium, intravenously. This treatment protocol duplicates our prior study⁴ and was approved by our Animal Care Committee. The animals were examined daily: they moved about freely on three legs, and the casts were changed as needed, usually once each week.

Twenty-seven to 32 days after the initial immobilization, the dogs were anesthetized with 25-40 mg/kg pentobarbital sodium, intravenously. The tracheas were intubated and the lungs ventilated by a Harvard® pump with 60 to 70 per cent nitrous oxide and oxygen. Ventilation was controlled to maintain PaCO₂ at 35-40 torr.

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Muscle (needle thermistor, deep thigh) and esophageal temperature were maintained at 37.0-38.0°C by covering the dogs and using heat lamps. Arterial blood pressure and heart rate were monitored. Two additional dogs (four gastrocnemius muscles) not subjected to hind limb immobilization served as "normal" animals.

With the dog in the supine position, both knees were immobilized with external clamps holding the thighs at right angles to the trunk with the lower legs horizontal. The gastrocnemius tendons were dissected free bilaterally and fastened to transducers (2,300 g maximal capacity). The sciatic nerves were dissected free at the inferior margin of the gluteus maximus muscle bilaterally, and laid across bipolar silver electrodes from a Grass S4G stimulator. Base-line tension of the muscle was the optimal length,⁵ as determined from a length-tension curve using supramaximal voltage, single twitches, duration 0.1 ms. Tension of the two gastrocnemii was recorded continuously.

The train-of-four stimuli pattern⁶ was used each 5 min, and incremental doses of pancuronium were administered intravenously every 15 min; during this 15-min period the effect of pancuronium with time was compared in casted and uncasted muscle. Studies were complete when neither muscle contracted in response to electrical stimulation of the nerve; the gastrocnemii were then excised, blotted dry, and weighed, and the dogs killed by a barbiturate overdose.

The degree of muscle atrophy was expressed as the ratio of the muscle weight (g) to the body weight (kg). Muscle tension during the first twitch in the train-of-four (T₁) was expressed as per cent depression of the control twitch tension in the absence of pancuronium. Linear regression was used to establish linearity of T₁ responses, and analysis of covariance was used to compare casted and uncasted T₁ responses.⁷

Results

Muscle with immobilization disuse atrophy was resistant to pancuronium in comparison to uncasted muscle (fig. 1). Regression analysis and analysis of covariance demonstrated that the T₁ response to pancuronium (0.02-0.10 mg/kg) was linear in both casted and uncasted muscle; the slopes were greater than 0 and virtually identical, and there was a significant difference between casted and uncasted responses, $P < 0.001$. The ED₅₀ (95 per cent confidence limits) for casted muscle was 0.051 (0.026-0.087); for uncasted muscle ED₅₀ was 0.027 (0.002-0.080). The ED₅₀ potency ratio was 1.89.

PANCURONIUM IN DISUSE ATROPHY

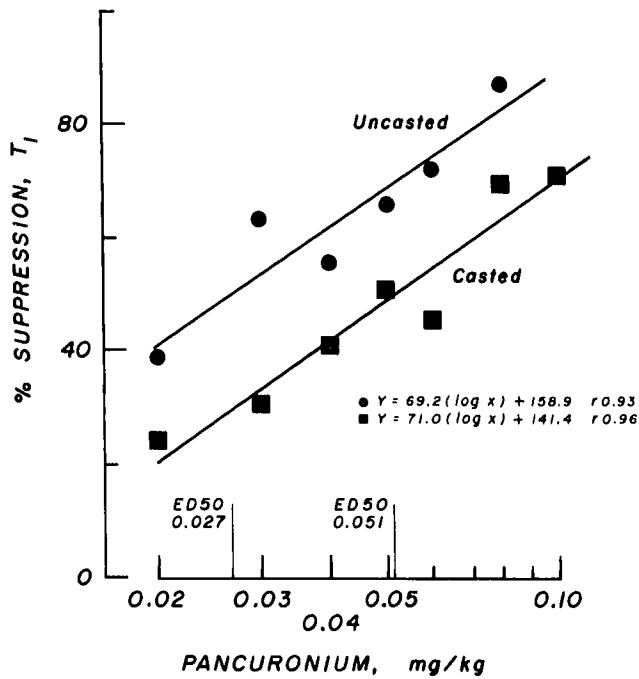


FIG. 1. Per cent suppression by pancuronium of the first twitch of the train-of-four (T_1) in gastrocnemius muscle immobilized *in vivo* in a plaster cast for one month *vs.* T_1 in the contralateral uncasted muscle. The lines are different by analysis of covariance ($P < 0.001$) suggesting resistance in muscle with disuse atrophy; ED_{50} ratio 1.89.

While paralysis was greater from comparable doses of pancuronium in uncasted gastrocnemius muscle, the time of onset was about the same during each 15-min period of observation in both casted and uncasted muscles. In both muscles, depression of the train-of-four five and ten min after pancuronium was similar, while occasionally, the blockade at 15 min was beginning to dissipate. Thus, the reported data are 10-min values.

Disuse atrophy was a consistent finding in the immobilized muscle (table 1), but it surprisingly also occurred in some of the paired uncasted gastrocnemius muscles as shown by the muscle-to-body weight ratio (table 1, dogs 2 and 5). Variations in muscle weight were not a criterion for selection in the analysis of T_1 muscle responses described above; comparisons were on the basis of casted *vs.* uncasted muscle.

Control T_1 tension (g/100 g muscle wet weight) was 167.6 ± 109.0 casted, 49.2 ± 9.4 uncasted, and 58.7 ± 17.2 "normal." In order to eliminate the effect of atrophy in magnifying tension values expressed as g/100 g, control T_1 tension was also expressed as tension per entire gastrocnemius muscle: casted muscle tension was 39.3 ± 21.7 g, uncasted 17.9 ± 3.8 , and "normal" 27.4 ± 8.1 g. While there was a trend towards greater T_1

tension in atrophic casted muscle, neither method of expressing tension resulted in significant differences, paired *t* test, $P > 0.10$. "Normal" muscle paralysis occurred at doses similar to uncasted muscle. Based upon measurements each 30 min, vital signs of the animals remained within normal limits or within those described in Methods for arterial blood pressure, heart rate, and Pa_{CO_2} . Muscle temperature was $37.4 \pm 0.1^\circ C$ and Pa_{O_2} ranged from 120–200 torr throughout the period of observation.

Discussion

Disuse atrophy following immobilization was associated with an almost twofold resistance to the nondepolarizing relaxant pancuronium. Pharmacokinetic differences⁸ probably do not account for this resistance; they also do not account for the resistance observed in patients with burns.⁹ Plaster cast immobilization for four weeks results in true atrophy rather than, for example, loss of water, as potassium content was not different from normal, 8.4 ± 0.3 mEq/100 g (disuse)⁴ *vs.* 9.1 ± 0.2 ,⁴ 7.8 ± 0.2 ,¹⁰ and 8.8 ± 0.3 ¹⁰ (normal). Muscle blood flow was not different, although these measurements were made during halothane rather than pentobarbital/nitrous oxide anesthesia— $9\text{--}12 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ (disuse)⁴ *vs.* $8\text{--}15$ (three groups of normal).^{4,10} The design of this study was to search for differences in the responses of muscle with disuse atrophy. For this reason, incremental doses of pancuronium were given each 15 min so as to compare both time of onset and any changes in the degree of blockade during that 15-min period. This regimen provided us with further evidence, albeit crude, against a pharmacokinetic explanation for this resistance to pancuronium. The time of onset was similar in both types of muscle and the degree of blockade, although less in casted muscle, did not otherwise vary from that of uncasted muscle during the 15-min period of observation.

Differences in pharmacodynamics⁸ may be a factor in

TABLE 1. Degree of Disuse Atrophy

Dog Number	Days Immobilized	Gastrocnemius Weight (g)		Muscle Weight (g) Body Weight (kg)	
		Casted	Uncasted	Casted	Uncasted
1	27	27.4	32.1	2.38	2.79
2	27	18.0	20.2	1.07	1.20
3	28	33.4	43.3	2.57	3.33
4	28	34.9	45.7	2.55	3.34
5	29	20.0	32.9	1.43	2.35
6	32	33.7	41.1	2.70	3.29
7	0	—	46.4	—	3.57
			47.1		3.62
8	0	—	46.1	—	3.69
			46.2		3.70

this resistance. Increasing sensitivity to acetylcholine of surface membranes of skeletal muscle is related to spread of receptor sites beyond the neuromuscular junction, and disuse atrophy slightly increases this sensitivity.¹¹ These extrajunctional receptor sites have binding properties for nondepolarizing relaxants and α -bungarotoxin that are little different from those properties of junctional receptors.¹¹ Therefore, in casted muscle it is likely that more nondepolarizing relaxant is bound at extrajunctional areas. Less certain is the possibility that the binding of pancuronium to junctional receptor sites is altered.

My data with disuse atrophy may explain the resistance to nondepolarizing muscle relaxants described in patients with upper motor neuron lesions^{1,2} or thermal trauma.³ While hyperactive reflexes might actually help to prevent disuse atrophy, some muscle groups should develop disuse. In the study of patients with burns, conclusions were based on blood levels of *d*-tubocurarine: these patients required a 4- to 5-fold higher blood level than did normal patients for 50 per cent and 95 per cent twitch suppression.³ As patients with burns have recognized alterations in protein and tissue metabolism, other factors may alter the effective blood levels of *d*-tubocurarine. Thus, disuse atrophy is probably a contributing factor to this resistance in patients with burns and upper motor neuron lesions. Based on my data, I believe that any patient with disuse atrophy is likely to require higher doses of nondepolarizing relaxant for paralysis of the affected muscle.

The 95 per cent confidence limits for the ED₅₀ of pancuronium are wide for both casted and uncasted muscle. This lack of precision in estimating ED₅₀ likely relates to experimental protocol and to variable disuse atrophy. Separation of increments of pancuronium by 15-min intervals may result in uneven blockade after 30–45 min due to redistribution of pancuronium.¹² Variable disuse atrophy (table 1) undoubtedly results in variable resistance to pancuronium. Nonetheless, the casted muscle group responses differed significantly from the uncasted responses. The unforeseen occurrence of atrophy in uncasted muscle remains unexplained; this was presumably related to voluntary inactivity of uncasted muscle during the period of limb immobilization. Although similar muscle atrophy of nonimmobilized limbs has been

reported in humans,¹³ this was not detected in our prior study of immobilization disuse atrophy.⁴

Patients with upper motor neuron lesions and thermal trauma have another common feature—they can develop hyperkalemia following the use of succinylcholine;¹⁴ this phenomenon has been suggested as being due to spread of receptor sites into extrajunctional areas. Should this response be interrelated with resistance to nondepolarizing relaxants, then further study of the potentially catastrophic hyperkalemic response may be possible through examination of the dose-response relationship of nondepolarizing relaxants.

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