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The Effects of Acute and Chronic Hydrocortisone Treatment on Neuromuscular Blockade in the Anesthetized Cat

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It is fairly widespread clinical practice to administer large doses of corticosteroids to patients in cases of shock; doses of hydrocortisone as high as 50 mg·kg^{-1} given intravenously have been proposed and used. Hydrocortisone, when administered in this way during surgery, has been implicated in interactions with neuromuscular blocking agents. In order to determine the type and mechanism of this interaction, the authors undertook further investigation. The effects of hydrocortisone were studied in two ways. Firstly, a constant 50% depression of the indirectly elicited twitch tension of the tibialis–anterior muscle was established in cats, using a constant intravenous infusion of either pancuronium (1.0 ± 0.2 μg·kg^{-1}·min^{-1}) or succinylcholine (3.6 ± 0.8 μg·kg^{-1}·min^{-1}). The effects of intravenous hydrocortisone then were studied on this block. Secondly, cats chronically were treated with 2 mg·kg^{-1} of intramuscular hydrocortisone three times a week for 1 month, and then dose–response curves were constructed for pancuronium or succinylcholine. Acute administration of intravenous hydrocortisone (1–15 mg·kg^{-1}) alone had no affect on the twitch tension of either the tibialis–anterior or soleus muscles, however, the corticosteroid (7 and 15 mg·kg^{-1}) did significantly ($P < 0.05$) enhance the 50% depression of the indirectly elicited twitch tension of the tibialis–anterior muscle produced by the constant intravenous infusion of pancuronium. The soleus muscle was affected similarly (n = 6). Under the same conditions, with a constant infusion of succinylcholine, hydrocortisone had no effect on the blockade of the tibialis–anterior muscle or the soleus muscle (n = 6). The chronic treatment of male cats with hydrocortisone had no effect on the sensitivity to pancuronium (n = 6) of both the tibialis–anterior and soleus muscles. However, this treatment did produce a significant ($P < 0.05$) change in sensitivity to succinylcholine (n = 6) on the tibialis–anterior muscle but not on the soleus muscle. Two of the 12 cats chronically treated with hydrocortisone exhibited histologic evidence of myopathy. It is concluded that hydrocortisone can enhance the neuromuscular blocking effect of pancuronium and that chronic hydrocortisone treatment can modify the response to succinylcholine. In either case, monitoring of neuromuscular transmission during anesthesia is suggested when a patient is receiving either high-dose acute or chronic hydrocortisone therapy. (Key words: Hormones: corticosteroids. Neuromuscular relaxants: pancuronium; succinylcholine.)

IT HAS BEEN RECOGNIZED for a long time that anesthesiologists need to be concerned with the role of corticosteroids in anesthetic practice[1–3]; indeed the anesthetic itself may affect the functioning of the adrenal glands and/or the levels of circulating steroids.[2] Patients suffering from myocardial infarction or septic shock have been treated with doses of intravenous hydrocortisone as high as 50 mg·kg^{-1}.[4,5] Recently, Symreng *et al.*[6] reported the beneficial effects of treating surgical patients who do not respond to the corticotropin stimulation test with a total dose of 25 mg hydrocortisone at the time of intubation. Thus, there is a likelihood of some patients who present for surgery having been treated with hydrocortisone. These clinical reports and others that indicate reversal of pancuronium-induced paralysis in patients receiving long-term steroidal therapy[7–9] suggested experiments designed to elicit evidence of such interaction between hydrocortisone and two commonly used neuromuscular blocking agents, pancuronium and succinylcholine, on the indirectly elicited muscle twitch tension.

The isometric twitch tension of the cat tibialis–anterior muscle reduced to 50% of control by a neuromuscular blocking agent was chosen as being particularly sensitive for revealing an interaction with hydrocortisone, since it has been demonstrated that a 50% reduction in twitch tension represents approximately a 90% receptor occupancy.[10] To overcome the problems related to the different sensitivities of fast and slow muscles to muscle relaxants, the responses of both muscle types were studied. The tibialis–anterior is a fast-contracting white muscle, while the soleus is a slow-contracting red muscle. An interaction between hydrocortisone and muscle relaxants would be relevant and important to practicing anesthetists. Some of the initial findings of this study have been presented previously.[11]

Methods

Healthy, adult cats of either sex weighing 3–5 kg were anesthetized with a mixture of α-chlorolose (Aldrich), 80 mg·kg^{-1}, and pentobarbital sodium (Med-tech), 5 mg·kg^{-1}, dissolved in polyethylene glycol and administered intraperitoneally. A tracheostomy was performed on the animals, and they were ventilated artificially at a rate and tidal volume sufficient to keep blood–gas values within normal physiologic limits. Blood pressure was recorded from the cannulated carotid artery via a Beckman® pressure transducer (type 4-327-0121). The tendon and belly of the tibialis–anterior and soleus muscles were dissected from surrounding tissues and each attached to a Grass® FT 10C force displacement transducer. Supra-

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maximal stimuli (4-14V, duration 0.2 ms at 0.1 Hz) were applied to the cut sciatic nerve via a fluid-filled (2% carboxymethylcellulose in normal saline) stainless steel, bipolar electrode from a Grass® S 88 stimulator and SIU5 isolation unit. Esophageal temperature was maintained at 36–38° C. All recordings were made on a Beckman® R612 dynograph.

Hydrocortisone sodium succinate, pancuronium bromide and succinylcholine chloride were administered via the cannulated jugular vein, except that in the chronic experiments, hydrocortisone was administered intramuscularly. When dilutions of drugs were required, they were made in normal saline, except hydrocortisone, which was dissolved in the supplied diluent.

Acute Experiments

Cats prepared in the manner described above were infused intravenously with either pancuronium or succinylcholine at a rate and concentration sufficient to sustain a 50% reduction in twitch tension of the indirectly stimulated tibialis–anterior muscle. Cumulative doses of hydrocortisone (1–15 $mg \cdot kg^{-1}$) then were administered intravenously and the effect on the partially paralyzed muscles noted. In control experiments, equivolume amounts of the supplied hydrocortisone diluent were administered with no effect. At least four cats each were used in control and experimental groups, respectively. Results are presented as the mean ± standard error of the mean. Statistical comparisons were made using the Wilcoxon *t* test for paired data, and $P < 0.05$ was regarded as significant.

Chronic Experiments

Male cats that had been in isolation for at least 30 days prior to use were caged individually and injected with hydrocortisone, 2 $mg \cdot kg^{-1}$, intramuscularly on Mondays, Wednesdays, and Fridays for a period of 30 days. The animals then were anesthetized and surgically prepared as in the acute experiments and recordings made of the indirectly elicited twitch tension. Six cats were administered a range of doses of iv pancuronium 2 h apart, and six cats were given a range of doses of iv succinylcholine 30 min apart. In this manner, dose–response curves could be constructed. Previous unpublished experiments in our laboratory with these two muscle relaxants demonstrated that these time intervals resulted in a neuromuscular block that was not significantly different in either depth or time course when the same dose was used repetitively. Bolus doses rather than cumulative doses were used in the construction of the dose–response curves in order to measure the time course of the neuromuscular block. The maximum per cent change in twitch tension was measured after each injection. Onset of neuromuscular block was taken as the time from injection to maximum effect, and duration was taken as the time from injection to 90% recovery. Muscle samples were taken from all the cats chronically treated with hydrocortisone and subjected to histologic examination with the use of hematoxylin and eosin stain.

As controls, 10 cats not treated with hydrocortisone were divided into two groups. Five cats were given a range of doses of pancuronium and five succinylcholine. Changes in twitch tension were measured and converted to probit values and a comparison of control and experimental groups made using Snedecor's F-test for the slope and intercept. $P < 0.05$ was regarded as significant.

Results

Acute Effects of Hydrocortisone

In a total of four control cats, hydrocortisone alone in cumulative iv doses of 1–15 $mg \cdot kg^{-1}$ had no effect on twitch tension development of either the indirectly stimulated tibialis–anterior or soleus muscles. This dose range additionally had minimal or no effect on blood pressure or heart rate, results that are consistent with those of previous workers who reported no response to a wide range of doses of glucocorticoids.[12–14]

When the twitch tension of the tibialis–anterior muscle was reduced to 50% of control by an intravenous infusion of pancuronium (1 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), cumulative administration of hydrocortisone (1–15 $mg \cdot kg^{-1}$) further reduced the twitch tension development in both the tibialis–anterior and soleus muscles in a dose-dependent manner (figs. 1 and 2). These reductions in twitch tension were consistent and significant ($P < 0.05$) at doses of hydrocortisone of 7 $mg \cdot kg^{-1}$ and 15 $mg \cdot kg^{-1}$ compared with control for both muscles. Blood pressure and heart rate were not affected significantly in the five cats treated with pancuronium and hydrocortisone.

In the presence of a constant intravenous infusion of succinylcholine (3.6 ± 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) to produce 50% reduction of the twitch tension of the muscle, hydrocortisone did not affect twitch tension of the tibialis–anterior or soleus muscles (figs. 1 and 3). Blood pressure and heart rate were not affected significantly in the five cats treated with succinylcholine and hydrocortisone.

Chronic Effects of Hydrocortisone

Log–dose response (converted to probits) regression lines were constructed for pancuronium and succinylcholine. The lines are shown in figures 4*A* and *B* for pancuronium and in figures 4*C* and *D* for succinylcholine. After pretreatment of six cats with hydrocortisone for 30 days (treatment discontinued at least 1 day before experiment), the dose–response relationship for pancu-

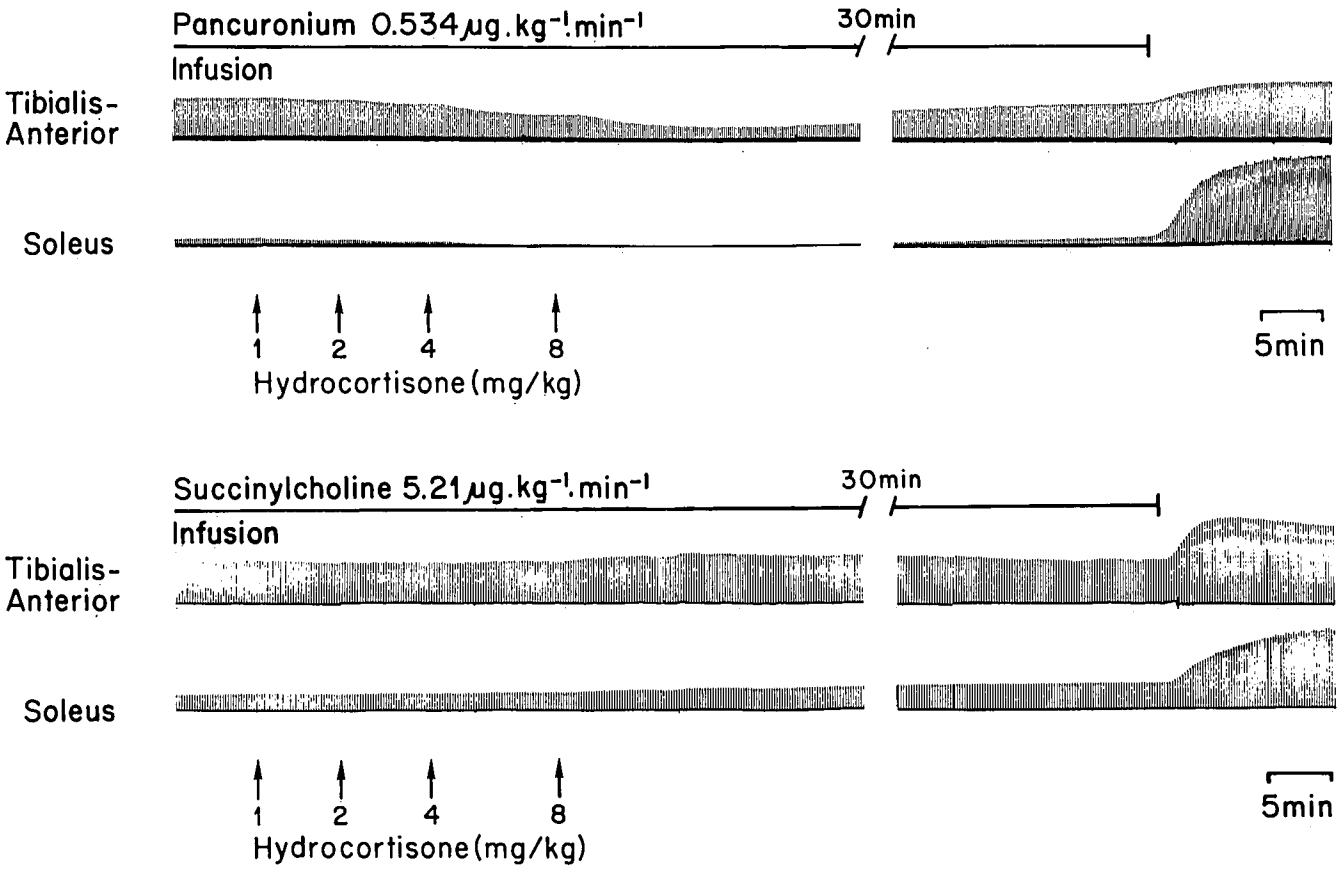

FIG. 1. Typical recording of twitch tension of tibialis–anterior and soleus muscles. The twitch tension of the tibialis–anterior muscle is reduced to 50% by constant intravenous infusion of pancuronium and succinylcholine. Bolus doses of intravenous hydrocortisone were administered at the arrows, and the total dose was calculated cumulatively. Full spontaneous recovery occurred when the infusion was discontinued.

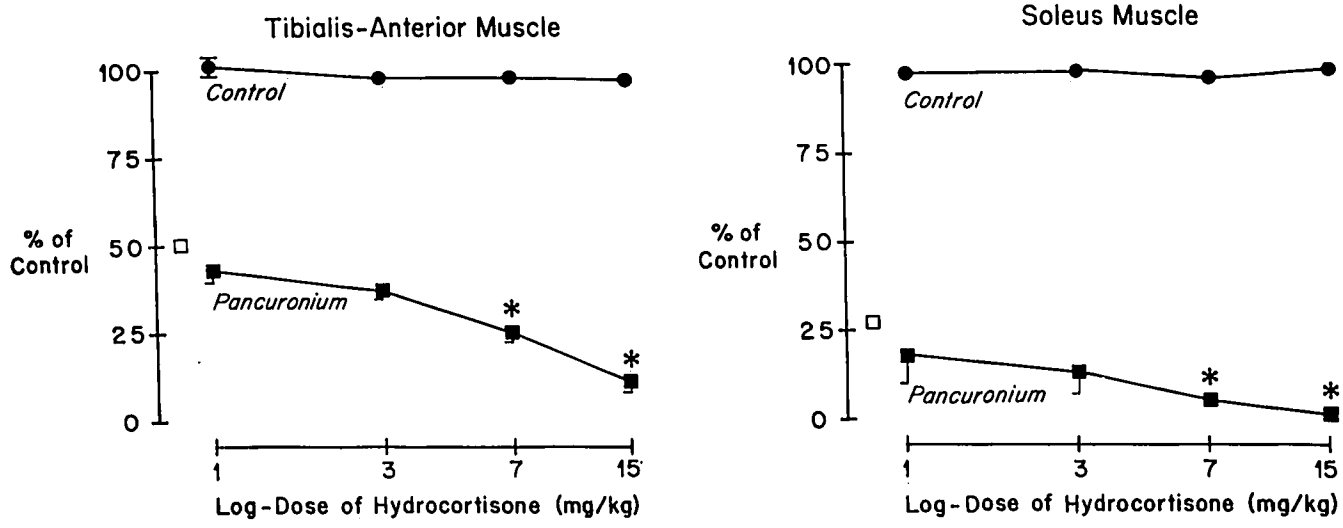

FIG. 2. Change in twitch tension (as percentage of control) of the tibialis–anterior and soleus muscles in response to hydrocortisone alone (●), constant intravenous infusion of pancuronium (□), and cumulative doses of hydrocortisone superimposed on the partial pancuronium blockade (■). The asterisks (*) indicate a significant ($P < 0.05$) difference from the response to hydrocortisone alone. The vertical bars indicate the standard error of the mean of six observations.

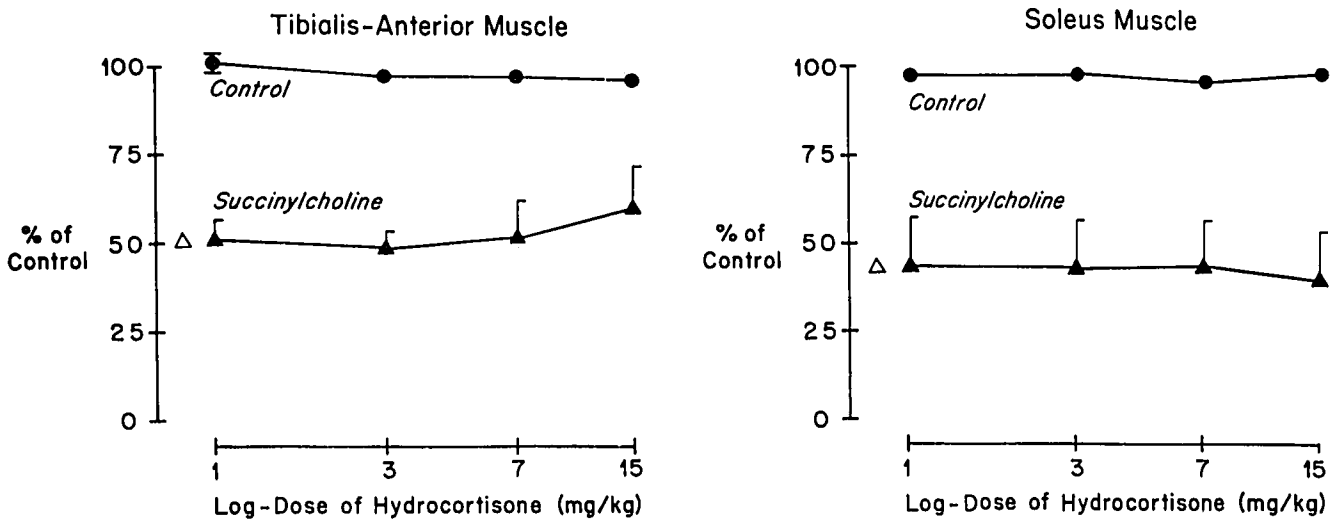

FIG. 3. Change in twitch tension (as percentage of control) of the tibialis-anterior and soleus muscles in response to hydrocortisone alone (●), constant intravenous infusion of succinylcholine (Δ), and to cumulative doses of hydrocortisone superimposed on the partial succinylcholine blockade (▲). The vertical bars indicate the standard error of the mean of six observations.

ronium was not affected significantly. In six cats pretreated with hydrocortisone, the dose–response relationship for succinylcholine was found to be significantly different from the control group for the tibialis–anterior muscle ($P < 0.05$) but not for the soleus muscle. The responses of the soleus muscle were not significantly different from control. The time course of effect of both pancuronium and succinylcholine was not affected significantly by the chronic treatment with hydrocortisone, and these results are shown in table 1.

Histologic samples from two of the hydrocortisone-treated animals revealed muscle myopathy of the tibialis–anterior muscle characterized as shrinkage and darker staining of some muscle fibers; this finding may account for the observed alteration in sensitivity of the tibialis–anterior muscle to succinylcholine.

Discussion

The present study clearly shows that in the anesthetized cat, while acute iv hydrocortisone alone has no effect on indirectly elicited twitch tension, it markedly does enhance the neuromuscular blockade produced by an infusion of pancuronium at doses of hydrocortisone greater than 3 $mg \cdot kg^{-1}$.

Our expectation in undertaking the present experiments was confirmation of a facilitatory action of hydrocortisone at the myoneural junction.[1,15–27] A large number of laboratory studies and clinical reports[7–9] suggest that corticosteroids and, in particular the glucocorticoids, exert a facilitatory effect. It has been suggested that this facilitatory action is manifest via mechanisms ranging from an action on adrenocorticotrophic hormone (ACTH) to an effect on the release of acetylcholine at the neuromuscular junction. Torda and Wolff[17] showed that, of several pituitary hormones, only ACTH could substitute for the pituitary gland in restoring muscle action potentials to normal in hypophysectomized rats. In this regard, cortisone was partially successful, and it was concluded that ACTH is the factor released by the pituitary gland, which is responsible for maintaining acetylcholine synthesis at an optimum level. Further, Torda and Wolff[17] found that ACTH and cortisone enhance production of acetylcholine in mouse-brain homogenate. A number of studies have shown that glucocorticoids increase motor nerve excitability,[22,23] spontaneous release of transmitter,[24] and choline transport.[21]

In the design of our acute experiments, the neuromuscular blocking agent under study was infused iv to maintain a 50% reduction in the twitch tension of the tibialis–anterior muscle, thus corresponding to approximately 90% receptor occlusion.[10] The administration of hydrocortisone under these conditions might be expected to have resulted in at least a partial reversal of the pancuronium-induced neuromuscular block, if indeed the corticosteroid exerted a facilitatory effect mediated via cholinergic action at the myoneural junction. Instead, our results showed hydrocortisone to potentiate the pancuronium-induced neuromuscular block. Conversely, it would be expected that if hydrocortisone acted via a prejunctional facilitatory mechanism to increase release of acetylcholine, that it would have had at least an additive effect with succinylcholine on the tibialis–anterior muscle, which exhibits depolarizing neuromuscular block in response to succinylcholine.[28]

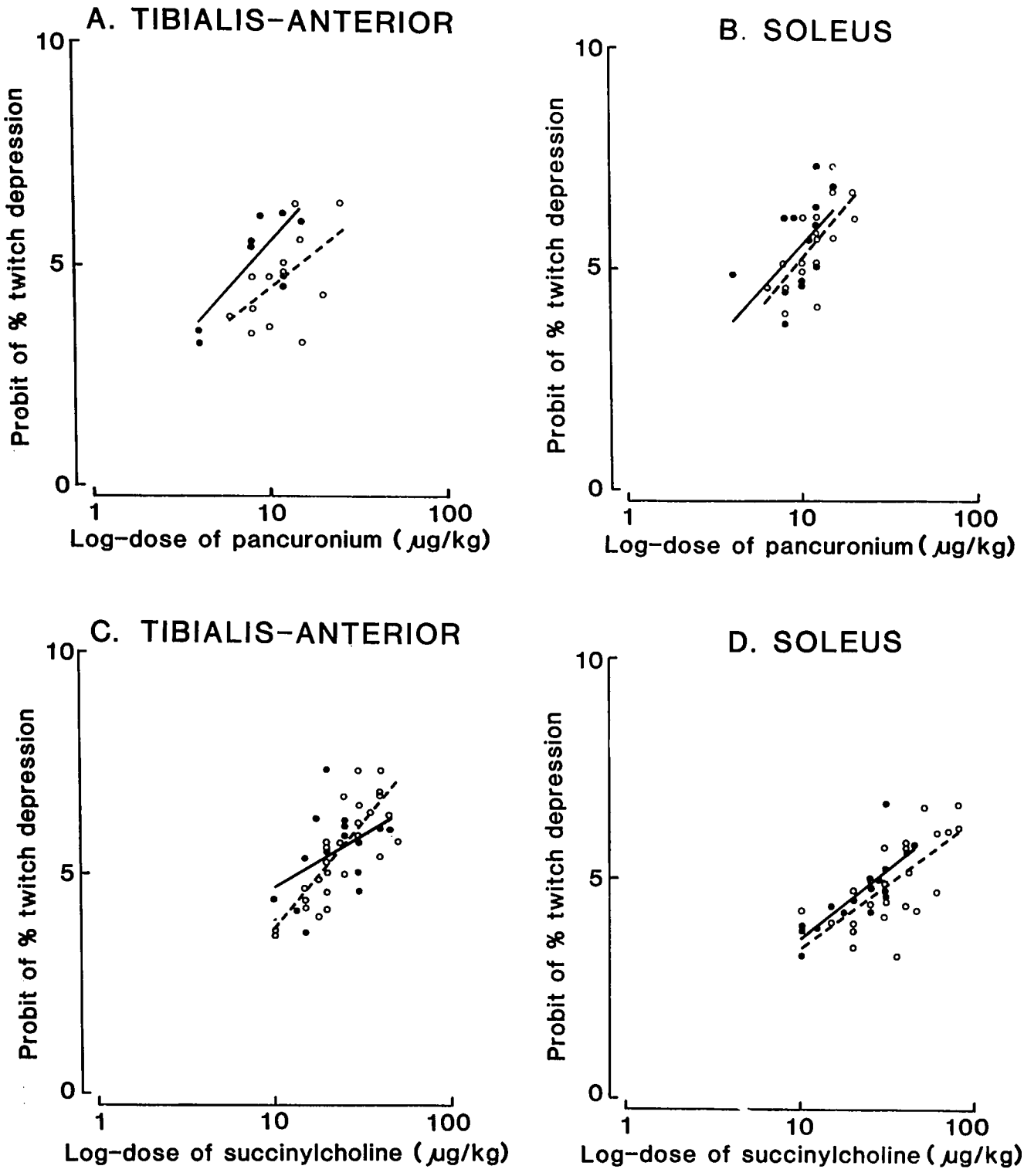

FIG. 4. Log dose–response curves for untreated (---, O) and chronically hydrocortisone treated (——, ●) cats for pancuronium (*A* and *B*) or succinylcholine (*C* and *D*), fitted by regression analysis. The percentage twitch depression is converted to probit values. Only the change of the succinylcholine dose–response curve on the tibialis–anterior muscle was statistically significant ($P < 0.05$) using Snedecor's F-test.

TABLE 1. Mean and Standard Error of the Mean for Onset and Duration of One of the Doses of Pancuronium and Succinylcholine Neuromuscular Block on the Tibialis–Anterior and Soleus Muscles with and without 30 Days of Hydrocortisone Treatment, 2 $mg \cdot kg^{-1}$ Three Times a Week

	Onset (min)		Duration (min)	
	Tibialis	Soleus	Tibialis	Soleus
Pancuronium 12 $\mu g \cdot kg^{-1}$	4.9 ± 0.9 (6)*	5.3 ± 0.9 (6)	11.0 ± 1.1 (4)	11.1 ± 2.3 (6)
Pancuronium after hydrocortisone treatment	5.5 ± 0.7 (5)	6.0 ± 0.6 (5)	12.8 ± 1.7 (4)	17.6 ± 4.5 (5)
Succinylcholine 30 $\mu g \cdot kg^{-1}$	1.4 ± 0.07 (6)	1.6 ± 0.4 (6)	5.5 ± 0.7 (5)	5.6 ± 0.9 (3)
Succinylcholine after hydrocortisone treatment	1.2 ± 0.3 (5)	1.8 ± 0.7 (5)	5.8 ± 1.4 (5)	7.3 ± 1.6 (5)

No statistically significant difference was noted between the untreated and hydrocortisone treated animals in these variables using the Mann–Whitney U-test.

* Number of observations is indicated in parentheses.

The observation that in the acute experiments the twitch tension returned to the prehydrocortisone level following drug administration suggests that the enhancement of the neuromuscular block produced by pancuronium spontaneously reverses when the muscle relaxant is no longer present, however, the neuromuscular margin of safety may well remain reduced for some time. It is possible that it was the existence of a postjunctional action of hydrocortisone that might have obscured a facilitatory effect, if it indeed took place at all.

The chronic experiments with hydrocortisone suggest that the long-term effects of the drug are different from the acute effects. The altered sensitivity to succinylcholine on the tibialis–anterior muscle may have been due in part to the muscle myopathy that was observed in two of the 12 cats that were tested. It therefore seems likely that hydrocortisone-induced myopathy may be one of the reasons for the change in sensitivity to succinylcholine observed in our chronic study.

While our results are not consistent with a facilitatory action of hydrocortisone, not all of the available literature is in unequivocal support of such an action of the glucocorticoids. Sprouse *et al.*[15] report that in the adrenalectomized rat, the motor nerve terminal excitability is restored by the mineralocorticoids aldosterone and desoxycorticosterone but not affected by the glucocorticoid, corticosterone. Several other studies report a postjunctional depressant action of glucocorticoids,[13,20,24] and Wilson *et al.*[25] suggest that the glucocorticoid, prednisone, has two sites of action, one of which is clearly presynaptic and facilitatory and the other postsynaptic and inhibitory. Which action predominates is determined by local drug concentration and is influenced by the duration of the drug treatment.

Our results indicate that it is a depressant action of hydrocortisone that appears to be important within the therapeutic dose range. Whether, in the acute studies it is an action of hydrocortisone on the postjunctional receptors remains to be clarified. Thus, in contrast to some previous workers, in both the acute and chronic studies we found no evidence of a facilitatory action of hydrocortisone.

It is concluded that during acute treatment with hydrocortisone, enhancement of the neuromuscular block produced may occur, particularly with large doses of the corticosteroid. It also is concluded that chronic treatment with hydrocortisone may cause modification of the response to muscle relaxants. Overall, our results illustrate that hydrocortisone can and does affect the response to muscle relaxants and that special regard should be paid to monitoring neuromuscular transmission in patients who are receiving high doses of hydrocortisone prior to or during anesthesia in which a muscle relaxant is used.

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References

1. Woodbury DM: Relation between the adrenal cortex and the central nervous system. Pharmacol Rev 10:275–357, 1958
2. Vandam LD, Moore FD: Adrenocortical mechanisms related to anesthesia. ANESTHESIOLOGY 21:531–552, 1960
3. Papper EM, Cahill GF: Anesthetic problems in hormonal disorders of the adrenal glands. JAMA 148:174–179, 1952
4. Mir MA, Rees S, Yahya AM, Williams JD, Reeves TL: Clinical appraisal of shock following acute myocardial infarction. Cardiology 59:69–82, 1974
5. Wilson RF, Chiscano AD, Quadros E, Tarver M: Some observations on 132 patients with septic shock. Anesth Analg 46:751–763, 1967
6. Symreng T, Karlberg BE, Kågedal B, Schildt B: Physiological cortisol substitution of long-term steroid-treated patients undergoing major surgery. Br J Anaesth 53:949–954, 1981
7. Meyers EF: Partial recovery from pancuronium neuromuscular blockade following hydrocortisone administration. ANESTHESIOLOGY 46:148–150, 1977
8. Laflin MJ: Interaction of pancuronium and corticosteroids. ANESTHESIOLOGY 47:471–472, 1977
9. Reves JG: Steroids and Anesthesia. Anesth Analg 57:379, 1978
10. Paton WDM, Waud DR: The margin of safety of neuromuscular transmission. J Physiol (Lond) 191:59–90, 1967

11. Durant NN, Briscoe JR, Lee C, Katz RL: The acute effects of hydrocortisone on neuromuscular transmission. ANESTHESIOLOGY 57:A266, 1982
12. Hofmann WW: Antimyasthenic action of corticosteroids. Arch Neurol 34:356–360, 1977
13. Patten BM, Oliver KL, Engel WK: Adverse interaction between steroid hormones and anticholinesterase drugs. Neurology 24:442–449, 1974
14. Dengler R, Rüdel R, Warelas J, Birnberger KL: Corticosteroids and neuromuscular transmission: Electrophysiological investigation of the effects of prednisolone on normal and anticholinesterase-treated neuromuscular junction. Pflügers Arch 380:145–151, 1979
15. Sprouse J, Baker T, Riker WF: Differential effects of mineralo- and glucocorticoids on mammalian motor nerve terminals. Fed Proc 41:1300, 1982
16. Del Pozo EC, Negrete MJ, Ibarra J, Fernández LM: Effects of cortisone on striated muscle contraction. Am J Physiol 171:354–358, 1952
17. Torda C, Wolff HG: Effects of pituitary hormones, cortisone and adrenalectomy on some aspects of neuromuscular function and acetylcholine synthesis. Am J Physiol 169:140–149, 1952
18. Hall ED: Glucocorticoid enhancement of guanidine neuromuscular facilitation. Exp Neurol 68:581–588, 1980
19. Dlouhá H, Vyskočil F: The effect of cortisol on the excitability of the rat muscle fibre membrane and neuromuscular transmission. Physiol Bohemoslov 28:485–494, 1979
20. Wilgenburg HV: The effect of prednisolone on neuromuscular transmission in the rat diaphragm. Eur J Pharmacol 55:355–361, 1979
21. Leeuwin RS, Wolters ECMJ: Effects of corticosteroids on sciatic nerve-tibialis anterior muscle of rats treated with hemicholinium-3. Neurology 27:171–177, 1977
22. Hall ED, Baker T, Riker WF: Glucocorticoid preservation of motor nerve function during early degeneration. Ann Neurol 1:263–269, 1977
23. Riker WF, Baker T, Okamato M: Glucocorticoids and mammalian motor nerve excitability. Arch Neurol 32:688–694, 1975
24. Arts WF, Oosterhuis HJ: Effects of prednisolone on neuromuscular blocking in mice in vivo. Neurology 25:1088–1090, 1975
25. Wilson RW, Ward MD, Johns TR: Corticosteroids: A direct effect at the neuromuscular junction. Neurology 24:1091–1095, 1974
26. Hall ED, Riker WF, Baker T: Glucocorticoid effects on the edrophonium responsiveness of normal and degenerating mammalian motor nerve terminals. Ann Neurol 2:404–408, 1977
27. Gruener R, Stern LZ: Corticosteroids. Effects on muscle membrane excitability. Arch Neurol 26:181–185, 1972
28. Zaimis EJ: Motor end-plate differences as a determining factor in the mode of action of neuromuscular blocking substances. J Physiol (Lond) 122:238–251, 1953