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 Title : GERMINE MONOACETATE, 4-AMINOPYRIDINE AND SUCCINYLCHOLINE
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Introduction. The ability of 4-aminopyridine (4-AP) to reverse non-depolarizing neuromuscular block is well established¹. However, the effect of the drug on succinylcholine (SCh) depolarizing and nondepolarizing neuromuscular block has not been described. Germinine monoacetate (GMA) is a veratrum alkaloid derivative which, like 4-AP, also reverses nondepolarizing neuromuscular block. Unlike 4-AP, which acts by raising evoked release of acetylcholine, the action of GMA is mainly due to a direct effect on the muscle fibers². In the cat, the tibialis anterior muscle maintains the characteristics of depolarizing block in response to SCh whilst the soleus muscle rapidly develops the characteristics of nondepolarizing block³. In the present study the actions of 4-AP and GMA on both types of SCh neuromuscular block in the anesthetized cat were investigated.

Methods. The sciatic nerve-tibialis anterior and soleus muscle preparations of the cat were used to determine neuromuscular block at a frequency of nerve stimulation of 0.1 Hz. A constant intravenous infusion of SCh was used to achieve a constant depression to 20% of control height of the twitch tension of the tibialis anterior muscle. Once the correct infusion rate was established it was maintained throughout the experiment. Four doses of 0.5 mg/kg (total = 2 mg/kg) of either 4-AP or GMA were administered intravenously at intervals of ten minutes and the change of twitch tension assessed. Only either 4-AP or GMA alone was tested in one cat at a time. Results are presented as the mean \pm SEM of five observations.

Results. 4-AP had little effect on the block of either the tibialis anterior or soleus muscles produced by SCh as shown in table 1.

	TIBIALIS (% of control)	SOLEUS (% of control)
SCh infusion	19 \pm 2	39 \pm 10
SCh + 4-AP 0.5 mg/kg	18 \pm 5	40 \pm 11
1.0 mg/kg	21 \pm 6	48 \pm 12
1.5 mg/kg	24 \pm 7	52 \pm 13
2.0 mg/kg	23 \pm 8	59 \pm 15

TABLE 1. The effect of 4-AP on SCh neuromuscular block (constant infusion) of the tibialis anterior and soleus muscles of the cat ($P > 0.05$ for all values compared to SCh alone by paired t-test).

In contrast to 4-AP, GMA produced almost complete reversal of SCh block of both the tibialis anterior and soleus muscles as shown in table 2.

	TIBIALIS (% of control)	SOLEUS (% of control)
SCh infusion	19 \pm 3	37 \pm 10
SCh + GMA 0.5 mg/kg	34 \pm 8*	44 \pm 12
1.0 mg/kg	71 \pm 16*	75 \pm 17*
1.5 mg/kg	91 \pm 23*	86 \pm 21*
2.0 mg/kg	90 \pm 15*	108 \pm 23*

TABLE 2. The effect of GMA on SCh block (constant infusion) of the tibialis anterior and soleus muscles of the cat (*indicates significant difference from SCh alone at $P < 0.05$ by paired t-test).

Discussion. The results of this study clearly show that GMA is a better reversal agent of both depolarizing and nondepolarizing SCh block whilst 4-AP is without effect. The effectiveness of GMA is most likely due to its known ability to cause repetitive firing directly in muscle fibers in response to a single nerve stimulus². Evidence of muscle fiber repetitive firing was observed as marked multiple peaking of the EMG in every cat after GMA (unpublished observation). It is more difficult to explain the lack of effect of 4-AP on the nondepolarizing block of the soleus muscle. Possible explanations are that the increased release of acetylcholine produced by 4-AP is insufficient to overcome the block, or that SCh might block the facilitatory effect of 4-AP on the nerve terminal. It is concluded that, in the cat, GMA is a satisfactory reversal agent of the depolarizing and nondepolarizing neuromuscular block of SCh. The lack of effect of 4-AP on both types of SCh block may provide further insight into the phenomenon of dual block.

References:

1. Bowman W C, Harvey A L, Marshall I G: The actions of aminopyridines on avian muscle. *Naunyn Schmiedeberg's Arch Pharmacol* 297:99-103, 1977
2. Brennan J L, Jones S F, McLeod J G: Effect of germinine acetates on neuromuscular transmission. *J Neurol Sci* 13:321-331, 1971
3. Cheymol J, Bourillet F: Inhibitors of post-synaptic receptors, Neuromuscular blocking & stimulating agents. Edited by Cheymol J. Oxford, Pergamon, 1972, pp 297-356