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Title : GERMINE MONOACETATE COUNTERACTS DANTROLENE SODIUM

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Introduction. Whether it is used for the relief of spastic neurological disorders, or for the prophylaxis or treatment of malignant hyperthermia, the therapeutic use of dantrolene sodium (DS) may cause excessive weakness by direct muscle depression (although this occurs rarely). Drug counteraction of the effect of DS is of pharmacological and clinical interest.

Methods. Twelve anesthetized and ventilated cats were given DS (q.s., intravenously) to produce a slightly over 80% depression of the contraction of the tibialis anterior muscle (quantified by measuring the mechanical force output with a Grass FT 10C force transducer). The sciatic nerve was stimulated supramaximally with 0.1 ms square electric pulse at 0.1 Hz. Spontaneous recovery of muscle power (to roughly 20% of control, 80% depressed) was observed for 30 minutes. Then, 6 cats received germine monoacetate (GMA), dissolved in 0.9% saline, 0.5 mg/kg i.v. two times 10 minutes apart to each cat. The other 6 cats received calcium chloride 10 mg/kg i.v., four times to each cat also at 10-minute intervals. Improvement in the force of muscle twitch following drug injections was quantified.

Results. Spontaneous recovery of DS-depressed muscle contraction was very slow, gaining by only 1~4% of control during the 30 minutes preceding the injection of GMA or $CaCl_2$. While GMA rapidly and completely reversed DS-induced muscle depression and caused a marked overshoot in the muscle contraction, $CaCl_2$ at the doses studied was without effect on the muscle contraction (table 1). The effect of GMA was long-lasting. No recurrent muscle depression was seen in 1 hour.

TABLE 1. Effects of GMA and $CaCl_2$ on DS-depressed muscle contraction*:

	DS	After GMA or $CaCl_2$** 10 min	20 min	30 min	40 min
GMA	24 (3)	32 (7)	140 (20)	153 (23)	149 (23)
$CaCl_2$	28 (3)	26 (2)	26 (2)	26 (2)	26 (3)

*Muscle twitch before DS=100. In parentheses are SEM, N=6, each. **GMA, 0.5 mg/kg X 2, q. 10 min; $CaCl_2$ 10 mg/kg X 4, q. 10 min., time started from the injection of the 1st dose of GMA or $CaCl_2$.

In the case of GMA, while a dose of 0.5 mg/kg was just enough to show some effect in some cats (threshold dose), 2 doses of 0.5 mg/kg uniformly caused the marked overshoot mentioned above.

Discussion.

1. DS probably depresses muscle contraction by impairing excitation-contraction coupling, reducing the intracellular Ca^{++} concentration surge triggered by the action potential of the muscle. Specific antagonism of DS by drugs which facilitate excitation-contraction coupling (uranyl ions, thiocyanate ions, adrenaline, caffeine, quazodine, quinine, calcium ionophore A23187, and 4-aminopyridine) has been examined in vitro by Bowman et al[1]. With the exception of 4-aminopyridine, these drugs have no foreseeable clinical potential for the counteraction of DS and were not studied with that intention. Most of these compounds also lack potency.

2. GMA probably acts by causing stimulus-bound repetitive firing of the muscle[2] (and of the nerve), which in turn causes accumulation of intracellular Ca^{++} and prolongation of the contraction time. Thus it rather specifically opposes the effect of DS. It has been considered a very effective anticurare agent. Because the dose requirement of GMA for the counteraction of DS, 0.5~1.0 mg/kg, is not greater than its dose requirement for the reversal of curariform block, it should also be considered very effective as anti-DS agent. Moreover, it has been tried clinically[3] for the treatment of myasthenia gravis, therefore, it has a clinical potential. Whereas respiratory support, if necessary, remains the therapy of choice for DS-induced muscle depression, drug therapy with GMA may become a useful adjunct in the future.

3. Calcium is not only ineffective for the counteraction of DS, but is also generally considered contraindicated in the case of malignant hyperthermia for which treatment with DS may cause excessive muscle depression. Failure of exogenous calcium to counteract DS in vivo, in doses large enough to facilitate neuromuscular transmission and to reverse nondepolarizing neuromuscular block, requires explanation.

Conclusion. GMA effectively and rapidly reverses DS-induced muscle depression, while calcium is without effect.

References:

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