Title: Predicting the Effect Priming with Atracurium with a Pharmacokinetic-Pharmacodynamic Model.

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Introduction. When testing the effectiveness of the priming technique, three variables can be modified: the size of the priming dose, the priming interval, and the size of the paralyzing dose. It is difficult to design studies which will test all of these variables at the same time, because of the large number of patients required. This study was designed to use known kinetic and dynamic properties of atracurium to calculate the predicted time to onset of neuromuscular blockade.

Methods. The two-compartment model with effect compartment was used. The parameter values for atracurium were (1): distribution half-life: 2 min; elimination half-life: 20 min; central volume: 0.05 ml/kg; distribution volume: 0.15 ml/kg; effect compartment rate constant (keo): 0.1 /min. The ED50 and ED95 were 0.12 and 0.21 mg/kg, respectively.(2) The relationship between the logit transformation of blockade and the logarithm of the concentration was assumed to be linear. The calculated effect of two doses of atracurium was that corresponding to the sum of the concentrations which would have been present if each dose had been given alone. The size of the priming doses was varied between 0 and 0.1 mg/kg; the priming interval was varied between 0 and 7 min; and the total dose given was varied between 0.21 (ED95) and 0.8 mg/kg. Onset time was defined as the time between administration of the second dose until either maximum blockade or 99% blockade, whichever occured first. Shortening of onset time was defined as the difference in onset times with and without priming, using the same total dose.

Results. Predicted onset times without priming decreased with increasing dose. They were 360 s with a dose of 0.3 mg/kg and 86 s with 0.6 mg/kg. Priming always shortened onset time. Acceleration of onset time was the same for priming intervals in the range 3-7 min, and this optimal interval was independent of the priming or paralyzing doses (Table I). However, the effect of priming doses increased slightly between 3 and 5 min (Table II), and doses larger than 0.05 mg/kg caused greater than 1% blockade. Onset time was reduced by increasing the priming dose (Table III), but this reduction was less important if large paralyzing doses were used. If a priming dose of 0.05 mg/kg was followed by 0.37 mg/kg (total = 2 x ED95), onset time was shortened by 12 seconds. If the same priming dose was followed by 0.58 mg/kg (total = 3 x ED95), onset time was shortened by 9 seconds.

TABLE I
Onset time for 0.05 + 0.45 mg/kg

Priming interval (min)	Onset time(sec)
0	113
2	105
3	102
5	102
7	102

TABLE II
Percent block after priming dose

Time(min) / Dose(mg/kg)	3	5	7
0.05	1%	1%	1%
0.07	2%	5%	5%
0.1	14%	22%	26%

TABLE III
Shortening of onset time (sec)

Priming dose (mg/kg) / Total dose (mg/kg)	0.03	0.05	0.07	0.10
0.21	15	26	39	59
0.4	7	12	17	28
0.6	5	9	13	17
0.8	4	6	8	12

Discussion. The results indicate that (1) a priming interval of 3 min is as good as longer intervals; (2) using large priming doses improves onset time but can produce significant blockade of its own; and (3) the acceleration of onset provided with priming decreases as larger doses are given. With a priming dose of 0.05 mg/kg, the expected acceleration of onset for total doses of 2-3 x ED95 (9-12 s) is clinically insignificant. Pharmacokinetic-pharmacodynamic modelling can help identify the important factors which affect the onset of relaxant drugs.

References:
(1) Weatherley BC, Williams SG, Neill EAM. Combined pharmacokinetics and pharmacodynamics and dose-response relationships of atracurium administered IV. Br J Anaesth 55:39S-45S, 1983

(2) Shanks CA. Pharmacokinetics of the nondepolarizing neuromuscular relaxants applied to the calculation of bolus and infusion dosage regimens. Anesthesiology 64: 72-86, 1986