

Pharmacologic Intelligence

Pharmacokinetics of Succinylcholine in Newborns

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A pharmacokinetic analysis of published data describing the degrees and durations of the neuromuscular blocks elicited by succinylcholine in nine newborns shows that the longer-than-average durations of effect in two of the infants resulted from relatively slow elimination of the drug. The unusually prolonged duration of effect in a third infant cannot be explained on the same basis, and may have been due, at least in part, to an unusual "dose"-response relationship. (Key words: Succinylcholine; Pharmacokinetics; Newborns; Kinetics of pharmacologic effects.)

THE neonate is known to be deficient in many drug-metabolizing enzyme systems; therefore, he eliminates most drugs much more slowly than the adult.¹ This is an important consideration in the use of drugs and in the rational design of dosage regimens for use during surgical operations on infants. It is reassuring, therefore, that the recent studies of Walts and Dillon have shown that the duration of neuromuscular blockade following equal doses (based on surface area) of succinylcholine are, on the average, similar in new-born infants and adults.² However, in three of the nine infants studied, considerably longer durations of effect prevailed than in the others. Pharmacokinetic methodology has been developed recently to permit assessment of the probable causes of unusually prolonged duration and/or slow decline of effect of a drug such as succinylcholine.^{3,4} It is the purpose of this report to identify the probable causes of the prolongation of neuromuscular blockade in three of the infants studied by Walts and Dillon.²

Theory

If a drug is eliminated by apparent first-order kinetics and if its metabolites are pharmacologically inactive, the following relation-

ship between duration of effect (t), elimination rate constant (k), dose (A^0), and minimum effective dose (A_{\min}) is likely to apply⁵:

$$t = \frac{2.3}{k} (\log A^0 - \log A_{\min}) \quad (1)$$

Based on this relationship, a plot of t versus $\log A^0$ should yield a straight line with the slope $2.3/k$, independent of the magnitude of the end-point chosen. Such is the case with succinylcholine,⁴ based on the extensive data reported by Walts and Dillon for adult subjects.⁵

If there is an essentially linear relationship (with slope m) between the intensity of a pharmacologic effect and the logarithm of the "dose" (actually, the amount of drug distributed in the body), and if the drug is eliminated by apparent first-order kinetics, it can be shown³ that the intensity of the effect is likely to decline at a rate (R) which is a function of k and m :

$$R = \frac{km}{2.3} \quad (2)$$

This relationship has been shown to apply to succinylcholine in adults.⁴

Rearrangement of equation 2, and substitution for $2.3/k$ in equation 1 yields

$$t = \frac{m}{R} (\log A^0 - \log A_{\min}) \quad (3)$$

Also,

$$tR = m (\log A^0 - \log A_{\min}). \quad (4)$$

Thus, according to these equations, the time course of a pharmacologic effect is a function of dose (A^0), minimum effective dose (A_{\min}), the elimination rate constant (k), and the slope of the response-log dose relationship (m). A change in any one or several of these variables may be responsible for an unusual time course of a pharmacologic effect. In a group of subjects given the same dose of suc-

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TABLE 1. Pharmacokinetic Analysis of Neuro-muscular Blocking Effects of Succinylcholine in Nine Infants*

Patient	Age (Days)	Duration (t) (min)	Rate of Decline (R) (% min ⁻¹)	tR (Per Cent)
11	28	5	40	200
10	24	6	40	240
14	37	6	40	240
15	38	6	40	240
7	10	7	20 (27)†	140 (189)†
4	3	9	27 (30)	243 (270)
2	1	12	27 (30)	324 (360)
5	10	14	16 (17)	224 (238)
8	20	26	9	234

* Based on data from Walts and Dillon.²

† Values in parentheses are calculated by the alternate method described in the text.

choline but showing different durations of effect, the product of duration (t) and rate of decline (R) of effect will yield a constant value if the differences in the observed time courses of effect are solely the result of differences in the elimination rate constant (k) for the drug (equation 4). If, however, the values of tR in the subjects showing prolonged effects differ substantially from those of normal subjects, we must conclude that these subjects differ with respect to m and/or A_{min} . This does not preclude the possibility that they may also differ with respect to k .

Results and Discussion

The nine newborn infants described by Walts and Dillon² are listed in table 1, with the numerical designations used by these authors but in order of increasing duration of effect of succinylcholine. The time for recovery of 50 per cent of the normal force of thumb adduction following administration of about 40 mg/m² succinylcholine was taken as the end-point. The rates of decline of neuro-muscular blocking effect were exactly constant in most of the subjects, nearly constant in the others, as calculated by dividing change in force of adduction (80 per cent, from 10 to 90 per cent of normal) by elapsed time. When not exactly constant the rate of decline of effect also was determined by averaging the

two segments of the curve (from 10 to 50, and from 50 to 90 per cent of normal). The results of the latter determinations are listed in parentheses in table 1. The first six subjects listed showed durations of effect comparable to those obtained with similar doses in adults (8.5 ± 1.6 min).² Five of the six subjects yielded tR values between 200 and 243 (or 270), similar to the average tR value in 20 adults (230) as calculated from the data of Walts and Dillon.² Of the three infants showing unusually long durations of neuro-muscular blockade, infants 5 and 8 yielded tR values of 224 (or 238) and 234, respectively. These are in the normal range and, therefore, we may conclude that the prolonged effects of succinylcholine resulted from unusually slow elimination of the drug (*i.e.*, low k). Infant 2, who also showed a prolonged duration of effect, yielded a tR value of 324 (or 360), well above the normal range. Unless this was the result of problems in determining accurately the time course of effect in this very young (one-day-old) infant, it is likely that this infant differed from the others with respect to m and/or A_{min} . This does not preclude the possibility that an unusually low k (or perhaps elimination of succinylcholine by other than apparent first-order kinetics) may have contributed to the prolonged response also. The data treatment presented here illustrates an aspect of a general approach³ which may be used to determine the probable causes of quantitatively unusual responses to certain drugs.

References

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