Effect of Hepatic Cirrhosis on the Pharmacodynamics and Pharmacokinetics of Mivacurium in Humans[1]

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INTRODUCTION

Mivacurium chloride is a relatively new, nondepolarizing neuromuscular blocking agent which is rapidly hydrolyzed by plasma cholinesterase (1). It was recently shown to have a prolonged duration of action in patients with liver disease and to exhibit a negative, curvilinear correlation between plasma cholinesterase activity and duration of action (2). However, it has not been established if the prolonged duration of action of mivacurium in patients with hepatic cirrhosis is due entirely to altered pharmacokinetics (clearance and half-life) or if it is caused in part by a disease-associated alteration in the pharmacodynamics (concentration–effect relationship) of this drug. It is known that the pharmacodynamics of some drugs can be altered by hepatic cirrhosis (3).

METHODS AND RESULTS

For rapidly reversibly acting drugs that are rapidly distributed in the body and eliminated by apparent first-order kinetics, the duration of action (t) is a function of the elimination rate constant (k_{el}), the bolus i.v. dose (A°), and the minimum effective amount of drug in the body (A_{min}),[3] provided that there is no rapid development of functional tolerance or occurrence of other relevant, rapid, time-dependent physiologic changes (4). Specifically,

$$t = (2.3/k_{el}) \log A^\circ - (2.3/k_{el}) \log A_{min} \quad (1)$$

Thus a plot of t versus $\log A^\circ$ should be linear, with a slope equal to $2.3/k_{el}$, if the above-stated assumptions are correct. In the case of mivacurium, there is an excellent, linear correlation between t and $\log A^\circ$ over a wide dose range, based on the tabulated data reported by Savarese *et al.* (5) for eight doses ranging from 0.03 to 0.30 mg kg^{-1} (correlation coefficient = 0.96). The biologic half-life determined from this relationship is about 7 min.

If mivacurium exhibits an essentially linear relationship between intensity of effect and $\log A^\circ$ (with slope = m) over the clinically relevant intensity of effect range, then the rate of decline of the effect (R) in that range is

$$R = k_{el} m/2.3 \quad (2)$$

i.e., the effect declines at a constant rate with time (4). That is the case with mivacurium (Fig. 1).

Substitution of Eq. (1) in Eq. (2) and rearrangement yields

$$tR = m (\log A^\circ - \log A_{min}) \quad (3)$$

with k_{el} canceling out (6). Thus, a change in tR reflects a change in one or both of the pharmacodynamic parameters m and A_{min} independent of whatever pharmacokinetic alterations may occur concurrently.

In Table I are shown tR data for healthy subjects and patients with hepatic cirrhosis of various degrees of severity, based on the recently reported data of Devlin *et al.* (2). The average duration of neuromuscular blockade ranged from 17.3 min in healthy subjects to 51.6 min in severely cirrhotic patients. On the other hand, the tR values of the four groups are quite similar, with no systematic change as a function of the severity of the disease. It may be concluded, therefore, that hepatic cirrhosis has no apparent effect on the pharmacodynamics of mivacurium.[4]

An estimate of the biologic half-life of mivacurium in patients with moderate and severe hepatic cirrhosis can be made if it is assumed that tR and therefore m values are essentially the same in these individuals and in healthy subjects, as is evident in Table I. Rearrangement of Eq. (2) yields $m = 2.3\, R k_{el}^{-1}$. Assuming that the $t_{1/2}$ is the same in the healthy subjects of Savarese *et al.* (5), calculated here to be about 7 min, and those of Devlin *et al.* (2), m is 140%. Solving for k_{el} and using the relationship $t_{1/2} = 0.693/k_{el}$ yields $t_{1/2}$ values of about 12 and 23 min for patients with moderate and severe cirrhosis, respectively.

It is customary in the literature to examine and plot the relationship between duration of action and plasma cholinesterase activity for neuromuscular blocking agents that are eliminated largely by cholinesterase-mediated hydrolysis. Such plots typically yield a continuous curve reaching an asymptote at high esterase activity (7). As shown in Eq. (1), the duration of action is *inversely* proportional to k_{el}. For enzymatic processes describable by Michaelis–Menten kinetics, $k_{el} = V_{max}/K_m$ when substrate concentrations are well below K_m. It is reasonable to assume that V_{max} is proportional to the enzyme concentration or measured enzyme activity in plasma provided that there are no phenotypic (K_m) differences between subjects. Consequently, a plot of duration of effect of mivacurium versus the *reciprocal* of plasma esterase activity may be expected to be linear and go through the origin provided that plasma cholinesterase activity is proportional to the activity of this enzyme at rele-

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[3] A_{min} is the extrapolated value of A at $t = 0$ in a plot of t versus $\log A$.

[4] Equation (3) assumes, by implication, that the apparent volume of distribution of the drug does not differ between groups. The apparent volume of distribution of mivacurium does not differ significantly between normal patients and those with hepatic or renal failure (7).

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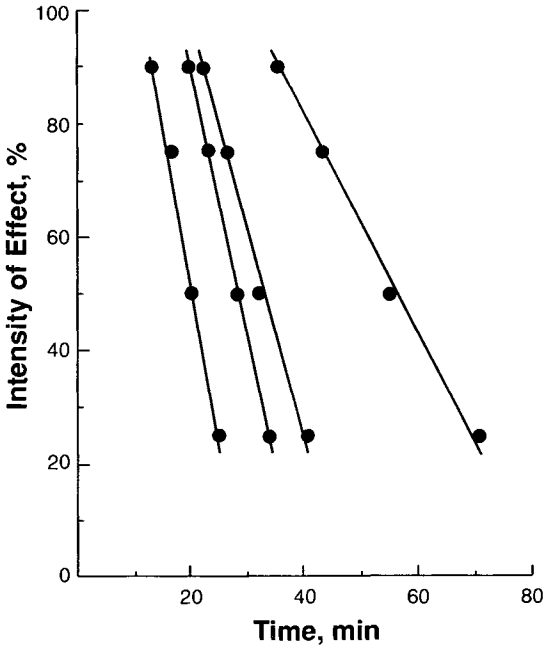

Fig. 1. Neuromuscular blocking effect of mivacurium chloride, 150 μg kg^{-1} by i.v. bolus, as a function of time. From left to right: healthy subjects (n = 10), patients with mild hepatic cirrhosis (n = 10), patients with moderate hepatic cirrhosis (n = 10), and subjects with severe hepatic cirrhosis (n = 5). The figure is based on the tabulated data of Devlin *et al.* (2).

vant sites in the body. However, deviations from linearity toward longer durations of action may be expected to occur at high enzyme activities (i.e., near the origin of the plot) because the elimination kinetics of the drug may be affected by tissue perfusion or by drug or enzyme diffusion under these conditions. A plot of duration of action of mivacurium versus the reciprocal of plasma cholinesterase activity, based on the data of Devlin *et al.* (2), is consistent with these characteristics: It is essentially linear and approaches the origin, with a positive deviation toward longer durations at higher enzyme activities (Fig. 2).

Table I. Effect of Hepatic Cirrhosis on the Product of Duration and Rate of Decline of the Neuromuscular Blocking Effect of Mivacurium Chloride, 150 μg kg^{-1}, in Human Subjects

Subjects	n	Duration of effect (min)[a,b]	Rate of decline of effect (% min^{-1})[a,c]	tR (%)[d]
Healthy	10	17.3	6.02	104
Mild cirrhotics	10	25.7	5.05	130
Moderate cirrhotics	10	29.8	3.42	102
Severe cirrhotics	5	51.6	1.80	93

[a] From Devlin *et al.* (2).
[b] Time to recovery of 50% of normal muscle contractility minus onset time (time to 95% neuromuscular blockade, which averaged from 2.2 to 3.0 min).
[c] In the 75 to 25% effect range.
[d] Product of duration (t) and rate of decline (R) of the effect.

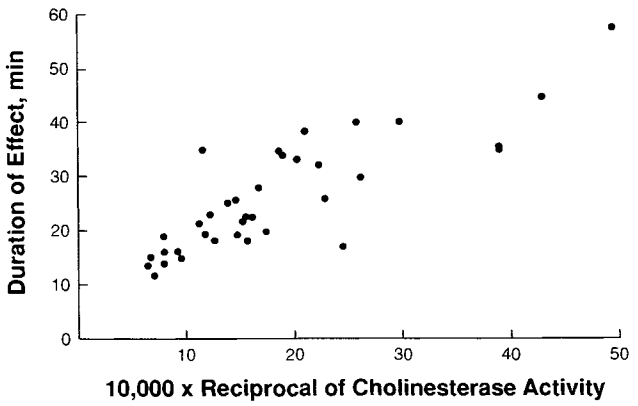

Fig. 2. Duration of neuromuscular blockade produced by mivacurium chloride, 150 μg kg^{-1}, plotted against the inverse of plasma cholinesterase activity (Liter * IU^{-1}) in healthy and cirrhotic subjects, based on the data of Devlin *et al.* (2).

DISCUSSION

The data treatment presented here exemplifies the use of suitable pharmacologic effect data, without corresponding drug concentration data, for pharmacokinetic-pharmacodynamic analyses. These techniques are not suitable for indirectly acting drugs (8) or for drugs with pronounced multicompartmental characteristics (9). A linear relationship between t and $\log A_0$, an essentially constant rate of decline of the pharmacologic effect (Fig. 1), and R values independent of dose or rate of drug administration (bolus or infusion), as is the case for mivacurium (1), provide a basis for the techniques of data analysis used here.

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