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Plasma Concentrations of Pancuronium and Neuromuscular Blockade after Injection into the Isolated Arm, Bolus Injection, and Continuous Infusion

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To establish whether the plasma concentration of pancuronium reflects magnitude of neuromuscular blockade, the authors determined times of recovery from neuromuscular blockade and associated plasma concentrations following equipotent doses of pancuronium using three methods of pancuronium administration: the isolated-arm technique in conscious volunteers (n = 4), and the bolus intravenous injection (n = 7) and continuous-infusion methods (n = 3) in anesthetized patients. Although maximum depressions of twitch tension were similar (85 ± 11, 91 ± 6, and 92 ± 4 per cent, respectively) with the three techniques, times to recovery from neuromuscular blockade differed significantly, being 10 ± 2 min with the isolated-arm technique, 23 ± 7 min with the bolus-injection technique, and 46 ± 5 min with the continuous-infusion method. The plasma concentration of pancuronium necessary for neuromuscular blockade was least with the isolated-arm technique and greatest with continuous infusion. At 25 and 75 per cent recovery, mean plasma concentrations were 0.07 ± 0.01 and 0.04 ± 0.01 μg/ml in the isolated arm; 0.13 ± 0.04 and 0.09 ± 0.02 μg/ml after bolus injection, and 0.20 ± 0.04 and 0.11 ± 0.01 μg/ml during continuous infusion, respectively. It is concluded that the relationship between plasma concentration of pancuronium and magnitude of neuromuscular blockade depends on the method of pancuronium administration. (Key words: Neuromuscular relaxants: pancuronium; measurement of response.)

THE CONCENTRATION of pancuronium at cholinergic receptors probably determines the magnitude of paralysis. If the receptors were located in the central compartment, one might except that factors that alter the plasma concentration of pancuronium should also alter directly the magnitude of neuromuscular blockade.

Following intravenous bolus administration of *d*-tubocurarine or pancuronium, a direct relationship was found between the concentration of the drug in plasma and the magnitude of neuromuscular blockade in anesthetized patients.[1–3] Although these results suggest that recovery from neuromuscular blockade is primarily dependent upon a decrease in the relaxant concentration in plasma, Feldman[4] proposed another mechanism. Using the isolated-arm technique,[5,6] the neuromuscular blockade produced by a local infusion of *d*-tubocurarine, gallamine, alcuronium or pancuronium persisted for as long as minutes after release of the tourniquet when fresh blood (with a presumed relaxant concentration near or actually zero) had flushed the limb. Feldman then proposed that the primary mechanism governing time to recovery from neuromuscular blockade was the dissociation rate constant of the relaxant–receptor complex. He further suggested that correlations between plasma concentrations and magnitudes of neuromuscular blockade in anesthetized patients following intravenous bolus administration of relaxant[1–3] did not represent a causal relationship. The plasma concentration would affect the dissociation of relaxant from the receptor in a secondary manner. If at the end of relaxant administration the plasma concentration remained elevated, the gradient between plasma and the receptor would be low, and therefore recovery from neuromuscular blockade would be delayed. The purpose of this study was to determine whether indeed the plasma concentration of pancuronium does reflect the magnitude of neuromuscular blockade, using three methods of pancuronium administration: the isolated-arm technique, and bolus injection or continuous intravenous infusion of pancuronium. We found that the plasma concentrations necessary for neuromuscular blockade differed with the three methods of pancuronium administration. These results indicate that a simple relationship between plasma concentration of pancuronium and magnitude of neuromuscular blockade does not exist.

Methods

Conscious volunteers were used for the isolated arm technique. Patients studied during bolus injection or continuous intravenous infusion of pancuronium received atropine, 0.25 mg, droperidol, 5 mg, and piritramide (a narcotic analgesic), 11 mg, intramuscularly,

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approximately an hour before induction of anesthesia. Anesthesia was induced with thiopental, 100–150 mg, gamma-hydroxybutyric acid, 60 mg/kg, and fentanyl, 1.5 μg/kg, intravenously. After topical application of lidocaine, 2 ml, 4 per cent, the trachea was intubated without the use of muscle relaxants. Anesthesia was maintained with nitrous oxide, 66 per cent, and incremental doses of fentanyl. Controlled ventilation kept Pa_{CO_2} between 31 and 40 torr.

In all experiments the ulnar nerve was stimulated at the wrist via needle electrodes with square-wave, supramaximal stimuli of 0.2 msec duration and 0.1 Hz. The resultant force of thumb adduction was measured with a force-displacement transducer and recorded on a polygraph. Control twitch tension was recorded for at least 10 min prior to the injection of pancuronium. The magnitude of and time to recovery from neuromuscular blockade were determined. The recovery time was defined as that time during which twitch tension recovered to 25 to 75 per cent recovery of control twitch tension.

The isolated-arm technique[5] was used in four healthy volunteers. After inflation of a tourniquet on the upper arm to 200 torr, saline solution, 40 ml, containing pancuronium bromide, 11 μg/kg, was injected into a vein on the dorsum of the hand over 20 sec. Two minutes after inflation, the tourniquet was released. Blood, 5 ml, was withdrawn from a vein on the contralateral arm under control conditions (before release of the tourniquet), at maximum blockade, and at the times when twitch tension approached 25, 50, and 75 per cent of control, and was later analyzed for pancuronium concentration.

Seven patients undergoing surgical procedures were given bolus injections. Control twitch tension had been constant for at least 10 min when pancuronium bromide, 50 μg/kg, was administered intravenously. Plasma concentrations of pancuronium when twitch tension had returned to 25, 50, and 75 per cent of the control tension were determined.

To three patients undergoing surgical procedures of at least three hours' duration, pancuronium, 1.0 mg, was administered as an intravenous bolus, after which it was infused continuously at a rate that produced a constant 50 per cent depression of twitch tension. When the infusion rate and depression of twitch tension had remained constant for at least 15 min, blood was withdrawn, from which the plasma concentration of pancuronium was determined. Fifteen minutes later the concentration of pancuronium was redetermined. When the difference between the two plasma concentration values obtained during the same period was 10 per cent or less, a steady state was considered to be present. The procedure was repeated at 25 and 75 per cent depression of the twitch height. The infusion rate was then increased until twitch tension was depressed 90 per cent. After a period of 15 min during which both the infusion rate and depression of twitch tension remained constant, the infusion was terminated, and recovery allowed to occur spontaneously. The times at which the twitch tension returned to 25 and 75 per cent of control were recorded.

The concentrations of pancuronium were determined by spectrofluorimetry.[7] Since this assay does not discriminate between the unchanged drug and its bisquaternary metabolites, the total concentrations of the bisquaternary ammonium compounds were determined throughout.

The data were analyzed by the Student t test and Wilcoxon's matched-pairs signed ranks test. $P < 0.05$ was considered significant.

Results

In the isolated-arm experiments, control injections of saline solution had no effect on twitch tension even when the cuff was inflated for 10 min. Maximum depressions of twitch tension were not significantly different among the three methods of administration of pancuronium (85 ± 11, 91 ± 6, and 92 ± 4 per cent with the isolated-arm, bolus-injection and continuous-infusion techniques, respectively).

Although the maximum effects were comparable, recovery from the bolus injection was significantly

TABLE 1. Plasma Concentrations of Pancuronium, Neuromuscular Blockades, and Recovery Times (Mean ± SD)

Mode of Administration	Pancuronium (μg/ml) at Twitch Tension (Per Cent of Control):			Recovery Time (Min)
	25 Per Cent	50 Per Cent	75 Per Cent	
Isolated arm (n = 4)	0.07 ± 0.01†	0.05 ± 0.01†	0.04 ± 0.01†	10 ± 2†
Bolus injection (n = 7)	0.13 ± 0.04†	0.10 ± 0.03†	0.09 ± 0.02*	23 ± 7†
Infusion (n = 3)	0.20 ± 0.04†	0.14 ± 0.01†	0.11 ± 0.01†	46 ± 5†

* $P < 0.05$, difference between concentrations at 25 and 75 per cent recovery.

† $P < 0.05$, difference between experimental methods.

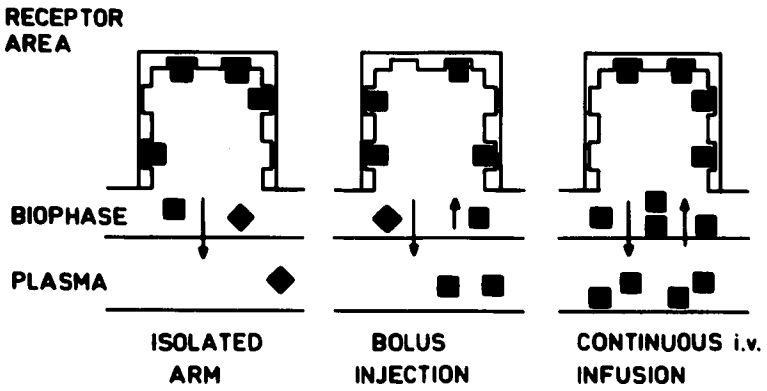

FIG. 1. Hypothetical representation of the neuromuscular junction, illustrating a possible explanation of why recovery is slower and serum concentration of pancuronium higher with the continuous-infusion method. At the same depression of twitch tension the proportions of receptors occupied by the drug are assumed to be similar. However, concentration gradients between the receptor area and plasma are different, being highest in the isolated arm after release of the tourniquet, less after the bolus injection, and almost nonexistent during continuous infusion.

slower than that seen with isolated-arm technique and faster than that obtained with the continuous-infusion method (table 1). The plasma concentrations of pancuronium associated with 25 and 75 per cent of control twitch height differed significantly among the three groups (table 1), with one exception. No significant difference existed between the plasma concentrations at 75 per cent recovery when the bolus-injection and continuous-infusion methods were used.

Discussion

We found that the plasma concentration necessary for neuromuscular blockade was the least with the isolated-arm technique. Recovery from neuromuscular blockade was fastest with the isolated-arm technique and slowest with continuous infusion. To interpret these results, we assume that the magnitude of neuromuscular blockade reflects the amount of pancuronium at the receptor sites, independent of the method of administration. After release of the tourniquet in the isolated-arm technique, the plasma concentration immediately decreases to less than the neuromuscular blocking concentration at the receptor site. This creates the highest concentration gradient between the receptor site and plasma (fig. 1), which explains the rapid rate of recovery from neuromuscular blockade. We believe that in this situation, time to recovery from neuromuscular blockade is little influenced by the plasma concentration of pancuronium. The drug–receptor dissociation rate constant and removal of the drug from the receptor site appear to be the primary factors controlling the recovery of neuromuscular transmission.

Following bolus administration (of approximately five times more pancuronium than used in the isolated-arm studies), the concentration gradient between the receptor area and plasma is much less; therefore, neuromuscular blockade will persist longer. Under this condition, both the dissociation rate constant and the rate of change of the plasma concentration influence the recovery time from neuromuscular blockade (fig. 1). However, when the inactive tissue depots are nearly saturated, pancuronium administered by continuous infusion produces plasma concentrations equal to those of the receptor area, because a steady state is more likely to exist. That is, the infusion rate necessary for constant depression of twitch tension is also constant. This represents a near-ideal case of dynamic equilibrium among all body compartments and the plasma. Most important is that little or no concentration gradient exists between the receptor area and plasma (fig. 1). Only with this situation does the plasma concentration of pancuronium probably accurately reflect the magnitude of neuromuscular blockade. Obviously, at equilibrium, the plasma concentration of pancuronium is considerably higher than that achieved after its administration either as an intravenous bolus or into the isolated arm. Consequently, recovery takes longer than with the other techniques after termination of the infusion.

Since the isolated-arm group was not anesthetized, one might question whether it is appropriate to compare this group with the two anesthetized groups. Anesthesia is well known to augment neuromuscular blockade from pancuronium. Therefore, if the isolated-arm group had been anesthetized, the plasma concentration of pancuronium at a given magnitude of neuromuscular blockade would have been even lower. This would have made the differences among the groups even more pronounced than those we observed.

We, therefore, believe that dissociation from the receptor and plasma concentration are both important in determining the rate of recovery from a pancuronium-induced neuromuscular blockade. The relative im-

portances of these two factors vary, depending on the method of pancuronium administration. With the isolated-arm technique, the drug–receptor dissociation rate constant and the rate of elimination from the receptor site are of prime importance; following bolus injection, these two factors will be masked to varying extents by the actual plasma concentration. The concentration of pancuronium necessary for a given degree of neuromuscular blockade is therefore best evaluated by use of the continuous-infusion technique, during which a relative steady state exists between the receptor, all other compartments, and plasma concentration.

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