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A bolus plus continuous infusion protocol for controlling neuromuscular blockade during anesthesia

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Abstract

Neuromuscular blockade is controlled during anesthesia by administering either bolus doses or a continuous infusion of a blocking agent. To test whether a constant infusion technique requires less attention and provides better control we used a computer to simulate neuromuscular blockade. Using the model we maintained 95% blockade with mivacurium, atracurium, and vecuronium. It required 1.2 changes per hour to maintain the blockade by continuous infusion; an average of 4.5 bolus per hour were required to maintain blockade by the bolus technique. When the bolus and continuous infusion techniques were combined, only 0.16 changes per hour were required. Atracurium was then given to ten patients during anesthesia, following the bolus plus continuous infusion protocol. After a bolus was given to obtain 100% twitch depression, for tracheal intubation, neuromuscular function was assessed by train-of-four stimulation of the ulnar or facial nerves by observing the resultant muscle movement. When the first twitch of the train-of-four returned, relaxation was maintained by continuous infusion. A bolus was given and the drug infusion rate was changed whenever the level of relaxation changed from the desired one twitch of the train-of-four. The infusion rate was adjusted only 1.12 ± 0.79 times per hour. The desired level of muscle relaxation was easily controlled using the bolus plus continuous infusion protocol. The infusion scheme might be implemented in future drug infusion pumps.

Introduction

Muscle relaxants are used routinely during anesthesia to facilitate endotracheal intubation, to simplify the control of artificial respiration and to make intra-abdominal and thoracic operations possible. Muscle relaxants are used in the ICU also, for intubation, to decrease ventilator pressures and to reduce oxygen consumption [1–5].

Post operative respiratory failure (residual curarization) is the most serious side effect of a muscle relaxant overdose. After anesthesia has ended, the patient may not be able to breath because of weak respiratory muscles. The risk of this hazard can be reduced by better control of the level of relaxation so that antagonism of the postoperative block is better facilitated.

Short acting, nondepolarizing muscle relaxants, such as atracurium and vecuronium are often selected for controlling neuromuscular blockade because of their short duration of action, resulting in rapid recovery [6]. Although their short duration of action is desirable, close attention is required to maintain effectively prolonged relaxation, especially when repetitive boluses are used.

Ali and others suggest that short acting muscle relaxants are best given by constant infusion [7]. To test whether the constant infusion technique does, in fact, require less attention than the bolus technique, we used a computer to simulate both delivery techniques and then tested the result in a clinical study.

Table 1. Overview of methods.

Task	Number of patients	Drug
Model validation	10 simulated patients	mivacurium
	10 simulated patients	atracurium
	10 simulated patients	vecuronium
Compare bolus vs.	20 simulated twins*	mivacurium
continuous infusion	20 simulated twins	atracurium
	20 simulated twins	vecuronium
Combination of bolus and	10 simulated patients	mivacurium
continuous infusion	10 simulated patients	atracurium
	10 simulated patients	vecuronium
Clinical evaluation	10 actual patients	atracurium

* One twin received boluses; one twin received a continuous infusion.

Methods

An overview of our methods is shown in Table 1. To validate our computer model, we simulated neuromuscular blockade in 30 simulated patients (with varying pharmacokinetic and pharmacodynamic characteristics), and compared our results with the clinical study published by Ali [7]. We next simulated neuromuscular blockade in 60 pairs of identical patients (twins). In one of the simulated twins, neuromuscular blockade was controlled by repeated boluses, in the other twin it was controlled by constant infusion. The protocol was repeated in 60 different simulated pairs of twins, each pair having different pharmacokinetic and pharmacodynamic characteristics. The bolus and constant infusion techniques were then used together, in simulated patients, to see if perhaps the ideal should be to combine the two techniques. The combined bolus and constant infusion technique was finally evaluated in 10 actual patients who were given atracurium. Atracurium was selected because its duration of action is shorter than vecuronium, but longer than mivacurium. The performance was measured in terms of: (1) how closely the protocol kept relaxation at the desired level (offset); and (2) how large were variations about the desired level of relaxation (stability).

Model validation

Neuromuscular blockade was simulated using a computer model with Hill-type pharmacodynamics and linear two-compartment pharmacokinetics [8]. The model predicts twitch depression and train-of-four ratio following the administration of atracurium, vecuronium or mivacurium.

To validate the computer model, we simulated the delivery of muscle relaxants to three groups of simulated patients, using the same doses and the same infusion protocol as those given to patients in a clinical study published by Ali [7]. In Group 1, 10 simulated patients (58–85 kg) received an initial bolus dose of mivacurium 0.15 mg/kg. When the twitch response recovered spontaneously to 5% of baseline (95% block), a continuous infusion of mivacurium was started at the rate of 10 μg/kg/min. This infusion rate was adjusted every three minutes until a stable twitch depression of 95% was obtained.

In Group 2, 10 simulated patients received an initial bolus of atracurium 0.5 mg/kg. After spontaneous recovery of the evoked twitch to 5% of control, an infusion of atracurium was commenced at 10 μg/kg/min and adjusted every three minutes to maintain 95% twitch depression.

In Group 3, 10 simulated patients received an initial bolus dose of vecuronium 0.1 mg/kg. Following spontaneous recovery of the evoked twitch to 5% of control, a continuous infusion was started at a rate of 2.0 μg/kg/min and adjusted every three minutes to maintain 95% depression. In each group, the infusion was discontinued after 90 min, and the time for spontaneous recovery recorded. The steady state infusion rate and recovery times, 5–95% and 25–75%, were compared with those measured in Ali's clinical study [7].

Table 2. Bolus doses and infusion rates used when comparing the bolus technique with continuous infusion.

	Bolus	Infusion rate
Mivacurium	0.24 mg/kg	7.5 μg/kg/min
Atracurium	0.5 mg/kg	6.5 μg/kg/min
Vecuronium	0.1 mg/kg	1.8 μg/kg/min

Bolus vs. continuous infusion

To compare the bolus and continuous infusion techniques, we measured the number of boluses given and the number of times the infusion rate was changed, while maintaining 95% blockade in 60 pairs of simulated patients (twins). Twenty twins received mivacurium, 20 received atracurium, and 20 received vecuronium. The 60 twins had different pharmacokinetic characteristics, selected at random from a normal distribution of expected values [8], however, both members of the twins themselves were identical (i.e., identical twins). Neuromuscular blockade was induced in Twin A, using the bolus listed in Table 2. The train-of-four response was observed every minute. Whenever the height of the first twitch (T_1) rose above 15% of the control value, an additional bolus was given (Table 2). Twin B, the second member in the pair, also received an initial bolus (Table 2). For this twin, a continuous infusion was started when T_1 returned to 5% of its initial value. The rate was increased whenever T_1 exceeded 15%, and decreased whenever it fell below 5%. The results were analyzed to compare the number of adjustments made in the infusion rate (Twin B) with the number of boluses injected (Twin A).

Combined bolus and continuous infusion

We developed a combined bolus and continuous infusion pharmacokinetic scheme to provide even better control of neuromuscular blockade. In our scheme, we assume that the level of neuromuscular blockade is appropriate if only one twitch is observed following a train-of-four stimulation (T_1) [9–11]. If two (T_2) or three (T_3) twitches are observed, then a bolus is given and an incremental change is made in infusion rate to increase the level of blockage (Table 3). If the first twitch is missing (T_0), then the infusion rate is turned off for 6–12 minutes to allow the drug concentration to decrease, after which the continuous infusion is restarted but at a lower rate. The actual bolus size and continuous infusion rates, as given in Table 3, were found by trial and error using computer simulation.

An example of the scheme follows. An initial intubating bolus is first given: three times the dose which gave 95% blockage (ED95) for mivacurium and two times the ED95 for vecuronium and atracurium [7, 12]. After spontaneous recovery from the intubating bolus (T_1 reaches 5%), a continuous infusion is started. The continuous infusion remains unchanged as long as only the first twitch of the train-of-four stimulation appears. If the second twitch of the train-of-four (T_2) appears, a bolus dose is given to rapidly increase the drug concentration in the plasma and tissue compartment, and the infusion rate is increased. If T_3 appears, a larger bolus was given, followed by a further increase of the infusion rate. If there is no response to the train-of-four stimulus (T_1 missing), the continuous infusion is turned off for long enough to lower the concentration in the tissue and plasma compartments, after which the continuous infusion is resumed, but at a lower rate.

To test this scheme, neuromuscular blockade was induced in 10 simulated patients. The combined bolus and infusion protocol described above was followed for 90 minutes.

Clinical study

A clinical study was approved by the Institutional Review Board. Informed consent was obtained from 10 patients (ASA physical status 1–3) who were 26 to 67 years of age. Patients were excluded from the study if they had a known history of 1) allergic reactions to relaxants, 2) neuromuscular disease, 3) renal dysfunction, or 4) liver dysfunction. Anesthesia was induced with sodium thiopental and maintained with halothane (0.2 to 2.0% inspired) and nitrous oxide (60%) in oxygen. Ventilation was controlled with a Dräger Narkomed 2B anesthesia machine and ventilator.

Neuromuscular relaxation was induced with succinylcholine for tracheal intubation, followed by atracurium (0.4 mg/kg) to produce 100% twitch depression. Neuromuscular transmission was assessed using supramaximal train-of-four stimulation of the ulnar or facial nerve at a rate of 2 Hz (Digistim II, Neuro Technology, Houston, TX). Before relaxation was induced, the supramaximal stimulus current was determined by increasing the stimulating pulse until the train-of-four response saturated. The current was then increased by 10 to 20%, to ensure supramaximal stimulation. Every 5 minutes the response to a train-

Table 3. Bolus doses and infusion rates used for the combined bolus and continuous infusion technique.

	Bolus	Infusion rate change
Mivacurium		
T_0	Turn pump off for 6 min	- 3.4 μg/kg/min
T_2	0.01 mg/kg	+ 2.0 μg/kg/min
T_3	0.02 mg/kg	+ 2.5 μg/kg/min
Atracurium		
T_0	Turn pump off for 12 min	- 4.0 μg/kg/min
T_2	0.023 mg/kg	+ 1.8 μg/kg/min
T_3	0.05 mg/kg	+ 2.3 μg/kg/min
Vecuronium		
T_0	Turn pump off for 12 min	- 1.0 μg/kg/min
T_2	0.007 mg/kg	+ 0.8 μg/kg/min
T_3	0.01 mg/kg	+ 1.2 μg/kg/min

of-four stimulation was observed visually or by touch. A fifth year medical student, who was not primarily responsible for patient care, spent 100% of his time monitoring and adjusting relaxation.

When the first twitch of the train-of-four first appeared, a continuous infusion was started at 6.0 μg/kg/min (Infus OR, Bard, North Reading, MA). As long as only the first twitch of the train-of-four stimulation (T1) was present, the continuous infusion remained unchanged. If the second twitch of the train-of-four (T2) appeared, a bolus dose was given to rapidly increase the drug concentration in the plasma and tissue compartment (25 μg/kg), and the infusion rate was increased by 1 μg/kg/min. If the third or fourth twitch (T3 or T4) appeared, a 50 μg/kg bolus was given, followed by a larger increase of the infusion rate (2.0 μg/kg/min). If there was no response to the train-of-four stimulus (T1 missing), the continuous infusion was turned off until T1 appeared again, after which the continuous infusion was resumed, but at a rate 1.0 μg/kg/min lower. After making a change in infusion rate, the protocol specified a waiting period of 5 min to assess the effect of the change, before making any further change in infusion rate. Near the end of the surgical procedure the infusion was stopped and relaxation was reversed by edrophonium (1 mg/kg) and atropine (8 μg/kg). Two patients were allowed to recover spontaneously.

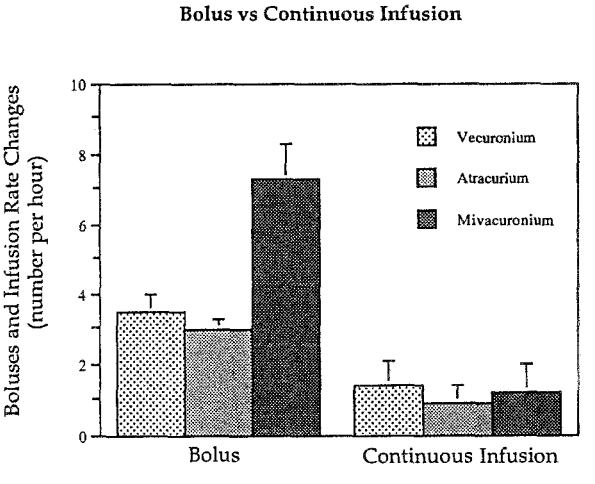

Fig. 1. The number of bolus doses and the number of changes in infusion rate needed to maintain a constant level of neuromuscular blockade for 90 minutes with vecuronium, atracurium and mivacurium.

Results

Model validation

Table 4 compares the steady state infusion rates in the computer-simulated patient with the steady state infusion rate found in Ali's patient study [7]. The recovery times, 5% to 95% and 25% to 75%, are also compared. Our simulation results were statistically different ($P < 0.05$) for recovery times, but these differences were never larger than 30%.

Table 4. Steady state infusion rate (SSIR) needed to maintain 95% block and recovery time once the infusion was stopped.

	SSIR	5–95%	25–75%
Mivacurium			
Model	8.8 (0.4) μg/kg/min	16.6 (0.3) min*	5.1 (0.1) min*
Ali	8.3 (0.7) μg/kg/min	13.6 (0.6) min	6.4 (0.2) min
Atracurium			
Model	7.7 (0.4) μg/kg/min	34.7 (0.3) min*	11.8 (0.1) min*
Ali	7.9 (0.4) μg/kg/min	26.6 (0.4) min	10.9 (0.3) min
Vecuronium			
Model	1.8 (0.1) μg/kg/min	36.9 (0.4 min*	11.8 (0.1) min*
Ali	1.2 (0.3) μg/kg/min	32.0 (1.2) min	13.8 (0.9) min

Each value in the table gives the mean value and the SEM (in parentheses). The values shown with * are statistically different ($P < 0.05$).

Table 5. Results obtained when comparing the bolus technique with continuous infusion.

	Mivacurium	Atracurium	Vecuronium
Bolus			
Number of boluses/hour	7.30 ± 0.87	2.80 ± 0.30	3.40 ± 0.50
Mean bolus size (mg/kg)	0.029 ± 0.007	0.14 ± 0.002	0.029 ± 0.007
Total amount of drug (mg/kg)	0.46 ± 0.13	1.05 ± 0.21	0.21 ± 0.07
Continuous infusion			
Number of changes in rate/hour	1.20 ± 1.03	1.00 ± 0.50	1.50 ± 0.80
Steady state infusion range (μg/kg/min)	7.8 ± 2.2	8.2 ± 1.1	2.1 ± 0.5
Total amount of drug (mg/kg)	0.48 ± 0.13	0.98 ± 0.14	0.25 ± 0.06

Each value is the mean for 20 patients ± one standard deviation.

Bolus vs. continuous infusion

To maintain neuromuscular blockade by continuous infusion required an average of 1.23 changes per hours in the infusion rate. To maintain blockade by the bolus technique required an average of 4.5 injections per hour (Table 5). Figure 1 compares the number of bolus injections with the number of changes in the infusion rate to show graphically the reduction in effort when the continuous infusion technique is used.

Bolus and continuous infusion

Table 6 shows the results when the combined bolus and continuous infusion scheme was followed. The simulated twitch depression, the mean deviation from 5% twitch height and the infusion rate after 90 minutes are listed. The number of changes per hour averaged 0.16.

Clinical results

A typical plot of train-of-four count and infusion rate is shown in Fig. 2. Every change in the train-of-four count was immediately followed by an adjustment in the infusion rate, according to the protocol (Table 2). A bolus was given according to the protocol whenever train-of-four count was greater than one. Table 7 summarizes the results. The desired level of neuromuscular blockage was maintained for 78.8% of the operating time with an average of 1.12 changes in infusion rate per hour.

Discussion

Pharmacokinetic infusion schemes have been proposed for intravenous barbiturates and narcotics; a bolus followed by a decreasing infusion rate produces a constant plasma level [13–15]. The bolus fills the central compartment and the pharmacokinetically decreasing infu-

Table 6. Results obtained for the combined bolus and continuous infusion technique.

	Average twitch depression	Mean deviation from 5% twitch height	Steady state infusion rate μg/kg/min (SEM)	number of changes in rate/hr ± SD
Mivacurium	4.0%	1.4%	7.9 (0.3)	0.13 ± 0.09
Atracurium	5.3%	1.1%	7.0 (0.3)	0.13 ± 0.09
Vecuronium	3.9%	1.3%	2.0 (0.1)	0.2 ± 0.10

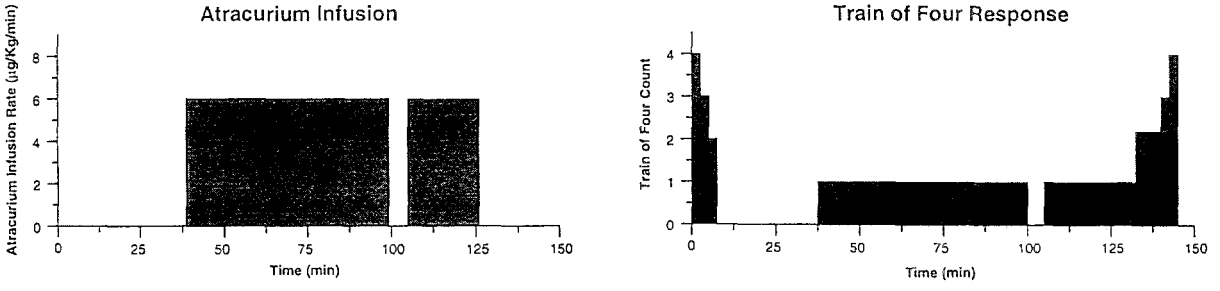

Fig. 2. Train of four count and atracurium infusion rate during 150 minutes of controlled muscle relaxation in a patient. The plot on the left shows atracurium infusion rate 0–8 μg/kg/min. The plot on the right shows train of four count 0–4.

Table 7.

Number of patients	10
Operating room time (min)	147.6 ± 73.0
Protocol time (min)	107.5 ± 74.4
% time relaxation at T1	78.8% ± 14
Number of adjustments/operation	2.00 ± 1.41
Number of adjustments/hour	1.12 ± 0.79
Steady state infusion rate at end of study (μg/kg/min)	6.7 ± 1.77

sion rate keeps the concentration in the central compartment constant, by compensating for distribution to the peripheral compartment and replacing clearance. For the intravenous narcotics, it is important to avoid excessively high concentrations in the central compartment and hence pharmacokinetic infusions are designed to control the central compartment concentration.

For the neuromuscular blocking agents there is generally no serious penalty for high concentrations in the central compartment. One can give a large bolus, which creates a high concentration in the central compartment, thus speeding the transfer to the peripheral compartment. Once steady state is reached, when the peripheral and central compartments have reached equilibrium, the final concentration will be a function of the amount of drug administered, the partition coefficient and the volume of distribution.

Our computer simulation of neuromuscular blockade showed that the combined bolus plus continuous infusion technique is more convenient and more effective than either a bolus or constant infusion technique alone. Only 0.16 adjustments per hour were needed to maintain 95% blockade with the bolus plus continuous infusion technique. With boluses alone, 4.5 changes per hour were needed. With continuous infusion alone, 1.2 changes per hour were needed. When a change is needed in the level of paralysis, the change can be most rapidly instigated by delivering a bolus to bring the volume of distribution to a new level. The bolus size is calculated from the desired change in concentration, the partition coefficient and the volume of distribution. Assuming muscle relaxants follow two-compartment pharmacokinetics, the most rapid way to change the peripheral drug concentration is by giving a bolus to the central compartment. The continuous infusion is then increased to compensate for increased elimination rate caused by the higher concentration in the central compartment. The bolus plus continuous infusion protocol was developed in a way that it can easily be implemented in future drug infusion pumps.

Computer simulation was an effective way of comparing the drug infusion techniques. Techniques could be compared in two identical patients (identical twins), thus ruling out patient-to-patient variability. The two-compartment pharmacokinetic model used pharmacokinetic and pharmacodynamic coefficient values from the literature. Its simulation of neuromuscular blockade compared well with steady state infusion rates and recovery times published by Ali [7]. When the infusion protocol from the clinical study was followed exactly with our computer stimulation, the recovery times were statistically different, but the differences were all less than 30%, allowing us to see several orders of magnitude differences between infusion techniques.

Computer simulation had the disadvantage in that changing anesthetic level, patient variability from disease, and surgical stimulation were not simulated. Each is undoubtedly a factor which influences the regulation of neuromuscular blockade. These factors alter the potentiation and elimination rate. Because of these factors, there may be the need for more frequent changes in infusion rate clinically than that predicted by our simulation. Indeed, we found in the clinical study that the patient-to-patient variation was consistently larger than it was in the simulation (standard error in Table 4).

We found the need for 1.12 changes per hour in atracurium infusion rate.

We chose to use atracurium in the clinical study because its duration of action is shorter than vecuronium but longer than mivacurium. We expect that when used clinically our technique will require more frequent changes with mivacurium and less frequent changes with vecuronium.

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