AUTOMATIC CONTROL OF NEUROMUSCULAR BLOCK WITH ATRACURIUM

A. D. MACLEOD, A. J. ASBURY, W. M. GRAY AND D. A. LINKENS

Steady neuromuscular block at a predetermined level is valuable during long operations; this may be difficult to achieve using a manually controlled infusion. Automatic control of neuromuscular block has been achieved in patients with drugs such as pancuronium and vecuronium [1-3]. Atracurium has a relatively short duration of action and non-hepatic elimination and is likely to be more amenable to automatic control than pancuronium and vecuronium [4,5].

Wait and co-workers [4] described a simple on-off control system which, despite being intrinsically oscillatory, performed well and produced a mean maximum deviation above the target T1 of 3% in 11 patients. (T1 is the Relaxograph ratio of electromyograph (EMG) after block to that before the block). Webster and Cohen [5] described a portable control system incorporating proportional and derivative terms, which produced a mean T1 of 8.9% for a target of 10% in 20 patients.

The object of this study was to devise a simple, robust control system capable of controlling block to a predetermined level and able to work within the time constraints of a routine session. This requires rapid achievement of the target level, as surgeons invariably require adequate paralysis early in the operation. We have also quantified the stability of the system in order to assess the extent of control.

SUMMARY
We have developed and tested a system for providing automatic control of neuromuscular block with atracurium. The degree of neuromuscular block was monitored in the small muscles of the hand using a Datex Relaxograph, and the signal was used as the controlled variable for a proportional plus integral controller. A preloaded integral was used to shorten the period of stabilization. The system was tested in 36 patients undergoing surgery and found to produce stable block. For a target T1 of 20% of control value, the mean block was 18.7 (SD 1.3)% of baseline T1 and the mean consumption of atracurium was 5.39 (SD 1.23) μg kg⁻¹ min⁻¹. The block was sufficiently stable to act as a background for studies of pharmacological and physiological interactions with atracurium.

PATIENTS AND METHODS
After local Ethics Committee approval, we studied 36 patients (29 female) in ASA categories I or II presenting for elective general surgery. We excluded patients with known sensitivity to anaesthetic drugs or myoneural disorders and patients taking drugs known to affect neuromuscular transmission.

Anaesthetic technique
The patients were premedicated with temazepam by mouth 90 min before surgery. In the anaesthetic room the Relaxograph electrodes were applied at the wrist, which was immobilized in a light splint. After insertion of a cannula into an appropriate vein, the lungs were preoxygenated and anaesthesia was induced with thiopentone 3–5 mg kg⁻¹. Baseline EMG recordings were obtained and atracurium 0.25 mg kg⁻¹ administered i.v.;
the trachea was intubated when $T_1$ reached 25% of the baseline value. The lungs were then inflated with 67% nitrous oxide and 1% enflurane in oxygen and the patient was moved into the operating room and connected to an automatic ventilator delivering the same gas mixture. The automatically controlled infusion was started when $T_1$ from the initial bolus had increased to 15% of the baseline value.

During surgery, enflurane anaesthesia was supplemented with boluses of fentanyl as indicated clinically. In addition to normal clinical signs, ECG and arterial pressure were monitored, and i.v. fluids were given as appropriate. At the end of surgery, residual block was antagonized with neostigmine and atropine. The level of block was monitored until the patient moved spontaneously, making further EMG recordings unreliable.

**Equipment**

The level of neuromuscular block was monitored using a Datex Relaxograph neuromuscular transmission monitor [6], which records an evoked EMG in the small muscles of the hypothenar eminence every 20 s. The Relaxograph rectifies and integrates the evoked EMG and calculates the ratio of the result during block to that before. This ratio is termed $T_1$.

The Relaxograph was connected via its serial interface to a Research Machines 380Z-D microcomputer, which was in turn connected to a modified Vickers IP3 pump loaded with a syringe containing atracurium 500 $\mu$g ml$^{-1}$ in saline. The syringe was connected to the dedicated cannula sited in a peripheral vein, thereby completing the control loop.

The computer calculated the dose of atracurium at 20-s intervals using the following proportional-plus-integral (PI) algorithm:

$$\text{Output of atracurium (ml h}^{-1}) = K_p e + K_i (\sum e + P)$$

where $e =$ difference between the actual $T_1$ and the target $T_1$; $K_p$ and $K_i =$ proportional and integral gains; $P =$ preloaded value for the integral, which is included to shorten the stabilization time. The target $T_1$ was always 20%. $K_p$ was set at 0.02 $\times$ weight (kg) and $K_i$ at 0.0007 $\times$ weight (kg); these values were calculated on the basis of four preliminary trials in which a steady infusion was administered until stable block was achieved and the infusion rate was reduced suddenly by 25%. The response of the $T_1$ to this step change in input was analysed to give appropriate values for the proportional and integral gains using the empirical rules described by Ziegler and Nichols [7]. The values of $K_p/\text{weight}$ and $K_i/\text{weight}$ quoted above were the mean values obtained from these trials. Ideally, the value of $P$ would be such that the infusion rate would be sufficient to maintain steady block with zero value for $e$, that is with no proportional component in the control signal. On the basis of data previously published [8], $P$ was initially set to 680. After the first three patients it was changed to 1000, which represented the mean dose required to maintain steady block at 20% in the three patients (see Results).

The computer was programmed to print all the data received from the Relaxograph and the corresponding settings sent to the syringe pump. This information was stored also on floppy discs.

**Analysis of data**

As we were interested mainly in studying the behaviour of the system during the period of steady neuromuscular block, we required an operational definition of the “stable period”. The start of this period was defined in two ways, depending on whether or not there was an overshoot above target after starting automatic control. If there was, the beginning of the stable period was the time at which $T_1$ returned to 20% after the overshoot. If there was no overshoot the stable period began when $T_1$ first started to decline after the controller had been started. The stable period ended when surgery finished. (For one patient, a different criterion was used, as described in the Results.) Figure 1 illustrates these definitions of the stable period.

We measured the extent of control by two indices: the root mean square deviation (RMSD) of the stable period points about the target block level (20% of the control EMG); and the point count (PC), which is the number of stable period points above the target expressed as a percentage of all the stable period points. The RMSD gives an index of the extent of spread of values about the target, irrespective of whether they were above or below the target, while the PC indicates if the block achieved tended to lie above or below the target. The consumption of atracurium was calculated as the mean dose rate over the stable period.
RESULTS

Details of the patients studied are presented in table I. The operations were mastectomies (23), major arterial surgery (six), and eye and general surgery (seven).

The degree of neuromuscular block obtained was clinically satisfactory in all patients, with one exception, in whom the surgeon reported that the abdominal muscles were "tight" on closure, although there had been no previous indication of unsatisfactory relaxation. The system proved easy to manage by a single-handed anaesthetist (A. MacL.) without delaying a busy operating list.

Results of the automatic control procedure are presented in table I, and representative Relaxograph traces from two patients are shown in figure 1. The initial atracurium bolus generally caused T1 to decrease to approximately 10%, although in two patients T1 decreased to 2%. After the start of automatic control in each of the first three patients, T1 displayed a considerable overshoot of the 20% target before it began to decline (maximum T1 were 28, 23 and 26% for patients Nos 1, 2 and 3, respectively). In an attempt to minimize this problem and the associated potential for patient movement, the value of the integral preload was increased from 680 to 1000 after these three patients had been studied.

In all patients except one, the end of the stable period was taken as the time when surgery

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>61.9</td>
<td>13.0</td>
<td>40-99</td>
</tr>
<tr>
<td>Duration of stable period (min)</td>
<td>43.9</td>
<td>16.3</td>
<td>21-77</td>
</tr>
<tr>
<td>Mean T1 (%)</td>
<td>18.7</td>
<td>1.3</td>
<td>16.3-21.7</td>
</tr>
<tr>
<td>SD of T1 (%)</td>
<td>1.47</td>
<td>0.69</td>
<td>0.6-3.6</td>
</tr>
<tr>
<td>RMSD (%)</td>
<td>2.21</td>
<td>1.01</td>
<td>0.8-4.4</td>
</tr>
<tr>
<td>PC (%)</td>
<td>25.2</td>
<td>21.7</td>
<td>0-81</td>
</tr>
<tr>
<td>Dose (µg kg⁻¹ min⁻¹)</td>
<td>5.39</td>
<td>1.23</td>
<td>2.7-8.6</td>
</tr>
</tbody>
</table>
finished. The one exception was patient No. 6, who had an aortic bifurcation graft, for whom the stable period was considered to end when the aortic cross-clamp was applied. It was felt that application of the cross-clamp could lead to alteration in the volume of distribution and possibly produce transient instability in the control system. However, there was little alteration in the degree of block after the cross-clamp was applied.

There was an overshoot at the beginning of the stable period in 23 patients. The highest peak T1 obtained in any patient was 29%. In those patients in whom there was overshoot, the mean peak value of T1 was 23.7 (SD 2.4)% The mean time from controller implementation until the beginning of the stable period was 11.0 (SD 9.1) min.

There was no significant correlation ($P < 0.05$) between age and dose of atracurium.

**DISCUSSION**

This work differs from previous studies in this area in the following ways. First, we have used a proportional plus integral system with a preloaded integral, in contrast with Wait and co-workers [4] who used a simple on-off system, and with Webster and Cohen [5] who used a proportional plus derivative system. The integral term is a standard control system strategy for removing steady state error [9], and we found such an error in preliminary trials without an integral term. The second innovation in our study is the quantification of the quality of control. This was achieved by means of the point count and the root mean square deviation; the use of such measures in future studies may allow comparison of different control strategies.

T1 20% of baseline proved clinically satisfactory in all patients, with one exception. The 20% target was chosen because we felt that it would provide satisfactory block, and because the working point would be on the linear region of the atracurium dose–response curve. Selecting a considerably lower target, say 10%, would lead to the possibility of the working point moving outside the linear region of the dose–response curve, where the use of a PI controller would be inappropriate. It may be that aiming for a target T1 of 15% would eliminate the occasional difficulty which might arise with a target of 20%.

The time that elapsed between the start of automatic control and the beginning of the stable period (mean 11.0 (SD 9.1) min) did not delay the start of surgery or cause other clinical problems.

The value of 1.47% for the mean standard deviation of T1 indicates that, in general, a steady level of block was obtained. The closeness of the mean RMSD to the mean SD (2.21% compared with 1.47%) indicates that the degree of block achieved was generally close to the target. As the overall mean T1 (18.7%) and the mean PC (25.2%) show, the trend was for the individual mean T1 to be slightly less than 20%. This probably may be explained by definition of the stable period. In those patients in whom there was an initial overshoot, the controlled period began when the T1 returned to 20% and at this point there was a downward trend in the value of T1. In the remainder of the patients (those in whom there was no overshoot), the stable period began at a value less than 20%. As a consequence the initial part of each stable period started with a series of T1 values below target. Therefore, some time elapsed from the beginning of each stable period before the T1 returned to 20% and it was probably the contribution of this initial portion that led to the overall mean T1 being less than target.

In general, the effect of the starting bolus gave a good indication of the subsequent behaviour of the patient. Those patients in whom the bolus caused the greatest decrease in T1 tended to be those who required the lowest infusion rates to maintain T1 at target and those on whom the bolus dose had the least effect tended to require a higher infusion rate.

The mean dose is at the lower end of the range recommended by the manufacturers for atracurium. This is not surprising, for three reasons. First, the use of enflurane potentiates the effect of atracurium [10]; second, constant infusion is probably a more efficient way of using atracurium than bolus injections; third, the manufacturer's recommended range is probably biased towards those patients who are least responsive to atracurium.

We found a considerable range in the atracurium dose required to maintain steady block, in agreement with other workers [11]. However, the three-fold variation found in this study is smaller than that for other myoneural blockers. D'Holander and colleagues [12] used vecuronium in 20 ASA I and II patients and found a 10-fold variation in the range of dose required to maintain 10% twitch tension. Part of this difference may be
explained by the fact that, in contrast with other relaxant drugs, there is no decrease in atracurium requirement in the elderly; this has been demonstrated in a previous study [13] and is supported by the lack of a significant correlation between age and dose of atracurium in this study. This relatively small range of atracurium requirement suggests that a simple control system such as this, in which no self-tuning occurs, should work better with atracurium than with other agents. Those patients who were particularly resistant to block would demonstrate a marked overshoot at the start of the control, while those who were especially sensitive would suffer a large initial depression of T1. In both groups there would be a considerable delay before the onset of the stable period, even if overt instability did not occur. It is possible that there are some patients whom our system would not control (those at each end of the range of sensitivity), but adequate control was obtained for a patient whose requirement was 50\% of the mean and for another whose requirement was more than 50\% greater than the mean.

The standard method of administering neuromuscular blocking drugs is to give an initial bolus followed by subsequent boluses of approximately 33\% of the initial dose. The replacement of these subsequent boluses by a continuous infusion under automatic control has the following advantages: there are no periods of serious over-or under-dosage; prompt antagonism can be achieved readily if surgery finishes unexpectedly early; and atracurium is used efficiently.

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REFERENCES