Closed-loop Infusion of Atracurium with Four Different Anesthetic Techniques

Dorene A. O’Hara, M.D., M.S.E.,* Garrett J. Derbyshire, M.S.E.E., M.D., Ph.D., † Frank J. Overdyk, M.S., M.D., ‡ Daniel K. Bogen, M.D., Ph.D., § Bryan E. Marshall, M.D., F.R.C.P.*

A new proportional–integral–derivative (PID) controller for the automated closed-loop delivery of atracurium was tested in 32 patients. Groups of 8 patients received halothane, enflurane, isoflurane, or N2O/morphine anesthesia. After induction of anesthesia with sodium thiopental 3–5 mg · kg⁻¹, a bolus of atracurium 0.2 mg · kg⁻¹ was delivered by the controller; this was followed by an infusion calculated by the controller to maintain the electromyogram (EMG) at a setpoint of 90% neuromuscular blockade. The average overshoot for the controller was 10.1% and the mean steady-state error 5.6%. The mean infusion rates for atracurium to maintain 90% blockade were calculated for each anesthetic group, with the inhalation anesthetics at 1 MAC. Infusion rates for N₂O/morphine, halothane 0.8%, enflurane 1.7%, and isoflurane 1.4% at 90% blockade were 5.7 ± 0.6, 4.9 ± 0.3, 3.5 ± 0.3, and 4.1 ± 0.5 μg · kg⁻¹ · min⁻¹, respectively (mean ± SE). The infusion rate for atracurium at 90% blockade under N₂O/morphine anesthesia was in general agreement with published values. The other infusion rates at 90% blockade have not been reported previously, but correspond to the known potencies of these inhalation anesthetics for augmentation of neuromuscular blockade. This controller performed well in comparison to previously developed controllers, and in addition was used as a research tool for rapid estimation of infusion rates. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Equipment: computers. Measurement techniques: electromyography; neuromuscular blockade. Neuromuscular relaxants: atracurium; continuous infusion.)

EFFECTIVE FEEDBACK CONTROL systems for the delivery of muscle relaxants in humans have been introduced over the past few years. Methods for control have included on–off,¹ proportional infusion,² state estimation,³,⁴ and proportional–integral–derivative (PID).⁵,⁶

A feedback controller uses the error signal to calculate the correct infusion rate of a drug for maintaining the response at or near the chosen setpoint. The error signal is the difference between the setpoint and the desired response. Closed-loop controllers require a specific monitoror of the desired response, which “feed back” to regulate the controlling agent. For muscle relaxant control, the measured response usually is the electromyogram (EMG). A PID controller takes three components of the measured response to increase the speed and accuracy of control: the error signal itself (proportional component), a summation of the area between the EMG response curve and the EMG setpoint level (integral component), and the rate of change of the error signal (derivative component).

Although the muscle relaxant controllers used in previous studies were effective, they did have some problems. The on–off controller was associated both with overshoot and with oscillation about the setpoint. The proportional controller was associated with a significant steady-state offset error, a poor response time, and some overshoot. In a clinical trial, the PID controller designed by Ritchie et al.⁵ was found to regulate succinylcholine-induced block effectively in humans, and in 1987 Jaklitch and Westenskow⁶ improved Ritchie’s model by developing a two-phase controller for the infusion of vecuronium. The two phases allowed a rapid bolus of the relaxant to be followed by a lower level of continuous infusion. This controller was not studied in a clinical trial, but when tested by computer simulation, the controller had a steady-state error of less than 1% and overshoot of 4%.

Although a number of controllers have been used with a variety of anesthetic agents and muscle relaxants, no single controller has been tested with a series of anesthetic agents to compare their different effects. In addition, the speed and reliability of a controller have not yet been used as research tools. Because a controller can rapidly achieve and maintain a desired degree of neuromuscular blockade, it also should be useful for estimating infusion rates rapidly and under a variety of conditions. This study was conducted to test the clinical efficacy of a new PID infusion controller using atracurium in conjunction with four different anesthetics (halothane, enflurane, isoflurane, and N₂O/morphine) and to measure the effects of these anesthetics on atracurium-induced neuromuscular blockade with the controller.

A series of different anesthetics was tested in this study for two reasons: 1) It provides a substantial test of the controller, since different inhalation anesthetics have been shown to potentiate the effects of muscle relaxants differently. Isoflurane and enflurane show the most potentiation, and halothane and N₂O/opioid show less poten-
tiation. There is also evidence for an additional time-dependent increase in blockade by curare, at constant end-tidal enflurane concentration and at constant plasma curare concentration. This effect may occur also with atracurium. Therefore, an effective controller would need to be able to compensate for highly variable anesthetic effects as well as individual patient variation. 2) It provides a test of the controller as a means of estimating mean infusion rates to maintain desired degrees of blockade for groups of patients, anesthetized with different anesthetics.

Materials and Methods

Thirty-two ASA physical status 1 or 2 patients, aged 18–65 yr, scheduled for general surgical, orthopedic, or gynecologic procedures were entered into the study. The study was approved by the Institutional Review Board, without the requirement for a written consent form. Patients having a history of neurologic or neuromuscular diseases or weighing more than 30% over ideal body weight were excluded from the study. Patients were randomly assigned to receive halothane, enflurane, isoflurane, or N₂O/morphine anesthesia. Monitoring included hemoglobin oxygen saturation (SPO₂), end-tidal CO₂ tension, blood pressure, heart rate, ECG, and temperature. End-tidal concentrations of anesthetic were monitored with an infrared (model 222, Datex) anesthesia gas monitor. End-tidal CO₂ tension was maintained at between 30 and 35 mmHg. All patients were kept warm with warmed fluids and blankets. The extremities were kept covered to minimize heat loss.

Anesthesia was induced with thiopental 3–5 mg·kg⁻¹. For the N₂O/morphine anesthetics, 50% N₂O and morphine sulfate 0.25–0.5 mg·kg⁻¹ were administered, with supplemental doses as judged necessary by the anesthesiologist to maintain anesthesia. Atracurium at a concentration of 5 mg·ml⁻¹ was placed in a 60-cc syringe that in turn was placed in a Harvard pump (model 22) and attached to the intravenous tubing. For the inhalation anesthetics, 50% N₂O plus halothane 0.2–1.0%, enflurane 0.4–3.0%, or isoflurane 0.3–2.8% were administered to maintain adequate anesthesia. In addition, the end-tidal anesthetic concentration was maintained at 1 MAC for at least 1 h so that the rate of infusion necessary to maintain steady-state blockade at a constant end-tidal concentration could be determined. (1 MAC concentrations for each inhalation anesthetic were: halothane 0.8%, enflurane 1.7%, and isoflurane 1.15%)

The controller consisted of an EMG monitor (NMT model 221, Datex), an IBM-compatible personal computer (model 386, Swan), and an infusion pump (model 22, Harvard), all interconnected by an RS232 serial communications interface. The EMG monitor stimulus consisted of a train of four 70-mA current pulses, 100 µs in duration and at intervals of 0.5 s. The EMG response to each pulse was integrated over 18 ms and expressed as a fraction of the reference response. The reference response was obtained in each patient after induction of anesthesia, but prior to the administration of atracurium, by using a current pulse that induced a maximal muscle response, as measured by the EMG integral. One problem encountered intraoperatively was transient noise from the electrocautery. Since this noise is of high frequency, and the integrated muscle response to the relaxant is of low frequency, an EMG signal differing from the previous sample by more than a preselected threshold level was ignored. (This crude, time-domain software filter adequately removed errant signals, such that a frequency-domain filter or hardware circuit was not necessary.)

The EMG surface electrodes were applied to the ulnar nerve at the wrist, and a train of four supramaximal stimuli, each 0.1 ms in duration and repeated every 20 s, was delivered. The integrated EMG response at the thenar eminence was recorded. After obtaining an EMG response to use as the 100% reference level, the controller was switched on. The controller software sampled the EMG signal every 20 s, and by using the PID controller equation (equation 1), calculated the infusion rate of muscle relaxant delivered by the pump. The PID controller equation is:

\[
I[j] = K_p \cdot e[j] + K_d \cdot \Delta e[j]/\Delta t + K_i \sum_{k=1}^{j} \Delta e[k] \cdot \Delta t
\]

where

- \[I[j] = \text{infusion rate (ml·min}^{-1}\) \]
- \[e[j] = \text{EMG}[j] - \text{EMG}_{\text{sett}} \]
- \[\Delta t = 20 \text{ s} \]
- \[\Delta e[j] = e[j] - e[j - 5] \]

This equation states the relationship between the infusion rate and the error signal. The error is the difference between the setpoint and the height of the first twitch response of the train-of-four. The heights of the twitches in the train-of-four are normalized by the initial 100% reference level. Equation 1 contains three terms, representing proportional, integral, and derivative control. The associated constants, \(K_p\), \(K_i\), and \(K_d\), respectively, were initially estimated based on the pharmacokinetics of atracurium (see appendix) and then were revised empirically in preliminary studies to obtain the fastest response time without losing stability.

The controller was programmed to allow four modes of operation: a bolus mode; a constant infusion; a PID
mode; and a four-phase control (described below). For this study we used the four-phase control. During the first phase, the controller delivered a bolus dose of atracurium, 0.2 mg·kg⁻¹, calculated by the computer according to patient weight. Once the bolus had been delivered by the pump, the controller switched to a constant-infusion phase. Once the EMG signal was within 35% of the setpoint (set initially at 80% blockade), the controller switched to a PD mode (i.e., $K_v$ set to zero). This prevented the accumulation of a large integral component when the signal was far from setpoint. When the EMG signal came to within 10% of the setpoint, the controller switched to PID control. The patient's lungs were ventilated manually by mask until at least 80% blockade was achieved, and the trachea was intubated.

Once the end-tidal concentration of anesthetic was steady at 1 MAC and the controller was at steady state with less than 4% oscillation of the twitch response, the mean infusion rate was calculated by the controller. The controller maintains a setpoint by delivering a continuously variable infusion, for which a mean can be calculated over time periods of at least 0.5 h. This mean infusion rate for each patient was recorded as the "PID infusion rate."

The mean and statistical standard error of the PID infusion rates were calculated for each anesthetic group. The time to the start of the PID infusion rate measurement was calculated. Controller characteristics were determined as the mean and standard errors of times to setpoint, degree of overshoot, the time to steady state, and the percentage of oscillation about the setpoint. The time to setpoint was defined as the time from the start of the bolus to the first time the EMG response curve crossed the setpoint line. The percentage overshoot was defined as the difference between the lowest EMG level after the bolus and the setpoint level. The time to steady state was defined as the time between the initiation of the bolus and the beginning of close oscillation about the setpoint. The percentage oscillation was the difference between the highest and lowest EMG levels during steady-state oscillation. (See figure 1 for a diagram of controller characteristics.)

To determine whether controller characteristics and PID infusion rates differed between anesthetic groups, data were analyzed by one-way analysis of variance with the null hypothesis rejected at $P < 0.05$. To determine whether specific differences existed between anesthetic groups, mean PID infusion rates were compared by a Tukey test.

**Results**

Figure 2 shows a graph of the EMG response in one patient with the controller in four-phase mode, and the corresponding infusion rate for the same patient is shown.
on the lower graph, using the same time scale for comparison. Figure 3, which shows the EMG response for another patient, demonstrates the controller's performance at two setpoints.

The mean and standard errors of the controller characteristics (onset time to setpoint, time to steady state, percentage overshoot, and percentage oscillation) for all groups are reported in table 1. There were no significant differences in the performance of the controller between the groups receiving inhalation anesthetics in terms of onset time, overshoot, or percentage oscillation. The performance of our controller as compared with other controllers is reported in table 2.

For the inhalation techniques, the infusion rate for atracurium at 90% blockade was estimated after at least 30 min of anesthesia at 1 MAC. The times (mean ± SE) to the start of this measurement for isoflurane, enflurane, and halothane, respectively, were 77 ± 5, 69 ± 4, and 76 ± 7 min, respectively, and the time to the start of the measurement under morphine anesthesia was 76 ± 4 min. These times were not significantly different.

The mean infusion rates for atracurium at 90% block in the four patient groups are listed in table 3. There were no significant differences in the infusion rates for the three inhalation agents. At 90% blockade, the infusion rates for N₂O/morphine were significantly higher than those for enflurane and isoflurane, but for halothane the difference did not reach statistical significance.

**Discussion**

The PID controller developed for this study can deliver atracurium in four modes: bolus mode, constant infusion, PID control, or four-phase mode, as described above. The controller rapidly achieved the desired setpoint with minimal overshoot and very small oscillations around the setpoint. As can be seen from table 2, this controller performed well in comparison to the variety of controllers developed previously.¹⁻⁶ These other controllers had overshoots ranging from 0.9 to 9.9%; our controller had an overshoot of 10.1%. Other controllers had steady-state errors ranging from 0.2 to 7.1%; our controller had a steady-state error of 3.0%. The time to setpoint of other controllers ranged from 5.47 to 14.3 min; our controller's time to setpoint was 7.0 min.

The atracurium infusion rate to maintain 90% blockade under N₂O/opioid anesthesia has been reported to be in the range of 6.1 to 6.8 μg·kg⁻¹·min⁻¹.¹⁴⁻¹⁶ We estimated the 90% infusion rate for N₂O/morphine to be 5.7 μg·kg⁻¹·min⁻¹, a result in general agreement with the previously published values.

Miller et al.¹⁷ noted that vecuronium and atracurium seem to show less difference in their requirements under different anesthetic techniques than do longer-acting agents such as curare and pancuronium. Shanks et al.¹⁸ found no difference in vecuronium requirements during halothane as compared to fentanyl anesthesia. In the current study, we found isoflurane and enflurane to differ significantly (P < 0.05) from N₂O/morphine at 90% blockade, but found no difference between the inhalation agents. Our data support the observation that for atracurium the effects of the inhalation anesthetics are similar.

In addition to testing a new controller, this study also used the PID controller in a novel fashion—as a tool for the rapid estimation of infusion rates to maintain a selected degree of blockade. In pharmacokinetic studies of muscle relaxants,¹⁴⁻¹⁷ infusion rates have been measured by estimating the rate and manually adjusting a constant infusion until the level of blockade is steady. This method is based on trial-and-error estimates and is slow. It has been well demonstrated¹⁹⁻²¹ that controllers can arrive at and maintain a setpoint more quickly and accurately than human operators, even those who are very familiar with the drugs involved. Jaklitsch et al.¹⁹ for example,

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Onset Time To Setpoint (min)</th>
<th>Onset Time To Steady State (min)</th>
<th>Overshoot (%)</th>
<th>Oscillation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>7.7 ± 0.4</td>
<td>26.9 ± 3.5</td>
<td>8.5 ± 2.3</td>
<td>2.5 ± 1.2</td>
</tr>
<tr>
<td>Enflurane</td>
<td>7.1 ± 0.67</td>
<td>25.9 ± 2.7</td>
<td>8.4 ± 1.5</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>7.5 ± 0.71</td>
<td>38.7 ± 5.6</td>
<td>12.9 ± 1.3</td>
<td>3.3 ± 0.8</td>
</tr>
<tr>
<td>N₂O/Morphine</td>
<td>5.6 ± 0.38</td>
<td>34.4 ± 5.6</td>
<td>10.0 ± 2.0</td>
<td>3.5 ± 0.6</td>
</tr>
<tr>
<td>All groups</td>
<td>7.0 ± 0.58</td>
<td>31.5 ± 4.0</td>
<td>10.1 ± 1.8</td>
<td>3.0 ± 0.5</td>
</tr>
</tbody>
</table>

Data expressed as means ± SEM.

The onset times, percent overshoot, and percent oscillation were not different (P < 0.05) for the four anesthetic techniques.
Table 2. Performance of Various Muscle Relaxant Controllers

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Relaxant</th>
<th>Time to Setpoint (min)</th>
<th>Controller Type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritchie (1985)⁹</td>
<td>Succinylcholine</td>
<td>5.47</td>
<td>PID</td>
<td>Overshoot 9.9%</td>
</tr>
<tr>
<td>Bradlow (1985)⁴</td>
<td>Atracurium</td>
<td>10.4</td>
<td>State est.</td>
<td>Overshoot 2.5%</td>
</tr>
<tr>
<td>Rametti (1985)⁹</td>
<td>Curare</td>
<td>14.3</td>
<td>State est.</td>
<td>SS error 0.2%</td>
</tr>
<tr>
<td>DeVries (1986)¹</td>
<td>Vecuronium</td>
<td>—</td>
<td>On-off</td>
<td>Overshoot 0.9%</td>
</tr>
<tr>
<td>Asbury (1986)²</td>
<td>Pancuronium</td>
<td>—</td>
<td>Proportional</td>
<td>SS error 2%</td>
</tr>
<tr>
<td>Jaklitsch (1987)⁶</td>
<td>Vecuronium</td>
<td>6.9</td>
<td>PID</td>
<td>SS error 4%</td>
</tr>
<tr>
<td>O’Hara (current)</td>
<td>Atracurium</td>
<td>7.0</td>
<td>Multiphase/PID</td>
<td>Overshoot 7.1%</td>
</tr>
</tbody>
</table>

The current study applies these findings by using the controller as a tool for measuring infusion rates. No differences were observed between the mean PID infusion rates calculated by our controller at setpoint (<3% oscillation) and a constant manually adjusted infusion. With first-order pharmacokinetics, the rate of elimination of a drug depends on its concentration, such that when large doses of a drug are given, the plasma concentration declines rapidly, following an exponential decay pattern. At lower concentrations, the rate of decay is lower. Maintenance of constant infusion to replace the amount of drug metabolized (at steady state) therefore requires less total drug than does intermittent bolus injection. It is expected that a controller with wide oscillations would use more total drug than would a constant-infusion device because it alternately over- and under-doses. The result of this oscillation would be overestimation of the infusion rate required to maintain the desired degree of blockade. Since our controller maintained the setpoint with only small oscillations, it is reasonable to conclude that the mean PID infusion rate delivered by our controller is effectively equivalent to a manually adjusted constant infusion. Therefore, a well-designed PID controller can be used not only to deliver muscle relaxants clinically, but also to measure infusion rates for research purposes.

Table 3. Atracurium Infusion Rates to Maintain 90% Blockade under Four Anesthetic Techniques

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Infusion Rate (µg·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>4.9 ± 0.3</td>
</tr>
<tr>
<td>Enflurane</td>
<td>3.5 ± 0.8*</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>4.1 ± 0.5*</td>
</tr>
<tr>
<td>N₂O/Morphine</td>
<td>6.2 ± 0.5</td>
</tr>
</tbody>
</table>

Data expressed as means ± SEM.

* Infusion rates are significantly different from morphine/N₂O but not from each other (P < 0.05).

In this study we chose to use the EMG rather than the mechanical twitch tension measurement (MMG) because of the ease of EMG measurement and the availability of the computer interface for the Datex device. The published infusion rates for atracurium under the various anesthetic techniques discussed above were obtained by MMG.¹⁴⁻¹⁸ A number of investigators²⁰⁻²⁶ have compared the EMG to the MMG response. The EMG has been found to be more sensitive than the MMG; i.e., the EMG is depressed to a greater extent than is the MMG when the two are measured simultaneously. However, Shanks and Jarvis²² as well as Katz²⁵ found little difference between the EMG and the MMG when 80% or more twitch depression was reached. Since our infusion rates were measured at 90% blockade, it is not surprising that our infusion rates are in general agreement with infusion rates obtained with MMG.¹⁴⁻¹⁸

In summary, we have developed a closed-loop controller for the delivery of muscle relaxants, used in this study to deliver atracurium. The controller performed accurately. It also was used to estimate muscle relaxant infusion rates under four different anesthetic techniques. Because the controller rapidly achieves a steady infusion at a desired setpoint, it can be used as a tool in pharmacokinetic and pharmacodynamic studies of muscle relaxant infusions.

The authors would like to thank Dr. Abrahm Noordergraaf for his advice on the theory and practice of PID control, Dr. Marc Bloom for his help in obtaining and assembling the computer, and Dr. Stanley Muravchik for his generosity in the use of his equipment.

Appendix

The constants for the PID controller were estimated by the following method:

1) The published¹⁴⁻¹⁶ mean infusion rate for atracurium, approximately 5 µg·kg⁻¹·min⁻¹, was assumed.
2) The equivalent pump rate, for a concentration of 5 mg·ml⁻¹, was calculated for a 70-kg patient.
Atracurium (mg/h) = 5μg · kg⁻¹ · min⁻¹ · 70 kg
× 60 min · h⁻¹ = 1,000 μg/mg = 21

Pump rate (ml/h) = 21 mg ÷ 5 mg · ml⁻¹
= 4 ml/h (approximately)

3) An error of approximately 4–5% was assumed. Initially, no contribution from integral or derivative terms was assumed. To achieve an infusion rate of 4 ml/h, the product K_p · error was determined. Therefore, a first estimate of K_p was 1.0–0.8.
4) The constants then were tuned manually according to the tuning rules described by Westenskow.²⁷

The resulting constants were:

K_p = 1.9
K_i = 0.05
K_D = 5.0

References
