INFUSION OF VECURONIUM CONTROLLED BY A CLOSED-LOOP SYSTEM

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The pharmacodynamic behaviour of vecuronium makes it suitable not only for administration as a single or repeated bolus, but also as a continuous infusion. As with any neuromuscular blocking drug, however, the considerable interindividual variability in requirement, and possible interactions with other drugs, make monitoring desirable. By combining the monitoring of neuromuscular transmission and the infusion of an appropriate drug, neuromuscular blockade can be maintained using a closed-loop system.

Automatic control in such a system can be achieved in two ways: proportional control (that is, varying the speed of infusion) or on-off control (switching the infusion pump on or off, thus injecting in a semi-continuous way). The present study was undertaken to assess the feasibility of controlling neuromuscular blockade by means of a closed-loop system based on the semi-continuous infusion of vecuronium.

PATIENTS AND METHODS

Closed-loop control system

A prototype of an evoked compound electromyograph (Neuromuscular Transmission Monitor (NTM), Organon Teknika) (Cruel, Booij and Robertson, 1983; Windsor, Sebel and Flynn, 1985) was used to stimulate an appropriate nerve, and to measure the compound EMG. The right ulnar nerve was stimulated via surface electrodes at the wrist using pulses of supramaximal intensity and of 0.15 ms duration at a rate of 0.1 Hz. The compound EMG of the hypothenar muscles was displayed on a pen recorder. The output signal of the NTM served as the input for an electronic device, developed in the Department of Medical Physics, which contained three elements (fig. 1). The passive element β served as an adaptor between the NTM and a comparator. The comparator had an adjustable reference voltage (preset value) with an adjustable hysteresis. The controller consisted of a solid state relay and syringe pump (Hospal K10). It was switched “on” when the input of the comparator exceeded value A and was switched “off” when it was lower than value B (fig. 2).

The syringe contained vecuronium 24 mg in saline 60 ml (0.4 mg ml⁻¹), and the rate of infusion was set at 3 µg kg⁻¹ min⁻¹. For comparison with the electromyogram, the mechanomyogram (MMG) was also measured in six patients using a Statham UC3 force displacement transducer, and recorded on the pen recorder.

Patients

Twenty-eight patients (ASA status I or II), scheduled for urological, neurosurgical, gynaecological or general surgery, were included in the study. All were premedicated with nicomorphine, a narcotic analgesic, 7.5–10.0 mg and haloperidol 5 mg i.m. 1 h before surgery. After the induction of anaesthesia with thiopentone 4 mg kg⁻¹ and fentanyl 2.5 µg kg⁻¹ i.v., baseline measurements of neuromuscular function were obtained. Subsequently, a bolus of vecuronium 0.07 mg kg⁻¹ i.v.

SUMMARY

Closed-loop control of neuromuscular blockade, using a semi-continuous infusion of vecuronium, is described. In 28 patients, the average neuromuscular transmission was between 13 and 17% of control. Requirements for vecuronium averaged 1.1 µg kg⁻¹ min⁻¹ (0.8–1.5 µg kg⁻¹ min⁻¹), being in the same range as for repeated bolus injections. No side effects were observed. After the infusion was stopped recovery was rapid. Only three patients required induced reversal of blockade.
was administered. The trachea was intubated when the twitch height had decreased to 30% of control or below. The closed-loop system was activated before neuromuscular blockade had recovered to 16% of control. Anaesthesia was maintained with 67% nitrous oxide in oxygen. Additional doses of fentanyl were given when required as judged by increases in heart rate and arterial pressure. Artificial ventilation was used throughout the procedure (end-tidal carbon dioxide concentrations between 4.5 and 5%). In neurosurgical patients, carbon dioxide concentrations were maintained between 3.5 and 4.0%. Approximately 20 min before the expected end of surgery the infusion of vecuronium was discontinued and blockade was allowed to recover spontaneously. Since there is spontaneous recovery during the ‘off-phase’ in the ‘on-off’ cycle, recovery time can be estimated from the slope of the curve (fig. 2).

FIG. 1. Schematic diagram of the control system (for explanation see text).

FIG. 2. Diagram showing oscillations around preset value (15%) attributable to control system. The difference between value "A" (16%) and "B" (14%) is called hysteresis (2%). Pump is on from A to B and off from B to A'.

RESULTS

After the bolus injection of vecuronium, twitch height decreased to less than 15% of control in all patients. After the closed-loop system was started, a depression of neuromuscular transmission was obtained which oscillated around the preset value—in general between 13 and 17% of control. This provided excellent operating conditions in all patients. A representative recording is shown in figure 3.

Using this technique, twitch heights of less than 10 or greater than 25% of control were not observed. On all occasions when the MMG was recorded simultaneously, the degree of relaxation measured with both methods was identical.

The duration of infusion varied between 45 min and 10 h. Even after 10 h of infusion, there was no sign of cumulation; spontaneous recovery was rapid and complete in 25 of the 28 patients at the
end of surgery. Although the average dose of vecuronium was 1.1 μg kg⁻¹ min⁻¹, there were considerable variations in the requirement for vecuronium between patients, resulting in a range from 0.8 to 1.5 μg kg⁻¹ min⁻¹. However, clinically stable blockade was easily obtained on all occasions. Once the infusion was stopped, recovery from neuromuscular blockade was rapid (average recovery time 11 min, range 5–22 min). At 70% recovery of twitch height, and at a train-of-four ratio of more than 50%, the patients were awakened. There were no clinical signs of residual neuromuscular blockade. In three of the 28 patients an antagonizing agent was required because surgery was terminated earlier than expected.

**DISCUSSION**

To date the most frequently used method of administering a non-depolarizing neuromuscular blocking drug is by bolus injection followed by additional increments, if required. When neuromuscular transmission is not monitored, this method may be satisfactory, especially when long-acting myoneural blockers are used. However, monitoring neuromuscular transmission allows better regulation of blockade because the administration of the neuromuscular blocker can be tuned to the individual patient. In addition, possible interactions with other drugs, such as antibiotics, can be detected. If the monitoring of blockade is performed in association with the continuous infusion of the drug, blockade can be controlled by means of a closed-loop system. Closed-loop control of neuromuscular blockade is not new: Ritchie, Spain and Reves (1984) developed a system using suxamethonium as the myoneural blocker. Brown and co-workers (1980) achieved the same using pancuronium and Cass and associates (1976) used gallamine, tubocurarine, alcuronium and pancuronium. In all of these studies the infusion was controlled by proportional regulation of the speed of infusion. Our method of choice was the "on-off" principle. The design of such a system is relatively simple in comparison with a proportional control system, and because of its pharmacodynamic profile, we regarded vecuronium as an ideal drug for use in such a system. Our system was tested in 28 patients during procedures which varied in duration from 45 min to 10 h. In all patients satisfactory neuromuscular blockade could be obtained easily. Oscillations in the degree of blockade were the result of the nature of the "on-off" system. The amplitudes of these oscillations depended on the hysteresis of the system, the "time-constant" of the drug, and the speed of infusion of the blocker (Gibson, 1963). A twitch height of less than 10% of control was regarded as excessive blockade because so many receptors are blocked that antagonism is difficult (Miller and Savarese, 1981). A twitch height greater than 30% of control provides insufficient surgical relaxation. In this study the oscillations never caused responses lower than 10% or higher than 25% of control twitch height and so did not interfere with the operative conditions. In 25 patients spontaneous recovery was rapid and complete. In only three patients was antagonism of residual neuromuscular blockade required—because surgery was terminated earlier than expected. Doses of vecuronium used (0.8–1.5 μg kg⁻¹ min⁻¹) were in the same range as found by d'Hollander and colleagues (1982) for continuous infusion and, as in our experience, for repeated single bolus injections.

We conclude that the closed-loop control of neuromuscular blockade using the semi-continuous infusion of vecuronium is a safe and simple method with which to maintain a sufficient degree of blockade for intermediate to long procedures, and is especially useful if stable degrees of blockade are essential.

**FIG. 3.** Representative recording of the EMG signal. After a loading dose of vecuronium, 100% neuromuscular blockade was obtained. The infusion was started when blockade started to recover. Continuous 85% blockade was maintained. When the infusion was stopped spontaneous recovery was allowed. The occasional vertical deflections represent artefacts caused by cautery.
REFERENCES


