MAINTENANCE OF CONSTANT 95% NEUROMUSCULAR BLOCKADE BY ADJUSTABLE INFUSION RATES OF PANCURONIUM AND ATRACURIUM

V. Y. HARALDSTED, J. W. NIELSEN, J. V. MADSEN AND L. HASSELSTRØM

Maintenance of neuromuscular blockade during surgery with the traditional non-depolarizing blockers (e.g. pancuronium) is achieved typically by an initial loading dose of the ED₉₅ multiplied by 1.5–2, supplied with smaller increments as required on clinical judgement [1]. This strategy poses two problems: unstable and poorly controlled levels of neuromuscular blockade, and accumulation. The latter may involve residual relaxation or undue prolongation of anaesthesia until adequate antagonism of blockade has been achieved [2, 3]. The new non-depolarizing drugs of intermediate duration of action may be given by the same scheme, but more appropriately as an infusion.

The aim of this study was to assess how easily a fixed level of 95% blockade could be maintained by giving a bolus of pancuronium or atracurium followed by an infusion at a rate adjusted to maintain this level of blockade.

PATIENTS AND METHODS

Thirty-nine patients (ASA groups I–II) were studied during elective surgery requiring muscle relaxation for more than 45 min (table I). Except for one mastectomy, the operations performed were intra-abdominal gastrointestinal and gynaecological procedures. All patients gave informed consent to the study and approval had been obtained from the local Ethics Committee.

SUMMARY

In a double-blind study, 39 patients (ASA groups I–II,) were given either pancuronium or atracurium as an infusion during surgery. The drugs were given as an initial loading dose of 0.064 mg kg⁻¹ or 0.30 mg kg⁻¹, respectively, followed by an infusion, the rate of which was regulated to produce a constant 95% depression of the evoked twitch response throughout surgery. No significant difference in the number of corrections of the infusion rate per hour was found (4.6 v. 4.9). Mean infusion maintenance doses were 35 and 356 μg kg⁻¹ h⁻¹, respectively. The inter-individual variability of maintenance doses for the two drugs did not differ, the coefficients of variation being 0.32 and 0.24. On stopping the infusion, the patients given atracurium recovered to a 15% twitch faster than those given pancuronium. In addition neostigmine produced a quicker recovery in this group. Thus atracurium may be a more satisfactory drug for use by infusion.

Exclusion criteria included: age below 20 yr or above 70 yr, neuromuscular disease and medication with tricyclic antidepressant, neuroleptic, aminoglycoside, peptide antibiotic or calcium antagonist drugs. An additional three patients

<table>
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<th>Table I. Details of patients. Mean values (range)</th>
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<td>Pancuronium</td>
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were excluded during operation because of malfunction of the syringe driver or displacement of the armboard.

The patients were allocated randomly to receive either pancuronium or atracurium. The investigation was blinded so that both patient and anaesthetist were unaware of which drug was given.

Premedication comprised diazepam 0.3 mg kg⁻¹ by mouth 1 h before surgery. Anaesthesia was induced with pethidine 1 mg kg⁻¹ and thiopentone 3–5 mg kg⁻¹ i.v. and maintained by means of 66% nitrous oxide in oxygen and supplements of pethidine 0.3 mg kg⁻¹ and thiopentone 0.8 mg kg⁻¹. All drugs were given through a constantly running infusion in a peripheral vein in the arm not suspended in the neuromuscular recording device.

Neuromuscular blockade was monitored by the use of a force displacement transducer measuring the evoked adduction force of the thumb. The transducer was interfaced to a Myograph 2000 (Biometer, Denmark). In each patient, resting thumb tension was maintained between 150 and 300 g during recordings. Supramaximal train-of-four (TOF) stimuli (2 Hz, 2 s) were delivered every 10 s to the ulnar nerve at the wrist via surface electrodes. Twitch height and TOF ratio were registered continuously digitally and on a chart recorder.

When stable neuromuscular recordings had been obtained, typically 5–10 min after induction, a bolus was given of pancuronium 0.064 mg kg⁻¹ or atracurium 0.3 mg kg⁻¹ (equipotent doses). The trachea was intubated when the evoked response of the adductor pollicis had declined to zero.

Maintenance of stable neuromuscular blockade was achieved by the i.v. infusion of pancuronium 0.1 mg ml⁻¹ or atracurium 1 mg ml⁻¹ (Dameca Injectomat syringe driver). The infusion (initial infusion rates of 0.037 mg kg⁻¹ h⁻¹ or 0.37 mg kg⁻¹ h⁻¹, respectively) was commenced when the first response to TOF stimulation had recovered to 5%. Bolus doses and initial infusion rates were found in earlier studies to be equipotent [4, 5]. The magnitude of the adjustments was approximately 25% of the initial infusion rate and at least 5 min elapsed between adjustments.

Infusions were discontinued 10–15 min before the termination of surgery and residual block was antagonized by neostigmine 2.5 mg and atropine 1 mg i.v. when twitch height had reached 15%. The block was considered fully antagonized when the TOF ratio was 0.7.

Arterial blood-gas analysis was performed during surgery and confirmed that normocapnia had been achieved. Heart rate and ECG were monitored continuously and non-invasive arterial pressure was recorded automatically at 5-min intervals (Dinamap, Criticon).

Skin temperature on the stimulated hand and temperature in the nasopharynx were measured at the beginning and end of anaesthesia.

The Wilcoxon Rank Sum Test was used for statistical analyses. P < 0.05 was chosen as the level of significance.

RESULTS

The two groups were comparable with respect to age, weight, height and sex ratio (table I). Characteristics of the block in each group as shown in table II.

Average maintenance doses of pancuronium and atracurium were found to be 35 µg kg⁻¹ h⁻¹ (range 17.6–58.3, SD 11.1) and 356 µg kg⁻¹ h⁻¹ (range 207–531, SD 87.2), respectively. Comparisons of dispersion in the two groups were made by calculation of F:

\[
F = \frac{(SD \text{ pancuronium divided by mean})^2}{(SD \text{ atracurium divided by mean})^2}
\]

yielding no significant difference.

| TABLE II. Characteristics of neuromuscular blockade. Mean values (range). Statistical significance by Wilcoxon's rank sum test: *P < 0.05 |
|-------------------------|-------------------------|
|                         | Pancuronium            | Atracurium            |
| Time from bolus to maximal blockade (s) | 138 (80–240)         | 116.5* (70–420)       |
| Duration of action from administration of bolus to 5% recovery (min) | 26.6 (6–45)          | 26.0 (0–39)           |
| Duration of infusion (min) | 65 (23–165)           | 71 (22–177)           |
| Spontaneous recovery from 5% to 15% (min) | 25 (10.5–37)         | 15* (6–34)            |
| Reversal by neostigmine from 15% to TOF ratio 0.7 (min) | 10.0 (4.5–17)        | 6.5* (3–11)           |
MAINTENANCE OF CONSTANT BLOCKADE

Fig. 1. Number and direction of changes of the infusion rate of pancuronium and atracurium expressed as percentages of number of patients during successive 10-min intervals. Initial infusion rates were 37 \( \mu \text{g kg}^{-1} \text{h}^{-1} \) and 370 \( \mu \text{g kg}^{-1} \text{h}^{-1} \), respectively, and the size of corrections approximately 25% of the initial rate. Numbers above bars refer to number of patients.

On average 4.6 (range 1–8) corrections per hour were required in the pancuronium group compared with 4.9 (range 2–10) in the atracurium group. Figure 1 shows the frequency and mode of adjustment of the infusion rate in successive 10-min intervals. The typical pattern of infusion rates in both groups was an increase during the first 10 min of infusion. In both groups the initial infusion rate (which was close to the average maintenance dose) had to be increased in approximately 50% of patients in order to maintain 95% blockade. Thereafter a slow but steady decline was seen in the pancuronium group, whereas six of 20 patients receiving atracurium had to be given increasing amounts of the drug after a further 20 min. The rate of adjustment of the infusion rate diminished only slightly with time and this is shown in figure 1 by a decreasing bar length.

The mean temperature of the nasopharynx at induction was 36.0 °C in both groups. At the end of anaesthesia it had decreased 0.5 °C in the pancuronium group and 0.6 °C in the atracurium group. Mean skin temperature of the stimulated hand was 32.4 °C and 32.2 °C and this decreased by 0.3 °C and 0.4 °C, respectively. In 10 patients, dispersed evenly in both groups, skin temperature increased by 0.1–2.0 °C.

DISCUSSION

We have confirmed that the time of onset from administration of the bolus to maximal blockade, the rate of spontaneous recovery from 5% to 15% and the duration from this point to full recovery produced by neostigmine were shorter for atracurium than pancuronium.

The durations of action from administration of the bolus to 5% recovery of the first twitch response were surprisingly similar, 26.6 min and 26.0 min for the pancuronium and atracurium groups, respectively. After a bolus dose of pancuronium 0.075 mg kg\(^{-1}\) and atracurium 0.33 mg kg\(^{-1}\) Gramstad, Lilleaasen and Minsaas [4] found a duration of action to 25% recovery of 45.1 min and 27.6 min. Our results are explained partly by the fact that spontaneous reversal is shorter for atracurium than for pancuronium. Hence, the time required to recover from 5% to 25% is considerably longer for pancuronium than atracurium. The relatively small bolus doses used in this study (ED\(_{95}\)) were not sufficient to suppress twitch response completely in all patients (six in the pancuronium group and three in the atracurium group). This may also account for measured duration of action, because kinetics may be influenced predominantly by redistribution rather than elimination of the drugs under these conditions.

The maintenance doses of pancuronium and atracurium used during infusion (35 and 356 \( \mu \text{g kg}^{-1} \text{h}^{-1} \)) are comparable to those found elsewhere [5–8]. The inter-individual variations of atracurium pharmacodynamics are claimed to be relatively small compared with other non-depolarizing drugs as a result of the unique and rather uniform rate of Hoffman elimination [9]. This was not confirmed in our study. Although we found a slightly smaller standard deviation and range (in relation to mean) for the average maintenance dose of atracurium as opposed to pancuronium, the difference was not significant.

The two drugs did not differ in respect of ease of control—four to five regulations of the infusion rate were required per hour to maintain 95%
blockade. However, the pattern of infusion rates differed, as shown in figure 1. We believe that this reflects different cumulative properties of the drugs, being smaller for atracurium.

Simpler infusion regimens inevitably lead to unacceptable variations of the level of relaxation when using a pre-fixed rate of infusion, because of inter-individual variation in dose responses. With a non-cumulative drug, many patients probably maintain a constant level of block, but not necessarily the level desired. Of course, one may choose an infusion rate large enough to keep the majority of the patients sufficiently relaxed, but this involves a considerable variation in the duration from the end of infusion to the point at which administration of an antagonist is effective. The quick spontaneous rate of antagonism of atracurium may partly obviate this problem. However, careful monitoring of the block is still necessary to ensure safe antagonism [2].

The temperature changes in the hand were small and of similar magnitude in both groups and are unlikely to have influenced our results. The difference in peripheral to central temperature gradient was not significant between groups. It is notable that the peripheral temperature increased in 10 patients, and it is likely that vasodilatation produced by pethidine was responsible.

In conclusion we have shown that, in order to maintain a uniform level of surgical relaxation produced by a bolus dose followed by infusion of pancuronium or atracurium, frequent and large corrections of the rate of infusion are necessary. With atracurium, at least as many adjustments of the rate of infusion are required as with pancuronium. However, the use of atracurium is associated with quicker spontaneous and induced reversal.

REFERENCES