COMBINED I.V. BOLUS AND INFUSION OF PANCURONIUM BROMIDE

A. A. SOMOGYI, C. A. SHANKS AND E. J. TRIGGS

SUMMARY

An i.v. bolus and concomitant infusion of pancuronium is proposed for use in prolonged anaesthesia. Plasma concentrations of pancuronium were measured in 16 patients receiving this regime. The desired steady-state concentration of 0.2 μg ml⁻¹ was achieved in most instances at approximately 45 min. Following the bolus, the neuromuscular twitch response decreased to low values or was abolished completely. Thereafter the response remained relatively constant or increased in intensity consistent with the mean steady-state plasma concentrations of 0.214 μg ml⁻¹ (SEM 0.012) maintained by the infusion. When the infusion was stopped, the mean twitch height was 23% of control and increased thereafter at approximately 1% per min, while plasma concentrations decreased by half in 69 min. One patient with renal artery stenoses exhibited complete neuromuscular blockade at a steady-state plasma concentration of 0.29 μg ml⁻¹; following cessation of infusion the twitch response was detected after 30 min (plasma concentration 0.20 μg ml⁻¹) and recovery was uneventful. Plasma clearance and apparent volume of distribution of pancuronium used to calculate the dosage regime were found not to differ significantly from those reported for a single dose. Following cessation of infusion, plasma concentrations declined in either a mono- or bi-exponential form depending on the ratio of the hybrid disposition rate constants (β/α). In all instances a two-compartment open model was used to describe the time course of the plasma concentrations.

The continuous administration of a non-depolarizing muscle relaxant to produce sustained neuromuscular blockade was employed first by Evans and Spencer Gray (1953). Following an initial, rapid infusion of gallamine, a slower infusion at the rate of 1 mg min⁻¹ was used, and the effects on abdominal muscular relaxation and spontaneous ventilation were observed. Ryan (1964) employed a similar procedure for tubocurarine, based on the rate of disappearance and accumulation of the drug in anaesthetized man. Following an initial bolus dose (usually 15 mg) of tubocurarine, neuromuscular blockade was maintained by a constant infusion at a rate equivalent to the bolus dose per hour. By clinical assessment, the rate of infusion “remained remarkably constant in the majority of cases”, although a few patients required a reduction in infusion rate during the 3rd and 4th hours.

Miller and Eger (1976) determined the potency ratios of tubocurarine and pancuronium. Following a bolus dose, a continuously changing rate of infusion was administered to produce a constant 90% reduction of twitch tension. Plasma concentrations of drug(s) were not measured. For their study, calculations were based on differences in the amount administered over different periods during the infusion of each relaxant. From the difference in potency ratios based on dose requirements for the first and last 30-min periods of observation, it was concluded that potency values determined by single injection techniques did not describe adequately the relative requirements for sustained neuromuscular block.

A single i.v. dose has been used to examine the pharmacokinetics of pancuronium bromide (Agoston et al., 1973; McLeod, Watson and Rawlins, 1976; Somogyi, Shanks and Triggs, 1976). In each case a multicompartment open model was used. It was noted by Somogyi, Shanks and Triggs (1976) that the mean plasma concentration of pancuronium, following recovery to 80% neuromuscular block, was 0.169 μg ml⁻¹.

With the assumption that a constant plasma concentration of pancuronium would produce a constant degree of neuromuscular block, we devised a drug dosage regime to produce such a situation. A desired plasma concentration of 0.2 μg ml⁻¹ of pancuronium was used in the calculation of the dosage, as this usually would produce neuromuscular blockade of more than 90% (Somogyi, Shanks and Triggs, 1976). This paper presents the clinical findings of a study in which a technique involving a bolus and an infusion of pancuronium was investigated to...
determine if a steady-state plasma concentration of pancuronium bromide could be achieved in patients undergoing prolonged surgery. The pharmacokinetic calculations used were based on previous observations (Somogyi, Shanks and Triggs, 1976).

METHODS

Calculation of the doses of drugs

The method used to determine the size of the bolus and infusion doses was that of Mitenko and Ogilvie (1972), for a drug obeying multi-compartment kinetics whereby

\[ \text{Bolus dose } (B) = V_{d,eff} \times C_{ss} \]  

and

\[ \text{Infusion rate } (I) = CL_p \times C_{ss} \]  

where \( V_{d,eff} \) represents the apparent volume of distribution of the drug, \( CL_p \) the plasma clearance and \( C_{ss} \) the desired steady-state drug concentration in plasma.

The decline in plasma concentrations of pancuronium following a single i.v. dose has been described by a multi-exponential equation (McLeod, Watson and Rawlins, 1976; Somogyi, Shanks and Triggs, 1976). Both groups of workers adopted a two-compartment open model. When the model has been defined adequately the plasma clearance may be determined from the product of the apparent volume of distribution \( (V_{d,eff}) \) and the slope of the log-linear terminal phase \( (\beta) \). Consequently, the relationship between the bolus dose and the infusion is

\[ \text{Bolus dose } (B) \times \beta = \text{Infusion rate } (I) \]  

It was shown recently in man (Somogyi, Shanks and Triggs, 1976) that, at the first sign of recovery from neuromuscular blockade (99% paralysis) following a 6-mg dose of pancuronium, the mean plasma concentration was 0.218 \( \mu g \) ml\(^{-1}\), and at 80% paralysis the concentration was 0.169 \( \mu g \) ml\(^{-1}\). A drug concentration \( (C_{ss}) \) of 0.20 \( \mu g \) ml\(^{-1}\) was selected for the present study, on the grounds that this would produce sufficient neuromuscular blockade for surgical requirements (Katz, 1971; Ali and Savarese, 1976). Further data from additional patients allowed slight modification of the pharmacokinetic parameters, so that the eventual values calculated to achieve the selected drug concentrations from equations (1) and (2) became

\[ \text{Bolus dose } (B) = 62.5 \mu g \text{ kg}^{-1} \]

and

\[ \text{Infusion rate } (I) = 0.35 \mu g \text{ kg}^{-1} \text{ min}^{-1} \]

As an example, for a 70-kg patient the bolus dose required would be 4.37 mg and the infusion rate 24.5 \( \mu g \) min\(^{-1}\). To determine the time at which a steady-state concentration of pancuronium would be reached using the proposed bolus/infusion regime, computer simulations were performed based on the averaged data. It was found that a plasma concentration within 10% of the desired steady-state concentration should be attained after approximately 45 min, within 5% at 60 min and within 1% at 75 min.

Details of the technique of pharmacokinetic analysis of the data obtained are shown in the Appendix.

Patients

Sixteen adult patients (table I) without renal or hepatic disease (except one patient who had renal artery stenoses) were studied during elective surgery for intra-abdominal or arterial vascular disease, or both. None of the patients received antibiotics or other agents known to affect neuromuscular transmission.

Premedication comprised a combination of a narcotic analgesic and atropine or hyoscine. Anaesthesia was induced with thiopentone i.v. and maintained with a combination of halothane 0.5% and nitrous oxide. Body core and peripheral temperatures were maintained by surface insulation and fluid losses were replaced by i.v. electrolyte solutions.

Neuromuscular response

The evoked twitch response was monitored by measurement of the contraction of the ring finger, using a Devices linear force displacement transducer, and displayed on a chart recorder. Immediately following induction of anaesthesia, subcutaneous needle electrodes were placed at the elbow and a supramaximal stimulus was applied at a rate of 0.2 Hz from a Burroughs Wellcome stimulator. Not less than 20 min later, after a stable control twitch height had been recorded, pancuronium was administered.

Dosage of pancuronium

Each patient was given an initial i.v. bolus dose of pancuronium of approximately 62.5 \( \mu g \) kg\(^{-1}\) and a constant infusion of the drug at a rate of approximately 0.35 \( \mu g \) kg\(^{-1}\) min\(^{-1}\). The infusion comprised 100 ml of normal saline containing 5 mg of pancuronium. For five patients the rate of infusion was
regulated by a paediatric microdrip set (Metriset, McGaw) and for the other 11 patients by a constant rate i.v. infusion pump (Volumetric Infusion Pump, McGaw).

**Blood collection and analysis**

Venous blood samples were obtained from each patient just before pancuronium was administered (blank), then at 5, 10, 15, 20, 30 and 45 min and thereafter every 20–30 min during the infusion period. When the infusion was terminated, blood samples were taken where possible at 10, 20, 30, 45, 60, 90 and 120 min after infusion. The samples were centrifuged and the plasma frozen and stored before analysis.

Pancuronium in plasma was measured by the spectrofluorimetric method of Kersten, Meijer and Agoston (1973), using a Perkin–Elmer model 204 spectrofluorimeter.

**RESULTS**

The mean total dose of pancuronium administered was less than 6.5 mg (approximately 0.1 mg kg\(^{-1}\)) (table I). The evoked twitch response decreased to low values within a few minutes following administration of the bolus dose and in more than half the group it was totally abolished. In most patients the twitch response could be observed during the latter part of the infusion; it usually remained constant or increased very slowly in height so that at the cessation of infusion the average twitch height was 23% of the control height. The maintenance of an adequate intensity of neuromuscular blockade was associated with a plateau in the plasma concentration of pancuronium (table II and fig. 1). The time required for plasma concentrations to decrease by one-half their original value from when the infusion ceased was examined. In the 16 patients the mean half-life was found to be 69 min (SD 17 min).

**TABLE I. Clinical details of patients (B.s.a. = body surface area)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>B.s.a. (m(^2))</th>
<th>Surgery</th>
<th>Duration of infusion (min)</th>
<th>Pancuronium (total dose) (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>52</td>
<td>65</td>
<td>1.81</td>
<td>Ilio–femoral and femoro–popliteal bypass</td>
<td>180</td>
<td>9.6</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>60</td>
<td>53.5</td>
<td>1.63</td>
<td>Femoral bypass</td>
<td>60</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>53</td>
<td>50</td>
<td>1.55</td>
<td>Cholecystectomy</td>
<td>120</td>
<td>6.3</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>76</td>
<td>60</td>
<td>1.83</td>
<td>Ilio–iliac artery bypass</td>
<td>120</td>
<td>7.2</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>60</td>
<td>61</td>
<td>1.79</td>
<td>Ilio–femoral artery bypass</td>
<td>90</td>
<td>6.0</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>46</td>
<td>53</td>
<td>1.63</td>
<td>Femoro–popliteal bypass</td>
<td>120</td>
<td>5.5</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>61</td>
<td>75</td>
<td>1.88</td>
<td>Ilio–femoral and femoro–popliteal bypass</td>
<td>120</td>
<td>4.7</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>64</td>
<td>69.5</td>
<td>1.79</td>
<td>Gastrectomy</td>
<td>120</td>
<td>7.4</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>34</td>
<td>86</td>
<td>2.10</td>
<td>Cholecystectomy</td>
<td>90</td>
<td>8.1</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>55</td>
<td>47</td>
<td>1.57</td>
<td>Repair of prolapsed rectum</td>
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<tr>
<td>11</td>
<td>M</td>
<td>65</td>
<td>78</td>
<td>1.97</td>
<td>Ilio–iliac arterial anastomosis</td>
<td>90</td>
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</tr>
<tr>
<td>12</td>
<td>M</td>
<td>73</td>
<td>70</td>
<td>1.96</td>
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<td>120</td>
<td>7.3</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>76</td>
<td>45</td>
<td>1.52</td>
<td>Resection of aneurysm</td>
<td>150</td>
<td>5.2</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>64</td>
<td>57</td>
<td>1.63</td>
<td>Cholecystectomy</td>
<td>43</td>
<td>4.5</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>22</td>
<td>88</td>
<td>2.05</td>
<td>Correction of bilateral renal artery stenosis</td>
<td>296</td>
<td>14.6</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>74</td>
<td>61</td>
<td>1.68</td>
<td>Ilio–femoral artery bypass</td>
<td>135</td>
<td>6.7</td>
</tr>
</tbody>
</table>

When the infusion of pancuronium was terminated the twitch tension increased rapidly at a mean rate of about 1% per min. However, the termination of surgery seldom permitted measurements to continue beyond 40% recovery of the control value. Antagonism of residual neuromuscular blockade with neostigmine was uneventful in all the patients.
A semilogarithmic plot of the mean plasma concentrations (± SD) of pancuronium for 15 patients. In the section labelled “A” these are shown for the first 60 min during the infusion (horizontal bar). The section labelled “B” begins at the point when the infusion was discontinued.

A typical example is shown in figure 2. This patient (No. 6) received a bolus dose of pancuronium 3.3 mg together with an infusion of 18.6 µg min⁻¹ for 120 min. Complete neuromuscular blockade resulted initially and the twitch response returned 20 min after administration had commenced. For the last 70 min of the infusion period the twitch increased from 10 to 16% and plasma concentrations of pancuronium remained fairly constant. However, as soon as the infusion ceased, the plasma concentration decreased rapidly and the twitch height increased at a rapid rate, so that 40 min after the cessation of infusion the twitch height had increased from 16 to 90% of control.

To obtain a plateau value, mean plasma concentrations of pancuronium were calculated for each patient from the values found between 45 min and cessation of infusion (table II). For the five patients who had the drug infused by paediatric microdrip there were larger fluctuations in the plasma concentrations, but the mean value for these five patients during that interval was 0.250 µg ml⁻¹ (SEM 0.017 µg ml⁻¹). For the 11 patients who received the infusion by the more accurate infusion pump, the average plasma concentration for the same period of time was 0.195 µg ml⁻¹ (SEM 0.011 µg ml⁻¹), giving a combined mean plasma concentration of pancuronium of 0.214 µg ml⁻¹ (SEM 0.012 µg ml⁻¹).

One patient (no. 15) had renal artery stenoses and consequently was not included in the mean data presented above. Figure 3 shows the pancuronium concentrations of this patient. The observed mean plasma concentration from 45 to 296 min (end of infusion) was 0.29 µg ml⁻¹ (SD 0.04 µg ml⁻¹); these high values were a result of the fact that the patient was clearing the drug at less than two-thirds of the rate of the other patients. Consequently, the steady-state plasma concentration should be one-and-a-half times that desired (0.30 µg ml⁻¹) which is in good agreement with the observed data. Although the twitch response for this patient was abolished completely during the infusion, the twitch did return after 30 min following infusion (plasma concentration 0.20 µg ml⁻¹) and increased in the usual manner.

FIG. 1. A semilogarithmic plot of the mean plasma concentrations (± SD) of pancuronium for 15 patients. In the section labelled “A” these are shown for the first 60 min during the infusion (horizontal bar). The section labelled “B” begins at the point when the infusion was discontinued.

FIG. 2. Plasma concentrations and twitch response relationship for patient no. 6 following a bolus dose of 3.3 mg and concomitant infusion of 18.6 µg min⁻¹ of pancuronium. The closed circles represent the observed plasma concentrations, the solid line the computed line of best fit, the numbers above the line represent the measured percent twitch height and the arrow indicates the time at which the infusion ceased.
FIG. 3. Semilogarithmic plot of the observed plasma concentrations (closed circles) for patient no. 15 with renal artery stenoses following a bolus dose of 5.5 mg and concomitant infusion at the rate of 31 μg min⁻¹ of pancuronium. The arrow indicates the time the infusion ceased, and the numbers above the line indicate the measured percent twitch height.

At the opposite extreme, patients 10, 12, 13 and 16 had twitch responses which exceeded 30% of the control height at the end of the infusion. However, this did not appear to produce relaxation which was inadequate for surgery. The steady-state concentrations which were achieved in these patients were 0.16, 0.20, 0.21 and 0.12 μg ml⁻¹ respectively.

For each patient the two parameters, plasma clearance (Clₚ) and apparent volume of distribution (Vₐβ), were determined (table III). When plasma clearance was calculated, both by division of the total dose administered by the area under the plasma concentration-time curve (as measured using the trapezoidal rule extrapolated to infinite time), and also from the computer estimates of the iterated parameters using the relationship Clₚ = αβ Vₐβ/k21, no significant differences were noted between the two methods. The apparent volume of distribution was determined from Clₚ and β (Vₐβ = Clₚ/β).

The two-compartment characteristics of pancuronium were examined by means of the ratio shown in the Appendix. Values for this ratio ranged from 0.03 which was visually a mono-exponential decrease in pancuronium plasma concentrations, to 0.46, when a bi-exponential decrease was obvious. This does not imply that the handling of pancuronium by some patients may be equated to a one-compartment model and others to a two-compartment model, for the ratio β/kₑ₁ (see table IV) indicates the two-compartment behaviour of pancuronium. The smaller the value of this ratio the greater is the amount of pancuronium in compartment 2 compared with the amount in compartment 1. Conversely, a value of 1.0 would indicate one-compartment behaviour. This ratio ranged from 0.14 to 0.61 (table IV), and in the seven patients studied previously it was between 0.19 and 0.49. Therefore all the patients studied had plasma concentrations of pancuronium which should be interpreted according to a two-compartment open model.

### DISCUSSION

A continuous infusion of pancuronium may be adjusted to provide a constant intensity of neuromuscular blockade (Miller and Eger, 1976). In contrast with this approach we selected a plasma pancuronium concentration (0.2 μg ml⁻¹) which was
likely to provide adequate relaxation for surgery, and attempted to achieve this using calculations made from pharmacokinetic data. Our technique of administration of pancuronium (bolus plus infusion) provided clinically adequate neuromuscular blockade, despite the effects of anaesthesia and surgery. As the technique of dosage was derived from averaged data, there were patients for whom the dosage administered was inaccurate, usually producing a suboptimal depression of the twitch response.

The decision to terminate the infusion was simplified by observation of the twitch response. If the response was detectable, then after cessation of infusion the twitch increased in height at the rate of approximately 1% per min. This rate of recovery is similar to that reported after a bolus dose of pancuronium 0.08 mg kg\(^{-1}\) (Katz, 1971), where relaxation was usually considered satisfactory when the twitch response was less than 25% of control. Katz (1971) also noted that the point in recovery from a neuromuscular block at which antagonism is initiated is a far more important determinant of neostigmine requirement than is the dose of neuromuscular blocking drug administered.

The effects of the regime produced an excessive dosage of the drug in one patient with an abnormal renal haemodynamic state (fig. 3). This type of response suggests that monitoring of neuromuscular transmission is necessary. Simple visual observation of the intensity of the evoked twitch response would allow gross deviations from normal to be detected and the rate of infusion to be modified. Similarly, patient 16 received an inadequate dose and this could have been modified.

The mean total dose of pancuronium administered to the patients was approximately 0.1 mg kg\(^{-1}\), for an average infusion period in excess of 100 min (table I). When a dose of 0.1 mg kg\(^{-1}\) was administered as a single i.v. bolus, the time reported for the first return of twitch was 60 min, and the time lapse before there was a clinical need for a supplementary dose of pancuronium was about 80 min (Vaughan and Cobb, 1974). However, the technique of continuous infusion would appear to offer a means of achieving uninterrupted neuromuscular blockade.

The main object of our study was to achieve a steady-state concentration of pancuronium, chosen to produce adequate muscle relaxation for intra-abdominal surgery. The actual intensity of the neuromuscular blockade would have been influenced by the presence of halothane (Miller et al., 1972), and this is one of the factors which precludes a clear-cut assessment of the relationship between peripheral nerve twitch response and abdominal muscle relaxation.

In conclusion, the bolus and infusion technique recommended consists of an initial i.v. bolus dose of pancuronium 62.5 \(\mu g\) kg\(^{-1}\), together with a constant infusion at the rate of 0.35 \(\mu g\) kg\(^{-1}\) min\(^{-1}\). This regime produced and maintained a predictable concentration of pancuronium in the normal population examined (fig. 1), but cannot be used inflexibly. An inadequate bolus dose will not produce sufficiently high concentrations for surgical relaxation, nor will a slower infusion rate maintain them. Conversely, an excessive dose of pancuronium administered by bolus and infusion will produce and maintain large plasma concentrations, with consequent profound paralysis. It should be emphasized that the dose regime is empirical and is based on data for pancuronium concentrations in normal patients. Any disease state, such as renal failure or biliary obstruction, which has been found to alter the rate of clearance of pancuronium (McLeod, Watson and Rawlins, 1976; Somogyi, Shanks and Triggs, 1977a, b) will invalidate this dose regime. The use of this regime should be accompanied always by assessment of neuromuscular transmission.

<table>
<thead>
<tr>
<th>Patient</th>
<th>(\beta/\alpha)</th>
<th>(\beta/k_{el})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.03</td>
<td>0.22</td>
</tr>
<tr>
<td>2</td>
<td>0.06</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>0.06</td>
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</tr>
<tr>
<td>7</td>
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</tr>
<tr>
<td>8</td>
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</tr>
<tr>
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</tr>
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<td>11</td>
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<tr>
<td>16</td>
<td>0.08</td>
<td>0.35</td>
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</tbody>
</table>

Single dose study (\(n = 7\)*

Range:

- \(\beta/\alpha\): 0.05–0.12
- \(k_{el}\): 0.19–0.49

* Data from Somogyi, Shanks and Triggs (1976).
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APPENDIX

Pharmacokinetic analysis

The decrease in plasma concentrations (C) of pancuronium with time (t) following an i.v. bolus dose can be described by the following bi-exponential equation:

\[
C = \frac{B(\alpha - k21)}{V_c(\alpha - \beta)} e^{-\alpha t} + \frac{B(k21 - \beta)}{V_c(\alpha - \beta)} e^{-\beta t}
\]  

(1)

This equation is consistent with a two-compartment open model, where B represents the bolus dose, \(V_c\) the apparent volume of distribution of the sampling (plasma) compartment, k21 the first-order transfer rate constant of drug between compartments 2 and 1, and \(\alpha\) and \(\beta\) are hybrid disposition rate constants.

When the drug is administered as a zero-order (constant rate) infusion, plasma concentration during the time of infusion can be described by:

\[
C = \frac{I(k21 - \alpha)(1 - e^{-\alpha T}) + I(\beta - k21)(1 - e^{-\beta T})}{V_c(\alpha - \beta)} e^{-\beta t}
\]  

(2)

When the infusion ceases the decrease in plasma concentration can be described by:

\[
C = \frac{I(k21 - \alpha)(1 - e^{-\alpha T})}{V_c(\alpha - \beta)} e^{-\alpha t} + \frac{I(\beta - k21)(1 - e^{-\beta T})}{V_c(\alpha - \beta)} e^{-\beta t}
\]  

(3)

where \(I\) represents the infusion rate (amount/time) and \(T\) is the time when the infusion ceases. Therefore, following a bolus dose and constant infusion for a specified period of time, the entire plasma concentration–time relationship can be described. From zero time to when the infusion ceases \((T)\), plasma concentrations can be described by the summation of equations (1) and (2), and after infusion by equations (1) and (3). Therefore, for each patient's set of plasma concentration–time data, the four parameters \(\alpha, \beta, k21\) and \(1/V_c\) were iterated using the computer program NONLIN (Metzler, 1969) and a non-linear least-squares fit obtained. All plasma concentrations were weighted appropriately according to the reciprocal of the square of their value standardized to the number of data points. Computer fitting and simulations (based on average data) were performed on a CDC CYBER 72 computing system. The two tailed Student \(t\) test was used for comparison of group means.

Following attainment of a steady-state concentration of pancuronium in the body, when the infusion ceases drug concentrations decrease in the usual bi-exponential manner. However, the ability to distinguish the two-compartment characteristics of pancuronium will be decreased. The two-compartment characteristics of a drug administered as an i.v. bolus can be determined from the zero-time intercepts \(A\) and \(B\). As the ratio \(A/B\) becomes smaller \((A \text{ approaches zero})\) a monoeXponential decrease in plasma concentrations will be observed, that is the model becomes a one-compartment open model. Following infusion to steady state the analogous ratio becomes \(A/B\). The ratio \(\beta/\alpha\) will always be smaller than \(A/B\) since, by definition, \(\beta\) will always be less than \(\alpha\) (Gibaldi and Perrier, 1975). Assuming \(A/B\) to be similar in all patients, the ratio \(\beta/\alpha\) was determined for each patient and is shown in table IV.

ACKNOWLEDGEMENTS

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REFERENCES


Eine intravenöse Bolusinjektion mit gleichzeitiger Pancuronium-Infusion wird zur Verwendung bei verlängerter Narkose vorgeschlagen. Die Pancuronium-Plasmakonzentrationen wurden bei 16 derartigen Patienten gemessen. Die erwünschte Dauerinfusionskonzentration von 0,2 μg ml⁻¹ wurde in den meisten Fällen nach etwa 45 min erzielt. Nach dem Bolus sank die neuromuskuläre Zuckreaktion auf niedrige Werte ab oder verschwand völlig. Danach blieb die Reaktion relativ konstant oder wurde intensiver, entsprechend dem mittleren Dauerplasmakonzentrationen von 0,214 μg ml⁻¹ (SEM 0,012), wie sie durch die Infusion erzielt wurden. Bei Einstellung der Infusion betrug die mittlere Zuckhöhe 23% des Kontrollwertes, und stieg danach um etwa 1% pro Minute, während sich die Plasmakonzentrationen innerhalb von 69 min um die Hälfte verringerten. Ein Patient mit Nierenarterienstenose zeigte eine vollständige neuromuskuläre Blockierung bei einer Dauerplasmakonzentration von 0,29 μg ml⁻¹; nach Beendigung der Infusion wurde nach 30 min (Plasmakonzentration 0,20 μg ml⁻¹) eine Zuckreaktion entdeckt, und die Erholung verlief ohne Komplikationen. Die Plasmakläerung und das ersichtliche Verteilungsvolumen von Pancuronium—benutzt zur Berechnung der Dosierungsweise—unterschieden sich nicht wesentlich von den bei Einzeldosierung gemeldeten Werten. Nach Beendigung der Infusion sanken die Plasmakonzentrationen entweder in monoeexponentieller, je nach dem Verhältnis der Konstanten (β/α) bei der hybriden Veranlagung, oder in biexponentieller Form, verlangsamte sich dann die Elimination von Pancuronium, und die Rückkehr erfolgte ohne Komplikation. In allen Fällen wurde ein offenes Modell mit zwei Abteilungen verwendet, um den Zeitablauf der Plasmakonzentrationen zu beschreiben.