EFFECT OF DIAZEPAM ON PANCURONIUM-INDUCED NEUROMUSCULAR BLOCKADE MAINTAINED BY A FEEDBACK SYSTEM

A. J. ASBURY, P. D. HENDERSON, B. H. BROWN, D. J. TURNER AND D. A. LINKENS

SUMMARY

The possibility of an interaction between diazepam and pancuronium bromide was investigated in six patients undergoing general anaesthesia maintained with fentanyl, droperidol and nitrous oxide. Neuromuscular blockade was controlled using a feedback mechanism which automatically adjusted the rate of injection of pancuronium to maintain between 71.4 and 72.9% blockade. Diazepam 0.14 mg kg\(^{-1}\) i.v. produced blood concentrations within the therapeutic range, but did not produce consistent changes in the level of blockade, pancuronium concentration in the blood or pancuronium consumption measured over 20 min.

The possibility of interaction between diazepam and neuromuscular blockers was first suggested by Stovner and Endresen (1965) in a letter describing the advantages of diazepam as an induction agent for anaesthesia in man. They found that it did not potentiate the effects of tubocurarine or diallylnortoxiferine and similar conclusions were drawn by Dretchen, Ghonheim and Long (1971) from studies of tubocurarine, gallamine and deca- methonium. The improvement of in vivo methods for measuring neuromuscular blockade, such as the train-of-four technique, led Bradshaw and Maddison (1979) to study diazepam 0.16 mg kg\(^{-1}\) with suxamethonium, tubocurarine, pancuronium, fazadinium and alcuronium. They concluded that there was no interaction.

The main evidence for an interaction between diazepam and a neuromuscular blocker comes from the work of Feldman and Crawley (1970) who found that diazepam increased the duration of action of gallamine, and decreased that of suxamethonium.

In studies of patients, drugs used as part of the anaesthetic technique may influence the neuromuscular junction and possibly obscure small changes produced by the test drug. Halothane and morphine, for example, have been found to possess neuromuscular blocking properties and have been used in some of the previous studies (Katz, 1971; Duke et al., 1979; Hughes and Payne, 1979). Other factors which may obscure an interaction include failure to maintain a stable acid–base state during the study and to achieve adequate blood concentrations of diazepam (Miller and Roderick, 1978). The patient's disease may cause changes in the distribution and elimination of drugs and it is important to confirm that following an appropriate dose i.v., a therapeutic concentration of diazepam is achieved.

This study was undertaken to examine the possibility of interaction between diazepam and pancuronium by providing a controlled pharmacological environment of steady neuromuscular blockade maintained by feedback control.

METHOD

Patients

Six healthy patients presenting for routine general surgery were studied. Patients with known neuromuscular disease or receiving drugs known to influence neuromuscular function were excluded. Results of biochemical investigations were normal. All patients gave informed consent. The patients received no premedication apart from aluminium hydroxide (Aludrox) 30 ml given orally 1 h before anaesthesia.

Anaesthetic technique

Anaesthesia was induced using methohexitone 1.0 mg kg\(^{-1}\) and endotracheal intubation facilitated with suxamethonium 1.0 mg kg\(^{-1}\). Nitrous

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oxide was used to maintain anaesthesia and doses of fentanyl 5.0 \mu g \cdot kg^{-1} and droperidol 0.14 \mu g \cdot kg^{-1} were injected over 1 min both to facilitate automatic ventilation and to obtain baseline electromyogram (e.m.g.) measurements. Ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 4.0% measured with a "Datex" carbon dioxide analyser. Cannulae were inserted to both arms for i.v. infusions and blood sampling. Further doses of fentanyl and droperidol were given during the anaesthetic according to the requirements of the patient. E.c.g. was monitored throughout the operation, and arterial pressure was measured using an oscillogonometry. If infusion of stored blood was necessary during the study period, the experiment was abandoned, as the addition of more binding sites from blood protein may have altered the feedback control system.

**Feedback control system**

The method of controlling neuromuscular blockade by a feedback system has already been described (Asbury, Brown and Linkens, 1980; Brown et al., 1980). The method involves supramaximal stimulation (0.1 Hz) of the ulnar nerve at the elbow and recording the resultant e.m.g. developed in the muscles of the hand. The e.m.g. is then rectified and integrated to give a voltage (RIe.m.g.) and compared with a reference voltage set to represent 80% blockade. The voltage difference is used to drive a small peristaltic pump which delivers pancuronium (1 mg in 20 ml) to the patient. The pancuronium is diluted with saline in a sterile infusion burette (Travenol) and the change in volume per unit time gives an indication of the consumption. The RIe.m.g., which is the indicator of the level of blockade, is recorded using a pen recorder and by hand from readings on a digital voltmeter.

In each case, as the levels of blockade were steady before and after diazepam administration, the mean and standard deviations were calculated from measurements of the RIe.m.g. trace sampled at 5-min intervals.

**Diazepam administration**

When a stable neuromuscular blockade had been achieved, the consumption of pancuronium over 20 min was calculated from the changes in burette readings. Venous blood samples were drawn without a tourniquet at 5-min intervals from a cannula for estimation of pancuronium concentration.

After 20 min of stable blockade, diazepam 0.14 \mu g \cdot kg^{-1} was injected to a peripheral vein over 1 min and flushed in with 10 ml isotonic saline. Recordings were continued as before, and further blood samples were drawn at 5-min intervals for pancuronium and diazepam estimations.

**Estimations of pancuronium and diazepam concentrations**

Pancuronium concentrations were measured to a sensitivity of 0.02 \mu g \cdot ml^{-1} using the fluorimeter technique developed by Kersten, Meijer and Agoston (1973).

Diazepam concentrations were measured to a sensitivity of 3 ng \cdot ml^{-1} using a gas chromatographic technique with electron capture detection described by Greenblatt (1978).

**Statistical analysis**

Student's t test was used to estimate the significance of differences in levels of neuromuscular blockade and blood concentrations with each patient acting as his own control. The nature of the experiment precluded randomizing the order of the test periods.

The consumptions can be treated as a series of pairs and the paired t test was used to calculate the level of significance.

**RESULTS**

The patients as a group (table I) were younger and lighter than is usual for general surgical patients.

Before diazepam was given (table II), the levels of blockade expressed as a percentage of the baseline readings in the unblocked state, ranged from 71.4 to 72.9%. The offset, the difference between the desired level of blockade (80% of baseline) and that actually obtained, was up to 8.6% and is compatible with that observed in previous studies. The standard deviations of the levels of blockade are small, suggesting that the feedback system maintained a steady state. The worst coefficient of variation was 3.3%.

After administration of diazepam (table II), the system was still under feedback control as mean levels of blockade similar to those before the diazepam were achieved; the worst coefficient of variation was 3.6%. In one case, there was a significant difference between the mean level of blockade before and after the diazepam.
TABLE I. Details of operations and patients

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Age (yr)</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>43</td>
<td>Right hemicolectomy</td>
</tr>
<tr>
<td>56</td>
<td>16</td>
<td>Highly selective vagotomy</td>
</tr>
<tr>
<td>76</td>
<td>63</td>
<td>Cholecystectomy</td>
</tr>
<tr>
<td>56</td>
<td>66</td>
<td>Roux-en-Y</td>
</tr>
<tr>
<td>71</td>
<td>20</td>
<td>Highly selective vagotomy</td>
</tr>
<tr>
<td>47</td>
<td>27</td>
<td>Pan procto-colectomy</td>
</tr>
</tbody>
</table>

Mean 62.0 39.2

TABLE IV. Changes in pancuronium consumption before and after diazepam 0.14 mg kg\(^{-1}\). The differences are not significant

<table>
<thead>
<tr>
<th>Pancuronium consumption ((\mu g kg^{-1} min^{-1}))</th>
<th>Before diazepam</th>
<th>After diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.53</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean</td>
<td>0.53</td>
<td>0.53</td>
</tr>
<tr>
<td>Mean</td>
<td>0.50</td>
<td>0.30</td>
</tr>
<tr>
<td>Mean</td>
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<td>0.36</td>
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<tr>
<td>Mean</td>
<td>0.49</td>
<td>0.70</td>
</tr>
<tr>
<td>Mean</td>
<td>0.48</td>
<td>0.43</td>
</tr>
</tbody>
</table>

The mean blood concentrations of pancuronium (table III) before and after the diazepam were in the same therapeutic range and in three patients there was a significant change in the mean blood concentration, one patient showing a decrease.

The changes in pancuronium consumption before and after the diazepam were not significant (table IV).

Diazepam concentrations following the 0.14 mg kg\(^{-1}\) dose (table V) showed the expected exponential decay, with concentrations in the therapeutic range (Greenblatt, 1978).

**DISCUSSION**

One of the reasons for embarking upon this study was that, with the aid of feedback control of neuromuscular blockade, it is now possible to maintain a stable pharmacological environment which gives the best chance of detecting interactions between pancuronium and diazepam. This approach necessarily places considerable reliance on the accuracy of the feedback control and emphasizes the basic assumption implicit in this study that, once under stable feedback control, the level of blockade and the consumption of pancuronium will remain steady, unless disturbed—for example by diazepam. The assumption that blockade and consumption remain stable has already been tested in patients by the authors and found to be true for periods up to 2 h.

If diazepam transiently potentiated the effect of pancuronium, rapid increase in blockade would occur followed by a gradual reduction to the original level of blockade. If the effect of the diazepam was prolonged, for example for 20 min, then a long-term change in offset would occur. Corresponding changes would also occur in the
consumption and in blood concentrations of pancuronium.

There was a significant change in the mean level of blockade only once, and this was a decrease in blockade instead of the expected increase.

The changes in blood concentration of pancuronium showed no consistent pattern. Although significant (P<0.01) changes occurred in two patients, the concentration increased when a decrease would have been expected. The changes in pancuronium consumption were equally unimpressive.

Thus there is no consistent evidence that diazepam interacts with pancuronium within the limitations of the experiment. This finding is in agreement with the conclusions of Bradshaw and Maddison (1979).

A negative result is always more difficult to prove than a positive one and therefore it is important to be aware of the limitations of this study. One is that the control might not have been stable enough and a fleeting effect of diazepam could be lost within the oscillations produced by the control system. This is unlikely, however, as the standard deviations of the levels of blockade are all small, suggesting close control.

Another possibility is that the concentrations of diazepam were insufficient to show the interaction effect. However, concentrations of diazepam achieved during this experiment compare favourably with those in other studies (Greenblatt, 1978) and are similar to those found clinically. We suggest that if these blood concentrations do not cause an interaction and a true interaction really exists, then it is probably unimportant in clinical anaesthesia and can usually be ignored.

ACKNOWLEDGEMENTS

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REFERENCES


DIE WIRKUNG VON DIAZEPAM AUF EINE DURCH PANCURONIUM EINGELEITETE NEUROMUSKULÄRE BLOCKIERUNG, AUFRECHTERHALTEN DURCH EINE FEED-BACK-ANLAGE

ZUSAMMENFASSUNG

Die Möglichkeit einer Wechselwirkung zwischen Diazepam und Pancuroniumbromid wurde an 6 Patienten untersucht, die einer allgemeinen Narkose mit Fentanyl, Droperidol und Stickoxyd unterzogen wurden. Die neuromuskuläre Blockierung wurde mittels eines Feed-back-Mechanismus kontrolliert, der die Zuführungsrate von Pancuronium automatisch so regelte, dass eine Blockierung zwischen 71,4 und

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EFFET DU DIAZEPAM SUR LE BLOCAGE NEUROMUSCULAIRE PROVOQUE PAR LE PANCURONIUM ET ENTRETIEN PAR UN SYSTEME DE RETROACTION

RESUME

Nous avons fait des recherches sur la possibilité qui existe d'une interaction entre le diazépam et le bromure de pancuronium sur six patients soumis à une anesthésie générale, entretien à l'aide de fentanyl, de droperidol et de protoxyde d'azote. Le blocage neuromusculaire a été contrôlé à l'aide d'un mécanisme de rétroaction qui ajuste automatiquement le taux d'injection du pancuronium afin de maintenir le blocage entre 71,4% et 72,9%. Le diazépam administré par voie intraveineuse à raison de 0,14 mg·kg⁻¹ a produit des concentrations dans le sang se situant dans la plage thérapeutique, mais il n'a produit aucune variation constante dans le niveau du blocage; les concentrations de pancuronium dans le sang ou la consommation de pancuronium ont été mesurées pendant 20 min.

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72,9% aufrechterhalten wurde. Diazepam 0,14 mg kg⁻¹, intravenös gegeben, bewirkte Blutkonzentrationen innerhalb des therapeutischen Bereiches, aber keine konsistenten Veränderungen der Blockierungsstärke, der Blutkonzentration von Pancuronium oder des Pancuronium-Verbrauchs gemessen innerhalb von 20 Minuten.

**EFFECTO DEL DIAZEPAM EN EL BLOQUEO NEUROMUSCULAR INDUCIDO POR PANCURONIO Y MANTENIDO POR UN SISTEMA DE RETROALIMENTACION**

SUMARIO
Se investigo en seis pacientes sometidos a anestesia general mantenida con fentanil, droperidol y óxido nitroso, la posibilidad de una interacción entre el diazepam y el bromuro de pancuronio. El bloqueo neuromuscular se controló usando un mecanismo de retroalimentación que ajustaba automáticamente el régimen de inyección del pancuronio para mantener un bloqueo de entre 71,4% y 72,9%. Diazepam 0,14 mg kg⁻¹ intravenoso produjeron concentraciones sanguíneas comprendidas dentro de la gama terapéutica, pero no produjeron concentraciones de pancuronio en la sangre ni una reducción de éste a lo largo de los 20 minutos de medición.