A METHOD FOR PRODUCING CONSTANT PLASMA CONCENTRATIONS OF DRUGS

Application to Methohexitone

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In 1968, Kruger-Theimer described the ideal i.v. drug input required to produce rapidly, and maintain, constant plasma concentrations of a drug: namely, the use of a single loading dose in combination with an infusion the rate of which declines exponentially towards that required to maintain the desired plasma concentration. This concept was further studied and developed by Vaughan and Tucker (1976). An exponentially decreasing infusion concentration can be produced by the mixing of two solutions of different concentration, but application of this theoretical knowledge has been hampered by the lack of a simple device which would produce this infusion with sterile solutions.

Recently, Riddell and colleagues (1984) described a method which seemed to overcome this problem. This consisted of a regimen in which a dilute solution of a drug was infused through a fine-bore needle, at a constant rate, to a sealed rigid mixing chamber containing a more concentrated solution of the drug. Infusion through the fine-bore needle created sufficient turbulence to ensure adequate mixing and the resultant exponentially decreasing mixture was displaced through a second needle. We report here the application of these principles in i.v. anaesthesia, using a methohexitone infusion in combination with 67% nitrous oxide in oxygen.

SUMMARY

A delivery system in which a dilute infusion of methohexitone is continuously added to a smaller volume of more concentrated solution has been used to infuse exponentially decreasing drug concentrations at a constant rate of infusion. The constants for calculation of concentrations and infusion rate are described. It was possible to achieve and maintain the target plasma concentration required to produce anaesthesia in conjunction with nitrous oxide in oxygen. Methohexitone is the only available drug suitable for this technique, but it requires frequent opioid supplementation and is not the ideal drug for such a technique.

PATIENTS, MATERIALS AND METHODS

Preliminary studies

An initial study was carried out in patients presenting for body surface operations. Following an induction dose of 1.6 mg kg⁻¹, methohexitone was administered intermittently in association with nitrous oxide in oxygen. The findings in 50 unpremedicated patients showed a skew distribution (fig. 1) similar to that found by Wright and colleagues (1984) for propofol. On the basis of figure 1, the median dose requirement was determined as 154 μg kg⁻¹ min⁻¹. Fractions of this dose (supplemented when necessary) were infused to 40 patients (four groups of 10 patients per group) and the following results obtained. When given alone, methohexitone 77 μg kg⁻¹ min⁻¹ was totally inadequate, 115 μg kg⁻¹ min⁻¹ was effec-
tive in 40% of patients, 154 μg kg⁻¹ min⁻¹ was effective in 90%, and 192.5 μg kg⁻¹ min⁻¹ was required to produce anaesthesia in 100%.

Later, pharmacokinetic studies were carried out following an initial dose of 1.6 mg kg⁻¹ followed by an infusion of 192.5 μg kg⁻¹ min⁻¹ which was continued for 90 min. Plasma samples were taken at frequent intervals and the methohexitone concentration determined using a modification of the high pressure liquid chromatographic technique developed for estimation of thiopentone (Toner et al., 1979) with methitural as internal standard. The coefficient of variation was less than 5% over the range of plasma concentrations studied. Pharmacokinetic parameters relating to the plasma concentrations (including post-infusion data) were derived using a non-linear curve fitting programme (NONLIN) (Meltzer, Eyring and McEwan, 1974). A weighting factor inversely proportional to the plasma concentration was taken into account. Results (table I) were similar to those of Breimer (1976), except that we found a lower initial volume of distribution (Dundee and McMurray, 1984; McMurray et al., 1984).

During the above studies, plasma samples were drawn at intervals in 28 unpremedicated patients to establish the effective concentration of methohexitone required for satisfactory anaesthesia. This averaged 10 μg ml⁻¹.

Materials

The apparatus consists of a 250-ml bottle containing dilute methohexitone, connected by means of a vented i.v. giving set, a peristaltic pump and a 27-swg needle, to a 50-ml multi-dose

![Graph showing distribution of total methohexitone dosage in 50 unpremedicated patients who received incremental dosage following an initial dose of 1.6 mg kg⁻¹.](image)

**Fig. 1.** Distribution of total methohexitone dosage in 50 unpremedicated patients who received incremental dosage following an initial dose of 1.6 mg kg⁻¹.

<table>
<thead>
<tr>
<th>( V^\alpha ) (litre kg⁻¹)</th>
<th>( k_{10} ) (min⁻¹)</th>
<th>( k_{10} ) (min⁻¹)</th>
<th>( k_{a1} ) (min⁻¹)</th>
<th>( T_{1}^{\beta} ) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td>0.23</td>
<td>0.0415</td>
<td>0.061</td>
<td>0.02</td>
</tr>
<tr>
<td>Breimer (1976)</td>
<td>0.29</td>
<td>0.0425</td>
<td>0.056</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Table I. Mean values of pharmacokinetic data for methohexitone*
vial of more concentrated methohexitone. This chamber is connected to the patient via a 21-swg needle and two extension sets with a total capacity of 4 ml (fig. 2).

The equations used to predict the concentrations in the two chambers, the loading dose and infusion rate were as follows:

\[ r = k_{21} \cdot V_{30} \]  
\[ M_{lt} = V \cdot C_{lt} \]  
\[ M_{40} = M_{lt} \cdot \frac{k_{10} \cdot V_{40}}{k_{31} \cdot V_{30}} \]  
\[ M_{30} = M_{lt} \cdot \frac{k_{12} + k_{10}}{k_{31}} \]  

The infusion rate \( r \) equals the product of \( k_{21} \) for methohexitone and the volume of the "concentrated" chamber \( V_{30} \). The loading dose \( M_{lt} \) equals the product of the initial volume of distribution for methohexitone \( V_{30} \) and the target concentration \( C_{lt} \). Equations (3) and (4) relate the masses of drug in the dilute chamber \( M_{40} \) and concentrated chamber \( M_{30} \) to the volumes of these chambers and other pharmacokinetic constants for methohexitone. A detailed analysis of the derivation of these formulae has been reported by Riddell and colleagues (1984).

The initial volume of distribution plays an important role in determining the loading dose and concentrations in the two chambers. It will be seen from table I that our findings and those of Breimer (1976) differ in this respect. Plasma concentrations using these two sets of constants have been reported by Dundee and McMurray (1984), who found that the target concentration was more easily achieved by using the mean \( V_{30} \) of the two studies (0.26).

The calculated concentrations for a 70-kg subject were: dilute chamber—1910 mg in 250 ml (0.76%); concentrated chamber—910 mg in 50 ml (1.82%).

The concentration of drug in the dilute chamber was obtained by preparing a 1% solution in 250 ml from which 59 ml was removed and replaced by an equal volume of water. The concentrated chamber was prepared by withdrawing 4.5 ml from 50 ml of 2% solution and replacing with 4.5 ml of water. The tubing between the concentrated and the dilute bottles was primed from the latter. As methohexitone produces dose-related excitatory effects (Barron and Dundee, 1967), the loading dose of 180 mg was divided by priming the giving set from the concentrated bottle to the patient with 4 ml of 2% solution and the remainder was administered as a bolus over 20 s into a freely-running infusion. The infusion rate was 60 ml h\(^{-1}\) (the product of \( k_{21} \) and \( V_{30} \)) and, therefore, the total loading dose was given over 4 min.

Patients

Only fit subjects who had agreed to repeated blood sampling were included in the study. Each was scheduled for elective body surface surgery. The concentrations in the two chambers and the loading dose were calculated for the ideal 70-kg patient and administered to each subject regardless...
of weight. If, on clinical grounds, using the criteria of Savaege and co-workers (1975), anaesthesia appeared to be inadequate, increments of fentanyl 25 μg were given.

Arterial pressure and heart rate were measured at frequent intervals throughout each procedure. The depth of respiration, as shown by movements of the chest wall or reservoir bag, was assessed carefully and respiration assisted or controlled if, on clinical grounds, there was any suspicion of respiratory depression. As it would not have been justified, on ethical grounds, to have an indwelling arterial catheter in these patients, measurements of arterial blood-gas tensions were not obtained routinely, but samples were taken in some patients when required. A capnograph was available for a few of the studies, but this necessitated tracheal intubation under local anaesthesia (aided by a small dose of suxamethonium).

All patients were visited on several occasions on the 2nd–3rd days after operation, when evidence of recall of intraoperative procedures was sought.

RESULTS

Figure 3 gives the actual concentrations delivered by the apparatus over 2 h. In this it is compared with a “simplified” method in which 1% and 2% solutions were “infused” at a rate of 50 ml h⁻¹. This latter delivered too high a concentration and it was not used clinically.

The scatter of plasma concentrations achieved over 60 min in 12 patients is shown in figure 4. These mostly fell within the desired range, except for some early low values and three which exceeded 13 μg ml⁻¹ (two patients).

A clinical impression was formed that, in some patients, anaesthesia tended to become “deeper” than desired. This presented as respiratory depression which could not be attributable to fentanyl. It rapidly responded to stopping the infusion temporarily. It was always possible to stop the infusion at 60 min, even if the operation continued for a further 15 min. On occasions, recovery was more delayed than expected. In one such patient T₁/₂ during recovery was 7–8 h.

No patient had any recall of events during operation.

Arterial pressure was well maintained in all patients and, apart from tachycardia, vital signs remained stable. Respiratory depression was not a problem, except as mentioned above. The “quality” of anaesthesia with methohexitone was often unsatisfactory, particularly at the beginning when excitatory effects and hiccup were a problem. The former always responded to a small dose of fentanyl, which however did not always stop the hiccup. More than one-half the patients required fentanyl in total dose of up to 200 μg.

DISCUSSION

This was primarily a study in which we applied a pharmacokinetic principle to clinical practice. Our aim was to see if, in day-to-day operating theatre conditions, we could achieve the desired plasma concentration of methohexitone. Our choice of this drug as our infusate was based on the ability of our laboratory to carry out a large number of accurate plasma analyses of this drug. Our first studies in this field (Wright et al., 1984) were with the initial clinical preparation of propofol which was solubilized in Cremophor and which was withdrawn because of hypersensitivity reactions (Briggs, Clarke and Watkins, 1982). Although Althesin would have produced better
anaesthesia, we were fortunate in not selecting it as it was withdrawn during the period of the study. Etomidate causes a high incidence of excitatory effects in the absence of concomitant opioid medication and doubt has been cast on its safety after prolonged use (Ledingham and Watt, 1983; Sear et al., 1983). In view of recent pharmacokinetic studies, it was expected that thiopentone would not have been suitable for our purpose (Hudson, Stanski and Burch, 1983), having a much longer elimination half-life than methohexitone.

Methohexitone induces a high incidence of extraneous muscle movement and hiccup, particularly after the rapid administration of large doses, and for this reason the induction dose was given in divided doses. However, despite this, induction was often "bumpy", and while this usually responded to fentanyl, in routine clinical practice it would be more satisfactory to use opioid premedication or "pretreat" the patients with fentanyl. It was satisfactory in that, being a rapidly acting drug, there was a quick response to alterations in the infusion rate. At this stage in the development of a new technique the use of a more slowly acting drug such as ketamine or midazolam would have been unwise.

Total i.v. anaesthesia necessitates the achievement and maintenance of drug concentrations sufficient to produce the desired response, but below those associated with undesirable side effects. Such may be obtained by the use of a single constant rate infusion, but it will take three to four times the elimination half-life before a constant minimal effective plasma concentration is achieved and, even with the shorter-acting agents, this will take a number of hours. Increasing the rate of delivery or the concentration of the infusion will increase the plasma concentration, but not the time taken to achieve a "steady-state" (Greenblatt and Koch-Weser, 1975). The use of a small loading dose followed by a single constant-rate infusion overcomes this problem to some extent. However, the plasma concentrations may decrease temporarily below therapeutic values and lead to a temporary lightening of narcosis. Increasing the size of the loading dose to avoid the decrease in plasma concentration increases the likelihood of early toxicity, while increasing the rate of infusion increases the likelihood of the side effects mentioned above.

These problems may be overcome by the use of multiple small bolus injections along with a constant-rate infusion, or by using, initially, a rapid constant-rate infusion and then decreasing this to a slower maintenance rate (Wagner, 1974). While these methods produce a more constant plasma concentration–time profile than infusion alone, they require interventions at strictly defined times after initiating therapy. Failure to carry these out at the appropriate times can lead to suboptimal conditions.

Our study shows that it is possible to achieve a
constant plasma concentration of a drug using this simple method of delivery of an exponentially decreasing concentration of anaesthetic. If, with our dosage, patients are given a neuromuscular blocking drug and subjected to artificial ventilation, one would have no fear of recall during operation. However, with spontaneous breathing, methohexitone is not the drug of choice for this technique.

The logical extension of this study is the use of opioid premedication or the concomitant use of infusions of short acting opioids. Alfentanil would appear to be suitable for this purpose (Bowen and Hull, 1982; Ausems and Hug, 1983) and worthy of study in this field. This could also eliminate the need for nitrous oxide and it would improve the quality of anaesthesia with methohexitone.

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REFERENCES