TOTAL I.V. ANAESTHESIA WITH PROPOFOL-ALFENTANIL OR PROPOFOL-FENTANYL

M. JENSTRUP, J. NIELSEN, K. FRUERGÅRD, A.-M. MØLLER AND F. WIBERG-JØRGENSEN

SUMMARY

In combination with propofol, alfentanil was compared with fentanyl for total i.v. anaesthesia in 29 women (ASA classes I, II) admitted for elective hysterectomy. Infusion rates of propofol and fentanyl were determined from the literature and from pilot studies, while alfentanil was given according to a computer program. Dosage was: propofol, bolus 1.5 mg kg\(^{-1}\), infusion 9 mg kg\(^{-1}\) h\(^{-1}\) for 10 min and thereafter 6 mg kg\(^{-1}\) h\(^{-1}\); fentanyl, bolus 7.5 \(\mu\)g kg\(^{-1}\), infusion 15 \(\mu\)g kg\(^{-1}\) h\(^{-1}\) reduced successively to 1.8 \(\mu\)g kg\(^{-1}\) h\(^{-1}\); alfentanil, bolus 60 \(\mu\)g kg\(^{-1}\), infusion 240 \(\mu\)g kg\(^{-1}\) h\(^{-1}\) reduced successively to 100 \(\mu\)g min\(^{-1}\). Induction was smooth and maintenance easy to manage in both groups. Plasma concentrations were stable with a ratio of alfentanil to fentanyl of 100:1. Recovery times were equal and short, but recovery tests performed 3 h after operation showed that alfentanil produced a greater effect on ability to concentrate and fine co-ordination.

KEY WORDS


Total i.v. anaesthesia (TIVA) has gained some popularity, partly in order to reduce pollution by volatile agents. Until recently the i.v. hypnotics have been unsuitable for infusion because their pharmacokinetic profiles make maintenance of anaesthesia difficult to control without nitrous oxide. However, propofol (Diprivan) has proven to be suitable as a hypnotic for TIVA. The drug has a fast onset of action and rapid metabolism without accumulation \[1,2\]. Propofol has no analgesic effect and is administered, therefore, in combination with a potent analgesic.

Both fentanyl (Haldid) and alfentanil (Rapifen) have been used in combination with propofol \[3-5\] for TIVA. The aim of this study was to evaluate which analgesic is preferable.

PATIENTS AND METHODS

Thirty women (ASA I, II) admitted for elective hysterectomy, were allocated randomly to two groups to receive TIVA with propofol and either alfentanil or fentanyl.

Patients were excluded if they had a history of hepatic, renal, cardiac, neurological, psychiatric, respiratory or metabolic disease, a body weight exceeding 20% of ideal \[6\], or a history of allergy or previous adverse response to general anaesthesia. All patients gave informed consent before participating in the study, which was approved by the local Ethics Committee.

Anaesthetic technique

The patients were premedicated with diazepam 0.2 mg kg\(^{-1}\) orally 2 h before surgery.

Drug doses were determined according to lean body weight as given by the metropolitan tables, estimating the ideal weight for height in proportion to build \[6\]. This was an attempt to assess the dose of anaesthetics according to volume of distribution.

The infusion profile of alfentanil was found using the computer program of Maitre and colleagues \[7\], which allows prediction of the alfentanil plasma concentration from input of a

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series of doses. The program acts as a computerized patient model. Applying the program, we calculated a dose scheme designed to produce a plasma concentration of alfentanil 300 ng ml\(^{-1}\) during maintenance. Pilot studies showed this gave a satisfactory anaesthetic.

The infusion profile of propofol was determined from the literature [3, 4, 8] and our pilot studies, as was that of fentanyl [9]. In the first group the patients had a bolus of fentanyl 7.5 µg kg\(^{-1}\) and propofol 1.5 mg kg\(^{-1}\). The initial infusion rates were propofol 9 mg kg\(^{-1}\) h\(^{-1}\) and fentanyl 15 µg kg\(^{-1}\) h\(^{-1}\). After 10 min the doses were reduced: for propofol to 6 mg kg\(^{-1}\) h\(^{-1}\) until last skin suture, and for fentanyl to 6 µg kg\(^{-1}\) h\(^{-1}\) for the first 1 h, then to 3 µg kg\(^{-1}\) h\(^{-1}\), and after 90 min to 1.8 µg kg\(^{-1}\) h\(^{-1}\). The infusion of fentanyl was stopped when the peritoneum was closed.

In group 2, propofol was given in the same dose as in group 1. Alfentanil was given as a bolus of 60 µg kg\(^{-1}\), followed by an initial rate of infusion of 240 µg kg\(^{-1}\) h\(^{-1}\). After 10 min, the rate was reduced to 180 µg kg\(^{-1}\) h\(^{-1}\) and successively after 30 min to 120 µg kg\(^{-1}\) h\(^{-1}\). After 1 h all patients received 100 µg min\(^{-1}\) until closure of the abdominal fascia.

Isotonic saline 15 ml kg\(^{-1}\) was given i.v. for the first 1 h, then 7.5 ml kg\(^{-1}\) to a total of 2000 ml and thereafter 3 ml kg\(^{-1}\) h\(^{-1}\). Loss of blood was replaced by saline 2.5 ml per ml blood lost. Depth of anaesthesia was gauged by clinical signs and by recording the peripheral pulse wave amplitude [10]. An increase in arterial pressure or heart rate of more than 15% above baseline, reduction in peripheral pulse wave amplitude by more than 50%, or both, were regarded as signs of light anaesthesia. If this persisted for more than 5 min, a bolus of analgesic was given: 50 µg of fentanyl or 0.5 mg of alfentanil, as appropriate. Pancuronium (Pavulon) 0.80 mg kg\(^{-1}\) was given to facilitate tracheal intubation and further boluses of 2.0 mg were given, depending on the degree of neuromuscular block as assessed by train-of-four (TOF) stimulation of the ulnar nerve (Myotest: Odense, Denmark). If involuntary movement occurred, the bolus of pancuronium was supplemented with propofol 0.5 mg kg\(^{-1}\). Residual neuromuscular block was antagonized with pyridostigmine (Mestinon) 10 mg with glycopyrrolate 0.4 mg. The peripheral pulse wave amplitude, TOF and peripheral temperature were measured in the arm opposite to the site of i.v. infusion. Ventilation was controlled using oxygen in air (\(F_{1O_2}\), approximately 0.4) and normoventilation was maintained as assessed by capnography (Normocap, Datex). The trachea was extubated when the patient was breathing spontaneously and able to open the eyes and raise the head on command.

ECG was monitored continuously. Drugs were given by infusion pump (Injectomat, Fresenius). Heart rate and arterial pressure were measured by automatic non-invasive monitor (Dinamap, Critikon) on arrival at the operating theatre, subsequently every 2 min for the first 10 min after induction, and at 5-min intervals thereafter. Measurements were obtained before and after skin incision, before insertion of a self-retaining retractor, during traction of the uterus, on removal of the self-retaining retractor and at the end of the operation.

A radial artery was cannulated and blood sampled 10, 30 and 60 min after the first bolus, at the end of infusion and when the patient opened the eyes. Blood was analysed for plasma concentrations of propofol, alfentanil and fentanyl. Plasma concentrations of fentanyl and alfentanil were estimated using the radioimmunoassays of Michiels, Hendriks and Heykants [11, 12]. Plasma concentrations of propofol were analysed using high pressure liquid chromatography with fluorescence detection [13].

Emergence time was defined as the interval from the end of infusion of propofol until tracheal extubation. Recovery time was defined as the interval from tracheal extubation until the patient could give her date of birth. For the following 3 h, morphine was given i.v. on demand in single doses of 5 mg. Analgesic requirements were noted and ventilation was assessed by arterial blood-gas analysis 30 and 60 min after operation. Side effects were recorded at induction, and during maintenance of anaesthesia and the first 3 h of recovery.

**Assessment of recovery**

After initial familiarization, patients performed a range of tests on the day before operation and again 3 h after operation. The difference between the two performances was used to assess quality of recovery. Vigilance and the ability to concentrate were assessed by the Bourdon–Wiersma test [14, 15]—a paper and pencil test in which the patient was shown a sheet of paper containing rows of o spaced randomly in groups of three, four and five. The patient was asked to draw a line through each group of four o and the test was scored by the number of lines completed correctly.
Immediate memory was assessed by asking the patient to repeat a span of digits up to nine [15, 16]; the number of sequentially correct remembered digits was recorded. To evaluate fine co-ordination and speed of function, we used the pegboard test [15, 17]. The patient was given a board with 48 holes, each containing a peg coloured black at one end, and asked to turn as many pegs as possible in 45 s. Co-ordination of visual and proprioceptive sensations was recorded using the post-box test [15, 18]. This comprised a box with 18 differently shaped holes and 18 appropriate bricks; the patient was to place as many bricks as possible into the box in 40 s.

Retrograde amnesia was assessed by showing a bank note immediately before induction. After anaesthesia, the patient was asked if she recalled having seen any object before induction. Ability to retain new facts (the degree of anterograde amnesia) was assessed by a picture card test [15, 19, 20]. As soon as the patient regained consciousness she was shown a card depicting nine every-day objects and was asked to memorize them. After 3 h the patient was shown a card depicting 15 objects and was asked which pictures she recognized as being of the original nine. The number of correctly identified pictures minus the incorrect ones was recorded.

Statistical analysis of data
Data were analysed using a one-sample rank sum test (Wilcoxon's one sample test) and a two-sample rank sum test (Mann-Whitney test). All values given are in medians and 1st and 3rd quartiles. When P < 0.05 the null hypothesis was rejected. Differences and changes are referred to in the text only when statistically significant.

RESULTS
The groups were comparable in age, weight and lean body weight and duration of anaesthesia and surgery (table I). One patient in the alfentanil group was excluded because of technical problems. Induction of anaesthesia was smooth for all patients and maintenance easy to manage.

Drug requirements and plasma concentrations
The total quantity of propofol given was equal in the two groups. Analgesic requirements for fentanyl were 9.6 (7.2-10.8) µg kg⁻¹ h⁻¹ and for alfentanil 153.6 (142.8-167.4) µg kg⁻¹ h⁻¹ (table II), a ratio of 1:16. An extra bolus of analgesic was given to six of 14 patients in the alfentanil group and eight of 15 in the fentanyl group.

The plasma concentration of alfentanil was stable from the first measurement (10 min) at approximately 350 ng ml⁻¹, while the plasma concentration of fentanyl was stable from the second measurement, 30 min after induction, at about 3.5 ng ml⁻¹. The plasma concentration of propofol was stable from the first measurement (10 min) and was equal in the two groups. Median values were in the range 2.5-3.0 µg ml⁻¹.

Haemodynamics
In both groups there was a significant reduction in systolic arterial pressure from control value until after induction, but before intubation (4 min). The decrease was 25 (14-40) mm Hg in the fentanyl group and 40 (24-54) mm Hg in the alfentanil group. Laryngoscopy and intubation (the period from 4 to 8 min after induction) caused no change in the alfentanil group and only a minor increase in diastolic pressure in the

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<th>Table I. Demographic data (median (1st and 3rd quartiles))</th>
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<td>Age (yr)</td>
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<td>Duration of anaesthesia (min)</td>
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<td>Duration of surgery (min)</td>
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<tr>
<th>Table II. Consumptions of propofol, fentanyl and alfentanil (medians (1st and 3rd quartiles))</th>
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<tr>
<td>Propofol (mg kg⁻¹ h⁻¹)</td>
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<td>Fentanyl (µg kg⁻¹ h⁻¹)</td>
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<td>Alfentanil (µg kg⁻¹ h⁻¹)</td>
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**TABLE III.** Emergence time (interval from end of infusion to time of voluntary headlift), recovery time (interval from extubation to time of giving correct date of birth), PaCO₂ 30 and 90 min after end of operation and requirement for postoperative analgesia (morphine) (median (1st and 3rd quartiles))

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<th>Fentanyl group</th>
<th>Alfentanil group</th>
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<tbody>
<tr>
<td>Emergence time (min)</td>
<td>10.0 (6.0–14.0)</td>
<td>11.5 (9.8–18.5)</td>
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<tr>
<td>Recovery time (min)</td>
<td>3.0 (1.0–4.0)</td>
<td>1.8 (0.5–4.0)</td>
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<td>PaCO₂ (kPa) 30 min</td>
<td>6.1 (5.7–6.7)</td>
<td>6.3 (6.1–6.8)</td>
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<tr>
<td>PaCO₂ (kPa) 90 min</td>
<td>5.7 (5.2–6.3)</td>
<td>5.7 (5.5–6.5)</td>
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<tr>
<td>Postop. morphine (mg)</td>
<td>13.3 (6.9–20.0)</td>
<td>16.0 (10.0–19.9)</td>
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**TABLE IV.** Decrement in performance of recovery tests after anaesthesia and result of picture card test (median (1st and 3rd quartiles))

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<th>Fentanyl group</th>
<th>Alfentanil group</th>
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<tr>
<td>Bourdon–Wiersma test (number of lines)</td>
<td>10.0 (5.5–17.3)</td>
<td>22.0 (15.8–30.3)</td>
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<tr>
<td>Post-box test (number of bricks)</td>
<td>2.8 (1.1–4.5)</td>
<td>5.0 (2.8–6.0)</td>
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<tr>
<td>Pegboard test (number of pegs)</td>
<td>13.0 (9.3–26.0)</td>
<td>34.5 (19.3–41.8)</td>
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<tr>
<td>Digit span test (number of digits)</td>
<td>0.2 (−0.3 to 1.3)</td>
<td>0.8 (−0.9 to 3.0)</td>
</tr>
<tr>
<td>Picture card test (number of pictures recognized)</td>
<td>3.5 (0.3–6.0)</td>
<td>0.2 (0.0–1.0)</td>
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There was no report of awareness or of pain at injection.

Mental abilities were greatly affected by anaesthesia. Ability to concentrate and co-ordinate as measured by the Bourdon–Wiersma test was reduced more in the alfentanil group (table IV).

Fine co-ordination and speed of function, as assessed by the pegboard test, were also depressed more in the alfentanil group.

Tests evaluating gross co-ordination and visual and proprioceptive sensation (post-box test), anterograde amnesia (picture card test) and retrograde amnesia (bank note test) were also affected, but there was no difference between groups (table IV).

**DISCUSSION**

During induction of anaesthesia, distribution kinetics affect potency ratio between drugs, but subsequently elimination kinetics exert an in-
creasing influence. Alfentanil and fentanyl have nearly the same distribution half-lives, while the terminal half-life of alfentanil is only 50% that of fentanyl [21, 22]. Therefore, the difference in ratio between alfentanil and fentanyl is least during induction and increases with time. In our study the ratio between alfentanil and fentanyl was 10:1 during induction (10 min) and 16:1 for the whole anaesthetic. We found a greater decrease in systolic pressure in the alfentanil group during induction, and an increase in diastolic pressure during laryngoscopy after fentanyl only. Both findings indicate a relative overdosage of alfentanil. During maintenance, the lack of haemodynamic difference between the two groups reflects equipotency.

Rucquoi and Camu [23] gave, in combination with etomidate, alfentanil and fentanyl in a ratio of 4:1 during both induction (the first 10 min) and maintenance of anaesthesia. They found no difference in MAP during induction, but an increase in both heart rate and MAP during maintenance in the alfentanil group. This suggests relative underdosage of alfentanil.

Scott, Ponganis and Stanski [24] measured the plasma concentrations of alfentanil and fentanyl before surgery that caused appearance of delta-waves on the EEG, and obtained a ratio of 75:1 (520 ng ml⁻¹ and 6.9 ng ml⁻¹, respectively); we found a ratio of 100:1. Any relative overdosage of alfentanil, however, was not reflected by a difference in cardiovascular response. Thus an equal number of patients in both groups were given an additional bolus of analgesics. Our median measured plasma concentration of alfentanil compares well with the findings of Ausems and Hug [25]. They found that an average alfentanil plasma concentration of 350 ng ml⁻¹ was needed, in combination with nitrous oxide only, to ablate the haemodynamic response in lower abdominal surgery.

Cockshott and colleagues [26] found that fentanyl caused the plasma concentration of propofol to increase by up to 50%. In contrast, Gepts and colleagues [27] found that propofol might increase the plasma concentration of alfentanil, but not vice versa. We found a greater concentration of alfentanil than that intended, and this may suggest an interaction between propofol and alfentanil.

In spite of the alleged shorter duration of action of alfentanil than fentanyl, our tests showed that the patients who had alfentanil were less able to concentrate and co-ordinate. Recovery after alfentanil and fentanyl has not been compared after TIVA of longer duration, but there are reports on mental ability after anaesthesia of short duration. Using the Trieger test, Fragen and colleagues [4] found that, 3 h after operation, patients were affected more after alfentanil, whereas Kay and Venkataraman [28] and Diephuis and colleagues [29] found in TIVA studies that patients recovered better after alfentanil.

Our findings are not explained by overdosage of alfentanil, as recovery and emergence times were the same in the two groups. Likewise, the need for postoperative analgesia and $P_{aCO_2}$ at 30 and 60 min after anaesthesia were equal. Variation in pharmacokinetics after recovery is possible; change in protein binding because of stress and disease lead to alterations in plasma concentrations and pharmacodynamic effects [30]. Alternatively, the difference may reflect a true side effect.

In conclusion, we found that both combinations of drugs were suitable for total i.v. anaesthesia, but the theoretical advantage possessed by alfentanil because of its pharmacokinetic profile was not confirmed.

REFERENCES


