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# Total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion

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**Summary**

*The combination of propofol and alfentanil was administered to 20 patients for total intravenous anaesthesia during general surgery. The infusion rates for both drugs were controlled by microprocessors in order to institute constant blood levels adapted to the patients' varying needs. The mean blood level of propofol required for adequate hypnosis during anaesthesia was 2.42 μg/ml (SD 0.43). Awakening occurred 7.9 minutes (SD 3.4) after the end of the infusion, at a propofol blood level of 1.59 μg/ml (SD 0.34). The plasma level of alfentanil was 285 ng/ml (SD 72) during major noxious stimulation and 148 ng/ml (SD 56) during minor stimulation. The computer-assisted infusions showed a measured/predicted ratio of 1.01 (SD 0.28) for alfentanil and 0.88 (SD 0.22) for propofol. This indicates that the administration device used in this study is reasonably reliable. The technique of total intravenous anaesthesia was characterised by a smooth induction without significant haemodynamic alterations, by good control during anaesthesia and by a very fast recovery without major side effects.*

**Key words**

*Anaesthetics, intravenous*; propofol.
*Equipment*; computer, infusion pumps.

The clinical acceptability of techniques for total intravenous anaesthesia is determined mainly by two factors. Firstly, the drugs for this purpose should guarantee, besides the lack of major side effects, a reasonable degree of control of their main pharmacodynamic effects, which will depend mainly upon their pharmacokinetic behaviour. Secondly, devices for the administration of intravenous anaesthetics have to be as easy to use as vaporizers for inhalational anaesthetics.

The pharmacokinetic properties of alfentanil[1,2] make it well suited to suppress the response to noxious stimuli adaptively during surgical interventions. Total intravenous anaesthesia with alfentanil combined with etomidate[5] proved to be feasible, but etomidate is not ideal for this purpose because of its adrenocortical depressant effects. Propofol in its emulsion formulation appears to be a good alternative, especially with regard to its rapid elimination.[6,7] The combined administration of propofol and alfentanil by a microprocessor controlled-infusion device, as easy to use as a vaporiser, was therefore investigated for total intravenous anaesthesia.

## Methods

Written informed consent after institutional approval was obtained from 20 patients of ASA grade 1 or 2, aged 18–52 years, weight 52–85 kg, who were scheduled for general surgery. They were premedicated with flunitrazepam 2 mg orally the evening before surgery and 1 mg orally one hour before anaesthesia. Anaesthesia was induced after the intravenous injection of vecuronium 2 mg, by a computer-controlled infusion of propofol which was aimed at a constant blood level of 2.5 μg/ml. The infusion of alfentanil was started 30 seconds later and aimed at a constant plasma level of 100 ng/ml; this was maintained for 5 minutes and re-introduced at the start of surgery. A large vein in the forearm was used to place the indwelling catheter used for infusion. Vecuronium 3 mg was given intravenously and tracheal intubation was performed 2 minutes later, after ventilation of the lungs with oxygen by face-mask. The lungs were then ventilated with oxygen in air ($FIO_2$ 0.5) to maintain a normal $PaCO_2$. The blood level of propofol was increased in steps of 0.25 μg/ml if signs of lightening of

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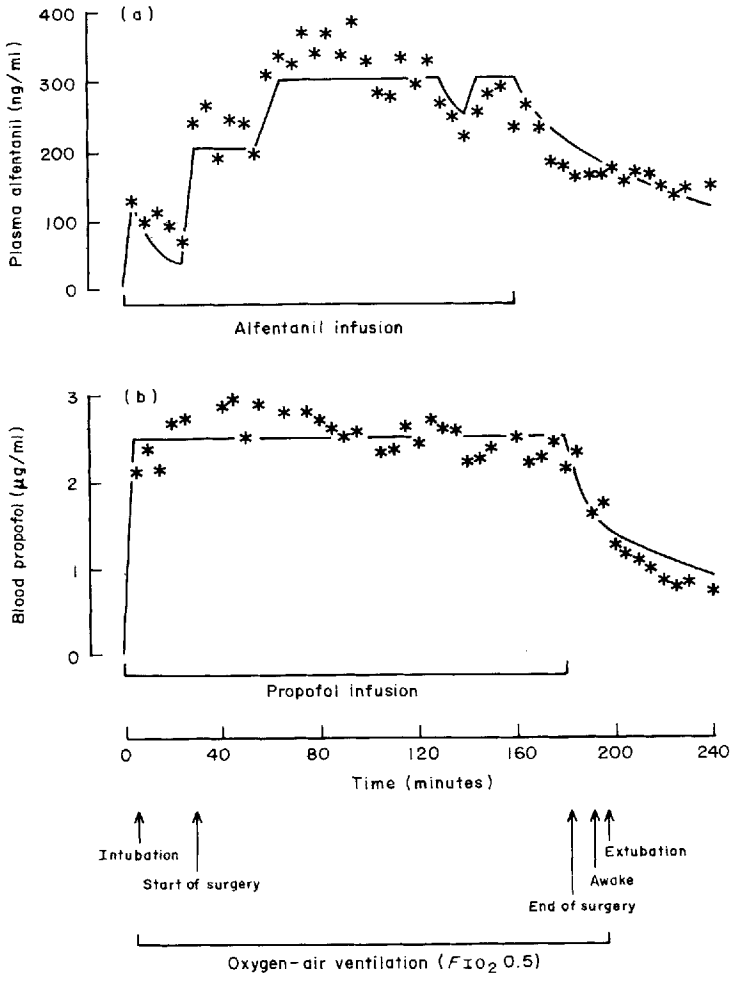


**Fig. 1.** (a) Plasma levels of alfentanil and (b) blood levels of propofol as predicted (——) by computer-assisted interactive infusions (solid line) and as actually measured (asterisks) in one representative patient who received the described anaesthetic technique.

anaesthesia occurred during the interval between induction and the start of surgery. The infusion of alfentanil was started again at the time of skin incision. Plasma alfentanil levels were adjusted according to the degree of noxious stimulation during the surgical procedures. In general, the administration of alfentanil was stopped 30 minutes before the end of operation. The infusion of propofol was kept stable until the last suture of skin closure. Recovery was assessed as the time from the end of the propofol infusion until the patient responded to verbal commands, and until extubation and proper orientation.

Blood levels of propofol were measured by high-performance liquid chromatography[7] and plasma levels of alfentanil by radio-immunoassay.[8] The measured concentrations were related to the predictions made by the computer-assisted administration device. Measured/predicted ratios (m/p ratios) were calculated and linear regression analysis was performed. Results are given as means (standard deviation). Statistical analysis was performed by Student's *t*-test.

The infusion schemes were based upon algorithms described previously.[9] The device differed from that in previous studies[5] because the anaesthetist had to operate only one dial to preset the blood level of choice, similar to a vaporizer for inhalational anaesthetics. The pharmacokinetic data incorporated into the system were taken from previous studies on alfentanil[1] and propofol.[10]

## Results

A representative example of plasma alfentanil and blood propofol levels during computer-assisted total intravenous anaesthesia is shown in Fig. 1. The blood level of propofol in this patient was kept constant at 2.5 μg/ml for the entire duration of anaesthesia. The plasma level of alfentanil was adapted in a stepwise manner at the start of surgery. The alfentanil infusion was terminated 20 minutes before the end of operation. There is good agreement between the predicted and measured concentrations of both drugs in this patient. Regression analysis for the predicted and measured values showed a highly significant correlation ($p < 0.001$) for both alfentanil (Fig. 2) and propofol (Fig. 3), although the variability of the propofol data was greater. There was a tendency to overpredict the propofol concentration which is indicated by an overall m/p ratio of 0.88 (SD 0.22) (Table 1). The m/p ratio for alfentanil, 1.01 (SD 0.28) (Table 1), in contrast, is nearly optimal.

The clinical results are summarised in Table 1. The mean duration of surgery was 104 minutes (SD 43). Propofol was

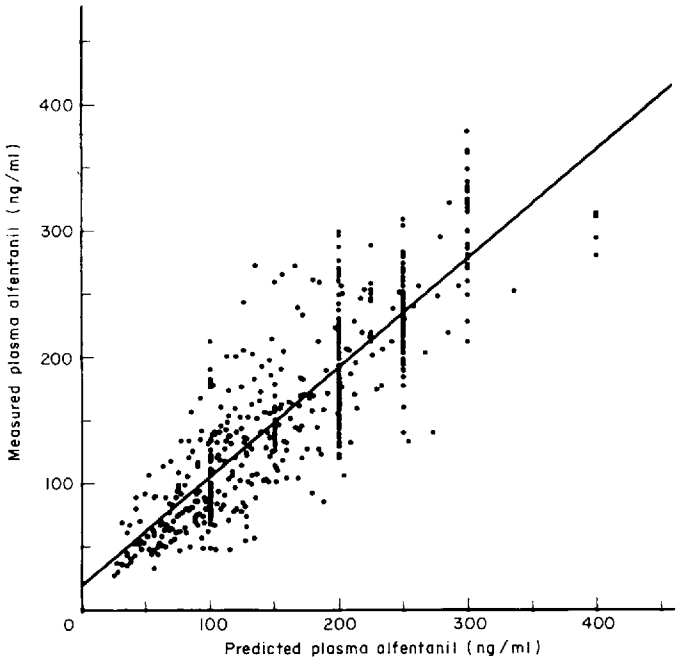


**Fig. 2.** Correlation between predicted plasma levels of alfentanil and measured concentrations during and after computer-assisted infusion. $n = 565$, $r = 0.87$, $m = 0.86$, $b = 19.3$.

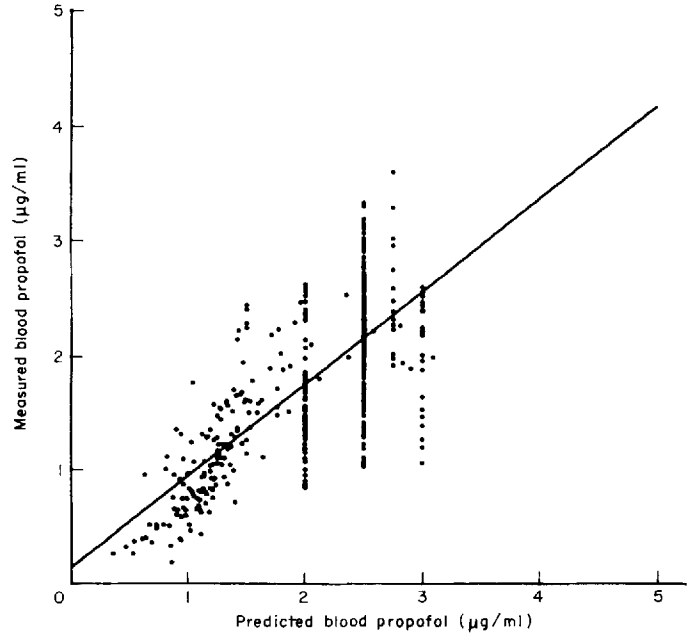


**Fig. 3.** Correlation between predicted blood levels of propofol and measured concentrations during and after computer assisted infusion. $n = 508$, $r = 0.75$, $m = 0.81$, $b = 0.13$.

infused for 131 minutes (SD 42) with a total dose of 838.7 mg (SD 193.8). The total dose for alfentanil was 13.8 mg (SD 5.3) with an infusion time of 112 minutes (SD 45). Induction of anaesthesia was smooth and without any side effects. Intubation could be performed in all subjects without difficulty. The haemodynamic response during this period (Fig. 4) did not exhibit significant alterations. It was possible to control the depth of anaesthesia satisfactorily during maintenance. Recovery was short; patients awoke 7.9 minutes (SD 3.4) after the end of the propofol infusion, and extubation could be performed after 11.9 minutes (SD 3.8). All patients were fully orientated and clear-headed by this time. Postoperative nausea occurred in only one case and no other side effects were observed.

## Discussion

The results of this investigation demonstrate that the practicability of total intravenous anaesthesia can be increased to

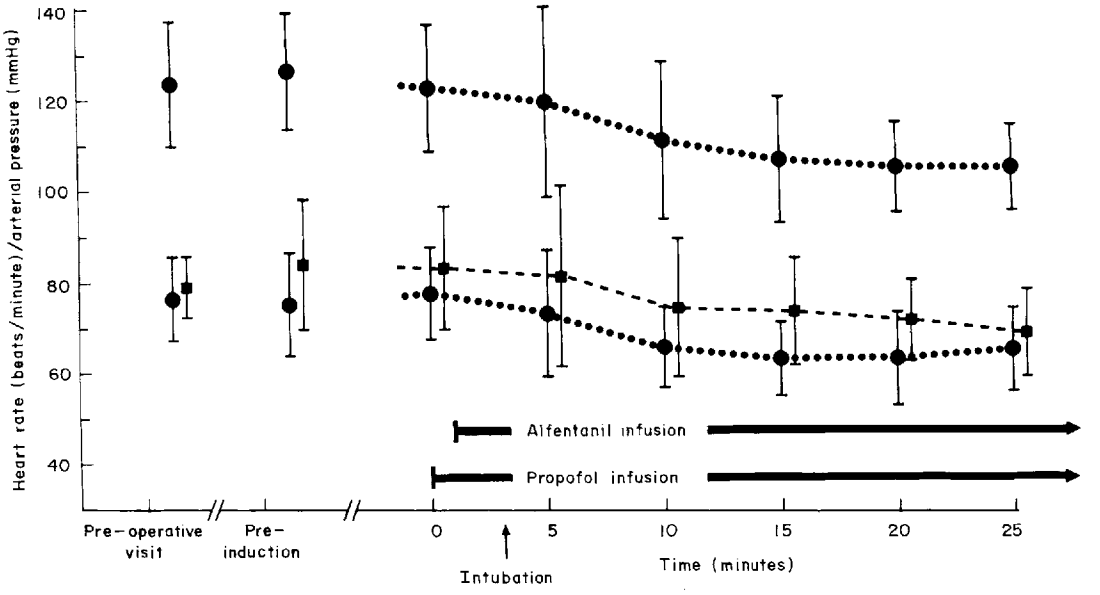


**Fig. 4.** Haemodynamic response during induction of anaesthesia in 20 patients with the described technique of total intravenous anaesthesia (mean, SD). ■, Heart rate; ●, arterial blood pressure (mmHg).

**Table 1.** Clinical data and drug concentrations in 20 patients undergoing total intravenous anaesthesia with propofol and alfentanil by computer-assisted infusion. Values expressed as mean (SD).

| | Propofol | Alfentanil |
|---|---|---|
| Duration of surgery, minutes | 104 (43) | |
| Duration of infusion, minutes | 131 (41.8) | 112 (44.5) |
| Total dose, mg | 838.7 (193.8) | 13.8 (5.3) |
| Maximum therapeutic concentration | 2.42 ug/ml (0.43) | 285 ng/ml (72) |
| Minimum therapeutic concentration | 2.11 μg/ml (0.45) | 148 ng/ml (56) |
| Time to awakening, minutes | 7.9 (3.4) | |
| Drug concentrations | 1.59 μg/ml (0.34) | 142 ng/ml (45) |
| Time to extubation or spontaneous ventilation and orientation, minutes | 11.9 (3.8) | |
| Drug concentrations | 1.37 μg/ml (0.31) | 136 ng/ml (41) |
| Measured/predicted ratio ($n$ = 1073) | 0.88 (0.22) | 1.01 (0.28) |

a considerable degree by the use of modern administration techniques based upon microprocessor support. However, for this approach it is necessary to know mean population data for the pharmacokinetic behaviour of the drugs to be employed. It is normal to use a set of data generated in a small ($n$ = 6–10), standardised study group[1,6,7] if drug administration is based upon pharmacokinetic principles. An alternative approach[2] investigates larger group sizes ($n$ = 40–50) to determine factors that are likely to influence the pharmacokinetic profile of a drug in a defined population. This study confirms the previous conclusion[4,5] that a pharmacokinetic data set for alfentanil generated from a small group is widely[1] applicable as a basis for calculated dosage schemes, without any weight corrections, in adult patients. The overall m/p ratio of 1.01 (Table 1) reflects a nearly optimal result. Variation (Fig. 2), however, is caused by many factors such as between-patients variability, changes in haemodynamics during anaesthesia, concurrent medication or disease. Technical factors also have to be taken into consideration; these include performance errors of the delivery device, errors at sampling, or measurement errors when drug concentrations are assessed. The greatest deviation of the measured alfentanil concentration from that predicted did not exceed 50% at therapeutic concentrations of 200–300 ng/ml (Fig. 2). The greatest deviation of measured from predicted blood levels for propofol was somewhat higher in the therapeutic range (2.5–3.0 μg/ml) but did not exceed 60% (Fig. 3). The total overall prediction error for propofol, as reflected by the m/p ratio of 0.880, indicates slight overestimation for the mean pharmacokinetic data set which was generated in volunteers in an infusion study for pharmacodynamic modelling.[10] This may be explained by a pharmacokinetic interaction between alfentanil and propofol or because an inappropropriate set of pharmacokinetic data, not applicable for clinical anaesthesia, was used. This needs further investigation.

Whether the observed variability is tolerable or not can be answered as follows. The performance of the system is acceptable when the mean variation of measured concentrations around the predicted values is about 20–30% and when the maximal variation does not exceed 50–60%. Under these conditions the blood level selected by the anaesthetist will be achieved in every case. If patient variability causes deviations of this magnitude the ability of the device to respond allowed the blood level to be adjusted easily and as necessary. The pharmacokinetic data set provided to the delivery system should be modified, however, if the variability becomes greater and if the total bias exceeds 10–20%.

The drugs chosen for total intravenous anaesthesia in this study permitted good control of the desired effect. There are normally no difficulties if the pharmacodynamic effect is to be enhanced: this is achieved simply by dosage schemes that generate either linearly increasing blood levels or produce elevations in a stepwise manner.[9] However, it is necessary to rely upon the pharmacokinetic decay profile of a drug after infusion if swift disappearance of pharmacological action at the end of anaesthesia is of interest. Here

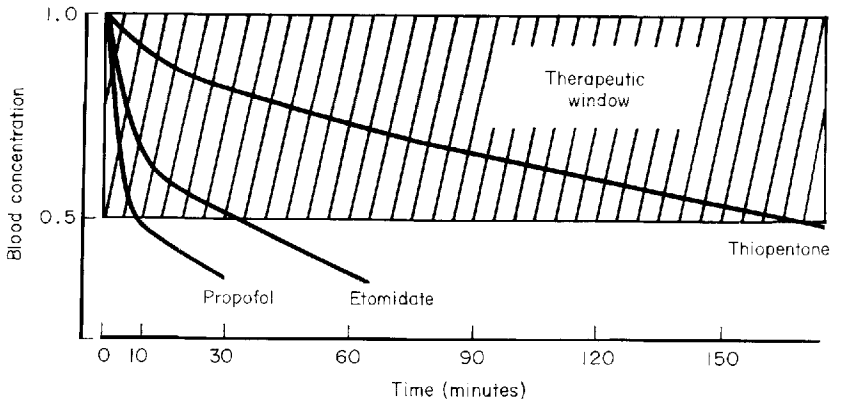


Fig. 5. Simulated blood level decay from optimal to minimal therapeutic concentration after a 3-hour infusion of propofol, etomidate and thiopentone. Concentrations are given as fractions of the optimal therapeutic concentration for each drug at the end of infusion.

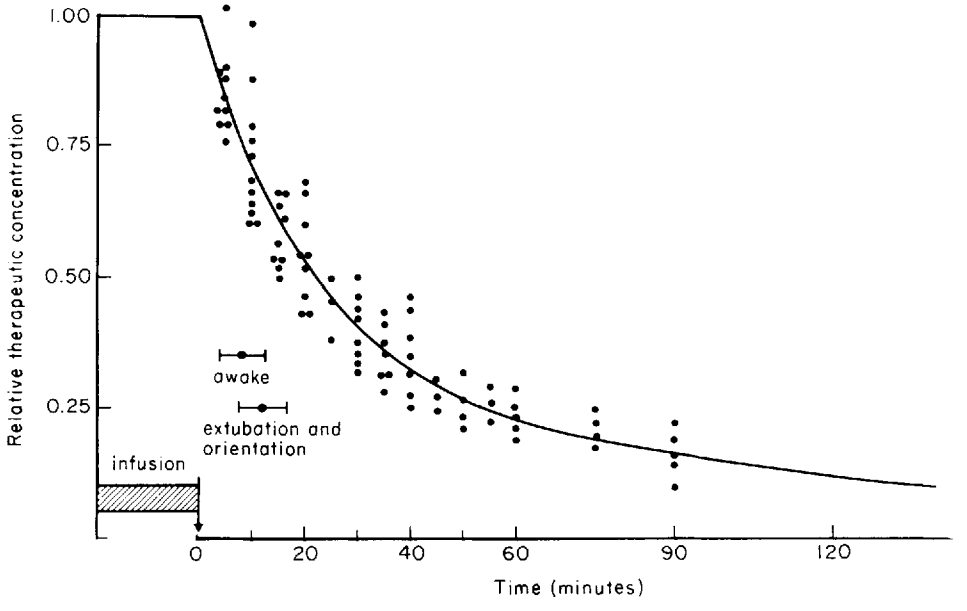


Fig. 6. Relative blood levels ($n$ = 89) of propofol in 20 patients during recovery from total intravenous anaesthesia. Concentrations are given as fractions of the individual therapeutic concentrations at the end of infusion.

predictions based upon dynamic-pharmacokinetic modelling indicate propofol to be a favourable intravenous anaesthetic (Fig. 5) compared to etomidate and thiopentone.

The individual propofol blood level decay curves of the 20 patients after cessation of the infusion reflected the predictions closely (Fig. 6). The rapid disappearance of propofol from the blood even after prolonged infusion, is responsible for the excellent control of its pharmacodynamic effects and allows fast recovery (Table 1). The decay of alfentanil after infusion[3,11] is not as fast, so long recovery periods are likely if high plasma levels (300–500 ng/ml) are maintained until the end of surgery. Therefore, it is necessary to adjust the alfentanil plasma concentration carefully and, whenever possible, to terminate the infusion about 30 minutes before the end of surgery. Recovery can be kept short (Table 1) if these rules are followed, with reasonable extubation times of the order of 10 minutes postoperatively.

Computer-assisted total intravenous anaesthesia with propofol and alfentanil proved to be very satisfactory from a clinical point of view. Haemodynamic variables did not change significantly during induction (Fig. 4), and the pronounced hypotension[12,13] observed after bolus injections of propofol 2.0 mg/kg did not occur in the present study. This can be explained by the difference in dosing technique. The initial bolus dose of about 65 mg is delivered in the first minute by the computerised infusion to achieve propofol blood levels of 2.5 μg/ml, the target concentration. Thereafter the infusion rate is about 10 mg/minute and declines exponentially to 5 mg/minute. Hypotension can be avoided in ASA grade 1 or 2 patients by this dosage scheme. Induction time appears to be prolonged in comparison to the higher bolus injections but this was not a disadvantage in this protocol which included vecuronium as the sole muscle relaxant. In addition, this dosage scheme compensates for the delayed onset of action of propofol,[10] and constrasts with relatively large bolus injections often used to overcome this effect. Pain on injection, movement during induction, restlessness and vomiting during recovery were not seen; nausea occurred in one case and postoperative analgesia was required in two. There was euphoria in 14 out of 20 patients during recovery.

The combined administration of propofol and alfentanil by computer-assisted infusion proved to be a very satisfactory alternative to inhalational anaesthesia with the same degree of control and lack of major side effects.

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