Pharmacodynamic interaction of eltanolone and alfentanil during lower abdominal surgery in female patients

M. J. Mertens1*, J. Vuyk1, K. Parivar2, F. H. M. Engbers1, A. G. L. Burm1 and J. G. Bovill1

1Department of Anaesthesiology (P5), Leiden University Medical Centre, PO Box 9600, 2300 RC, Leiden, The Netherlands. 2Department of Clinical Pharmacology, Pharmacia and Upjohn, Stockholm, Sweden

*Corresponding author

We have studied the influence of eltanolone on intraoperative alfentanil requirements in 18 female patients undergoing lower abdominal surgery receiving target-controlled infusions of eltanolone and alfentanil. While target concentrations of eltanolone were maintained constant, target concentrations of alfentanil changed in response to the presence or absence of responses. With serum eltanolone concentrations increasing from 500 to 2000 ng ml–1, the EC50 of alfentanil for suppression of responses to surgical stimulation decreased from 233 to 9 ng ml–1. The findings suggest that the interaction between eltanolone and alfentanil is synergistic.

Keywords: anaesthetics i.v., eltanolone; analgesics opioid, alfentanil; anaesthetic techniques, i.v.; pharmacodynamics, eltanolone; pharmacodynamics, alfentanil

In anaesthetic practice, hypnotic agents are frequently combined with opioids to reduce the dose requirements of individual agents, diminish side effects and/or increase the speed of recovery. Most i.v. hypnotics and opioids have been found to interact synergistically.1 We have examined the influence of varying serum concentrations of eltanolone, a steroidal hypnotic, on intraoperative alfentanil requirements.

Patients and methods

After obtaining approval from the Medical Ethics Committee and informed consent, we studied 18 unpremedicated female patients (ASA I–II, aged 18–65 yr), undergoing lower abdominal surgery. Patients with a history of mental or neurological disease, weight deviating >30% from normal, receiving psychopharmacological drugs, consuming >20 g alcohol day–1, smoking >10 cigarettes day–1, or with a documented or suspected soybean protein or drug allergy were excluded. Patients were allocated randomly to one of three groups and three subgroups.

In the operating room, cannulae were inserted into a forearm vein for combined drug infusion, and into a radial artery for monitoring arterial pressure and blood sampling. The deadspace of the infusion system did not exceed 0.5 ml. After breathing 100% oxygen for 3 min and administration of pancuronium 0.02 mg kg–1, anaesthesia was induced by target-controlled eltanolone infusion with target concentrations of 750, 1250 or 1750 ng ml–1 (groups A, B and C) maintained until the peritoneum was closed. Fifteen minutes later, the alfentanil infusion was initiated with target concentrations of 50, 150 or 300 ng ml–1 (subgroups 1, 2 and 3). Both infusion systems were provided with three-compartmental pharmacokinetic data. Pharmacokinetic values for eltanolone were2: $V_c = 90 \text{ ml kg}^{-1}$, $k_{10} = 0.27 \text{ min}^{-1}$, $k_{12} = 0.17 \text{ min}^{-1}$, $k_{21} = 0.045 \text{ min}^{-1}$, $k_{13} = 0.032 \text{ min}^{-1}$, $k_{31} = 0.004 \text{ min}^{-1}$ and $k_{eo} = 0.1 \text{ min}^{-1}$. Values for alfentanil were adjusted for age and weight.3 Twenty minutes after starting infusion of eltanolone, provided the patient had lost consciousness, pancuronium 0.06 mg kg–1 was administered, followed 2 min later by laryngoscopy and tracheal intubation. If a patient had not lost consciousness, the target alfentanil concentration was increased by 100 ng ml–1. After intubation, the lungs were ventilated with 30% oxygen in air to an end-tidal carbon dioxide partial pressure of 3.8–4.5 kPa, and the target alfentanil concentration was reduced to 10, 20 or 50 ng ml–1 for skin incision. During operation, target alfentanil concentrations were changed in steps of 10–50 ng ml–1 in response to the presence or absence of signs of inadequate anaesthesia.

The target eltanolone concentration was reduced to 500 ng ml–1 after closure of the peritoneum and the infusion discontinued during skin closure. Infusion of alfentanil was discontinued approximately 10 min before skin closure. When spontaneous ventilation was established, the trachea was extubated. Patients were interviewed 24 h after operation to evaluate side effects and recall of intraoperative events.

Arterial samples for measurement of eltanolone and
alfentanil concentrations were collected 15 min after the start of eltanolone infusion, at skin incision, on opening of the peritoneum, at skin closure and at extubation. During operation, samples for measurement of concentrations of eltanolone were collected every 20 min and samples for measurement of alfentanil were obtained 6 min (to allow blood–brain equilibration) after a new target concentration was reached. Serum concentrations of eltanolone and alfentanil were measured using gas chromatography–mass spectrometry with selected ion monitoring.\(^4\)\(^5\) Accuracy and precision were <10\% for the eltanolone concentration range and for alfentanil concentrations of 24–902 ng ml\(^{-1}\) and 9.8–19.6\% for control samples containing alfentanil 18.4 and 22 ng ml\(^{-1}\). Detection limits were approximately 1 and 11 ng ml\(^{-1}\) for eltanolone and alfentanil, respectively.

Concentration–effect relationships of alfentanil for suppression of responses to intra-abdominal surgical stimuli were determined in individual patients by logistic regression.\(^1\) Subsequently, the following interaction model was fitted to the data by unweighted least-squares non-linear regression:\(^1\):

\[
\frac{\bar{C}_{elt(i)}}{EC_{50 elt}} = \frac{EC_{50 alf}}{EC_{50 alf}} + \varepsilon * \frac{\bar{C}_{elt(i)}}{EC_{50 elt}} + \frac{EC_{50 alf}}{EC_{50 alf}} = 1
\]

where \(\bar{C}_{elt(i)}\) = mean intraoperative eltanolone concentration; \(EC_{50 alf(i)}\) = alfentanil concentration associated with a 50\% probability of no response to surgical stimulation in patient \(i\) when both agents are present; and \(EC_{50 alf}\) and \(EC_{50 elt}\) = concentrations associated with a 50\% probability of no response if either agent were administered alone. \(\varepsilon\) characterizes the nature of the interaction. Additive (i.e. \(\varepsilon = 0\)) and non-additive (i.e. \(\varepsilon \neq 0\)) interactions were explored and compared using an \(F\) test.

Predictive performances of the infusion systems were evaluated by examining the median performance error (MDPE) and median absolute performance error (MDAPE).\(^6\) If the interquartile (IQ) range of MDPE included zero, bias was considered not significant.

**Results**

There were three, seven and eight patients in groups A, B and C, respectively. One patient in group A was withdrawn because of a generalized urticarial reaction after induction of anaesthesia. In one patient in group B, insufficient data were obtained. In the remaining patients, mean duration of anaesthesia was 201 (SD 46) min. All patients in group A and three in group B had not lost consciousness after 15 min of infusion of eltanolone, but unconsciousness was induced within 3 min after starting infusion of alfentanil.

Because of the small number of patients, no attempt was made to determine the degree of interaction between eltanolone and alfentanil at specific events, such as laryngoscopy. Intraoperative serum eltanolone concentrations were stable in all patients. With eltanolone concentrations increasing from 500 to 2000 ng ml\(^{-1}\), the \(EC_{50}\) of alfentanil decreased from 233 to 9 ng ml\(^{-1}\) (Fig. 1). The coefficient of determination for the non-additive curve (\(r^2 = 0.32\)) exceeded that of the additive curve (\(r^2 = 0.27\)). However, residual sums of squares did not differ significantly.

Mean times to return of consciousness were 14 (SD 6) min, 22 (15) min and 35 (11) min in groups A, B and C, respectively. All patients breathed adequately at awakening. None reported awareness of any intraoperative event. Nausea occurred in seven patients. Urticaria were recorded in three patients, two of whom required treatment. Urticaria were not accompanied by haemodynamic changes which suggests they were local reactions.

MDPE and MDAPE were −10\% (interquartile range −22 to 4\%) and 15\% (8–25\%) for eltanolone (\(n = 138\)), and −33\% (−54 to −16\%) and 36\% (20–55\%) for alfentanil (\(n = 147\)), indicating a significant bias with alfentanil, but not with eltanolone.

**Discussion**

Before completion of the study, eltanolone was withdrawn, predominantly because of an unexpected high incidence of allergic reactions. At that time, 18 of the scheduled 36 patients had been enrolled. Therefore, the study in itself is not conclusive. Nevertheless, the profound decrease in intraoperative alfentanil requirements with increasing eltanolone concentration suggests a synergistic interaction. Further support for a synergistic mechanism comes from studies demonstrating that alfentanil cannot fully replace i.v. anaesthetics.\(^1\) When alfentanil is combined with propofol, a threshold propofol concentration can be defined below which satisfactory anaesthetic conditions cannot be obtained. Beyond this threshold (0.8 \(\mu\)g ml\(^{-1}\) alfentanil requirements (\(EC_{50}\)) decrease markedly with increasing propofol concentration, reflecting a synergistic interaction. In all likelihood, a threshold also exists for the combination of eltanolone and alfentanil. However, this could not be...
defined because of insufficient data in the low eltanolone concentration range.

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