Flumazenil reduces the duration of thiopentone but not of propofol anaesthesia in humans

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The effect of flumazenil (F) on the duration of anaesthesia produced by a single dose of thiopentone (T) and propofol (P) was investigated in a placebo-controlled double-blind trial. Eighty-four patients anaesthetized with N₂O in O₂ and either thiopentone 7 mg · kg⁻¹ or propofol 3 mg · kg⁻¹ for minor gynaecological procedures were studied. Patients were randomly allocated to pretreatment with either 0.5 mg of flumazenil (F) or 5 ml of normal saline (NS) in one of the following groups: T/NS, T/F, P/NS, or P/F. Anaesthetic requirements were assessed by recording the time between the injection of anaesthetic and the first movement observed during the procedure. The time elapsed from the administration of thiopentone to the first movement was 6.5 ± 1.6 min for the T/NS group and 5.3 ± 2.4 min for the T/F group (P < 0.05). The first movement after propofol administration was observed at 7.0 ± 2.2 min in the P/NS group and at 7.1 ± 4.5 min in the P/F group (NS). These data suggest that pretreatment with 0.5 mg of flumazenil iv reduces the duration of thiopentone but not of propofol anaesthesia.

Au cours d'une étude à double insu avec placebo, les effets du flumazénil (F) sur la durée de l'anesthésie produite par une dose unique de thiopentone (T) et de propofol (P) sont évalués. La population étudiée comprend quatre vingt-quatre patientes anesthésiées au protoxyde-oxygène associé à du thiopentone 7 mg · kg⁻¹ ou du propofol 3 mg · kg⁻¹ pour des opérations gynécologiques mineures. Les patientes reçoivent aléatoirement un pré-traitement au flumazénil (F) ou au soluté physiologique (NS) et sont repartis dans les groupes suivants: T/NS, T/F, P/NS ou P/F. Les besoins anesthésiques sont évalués par la

mesure de l'intervalle entre l'injection de l'anesthésique et l'observation d'un premier mouvement pendant l'intervention. Le temps écoulé à partir de l'administration de thiopentone et l'observation d'un premier mouvement est de 6,5 ± 1,6 min pour le groupe T/NS et 5,3 ± 2,4 pour le groupe TF (P < 0,05). Le premier mouvement noté après l'administration de propofol est observé à 7,0 ± 2,2 min dans le groupe P/NS et à 7,1 ± 4,5 min dans le groupe P/F (N.S.). Ces données suggèrent que l'administration préalable de Flumazénil 0,5 mg iv diminue la durée d'action du thiopentone mais non du propofol.

Flumazenil has been shown to antagonize the central effects of benzodiazepines by competitive displacement from the benzodiazepine receptor.¹⁻³ However, the possibility that flumazenil antagonizes the anaesthetic effects of the intravenous anaesthetics thiopentone and propofol has not been examined before. This placebo-controlled double blind study investigated whether pretreatment with flumazenil altered the anaesthetic requirements of thiopentone and/or propofol, when these drugs were administered to produce general anaesthesia for minor gynaecological procedures.

Methods

After approval of the Hospital Ethical Committee, 84 patients ASA I-II, scheduled for elective dilation and curettage (D & C) of the uterus under general anaesthesia were informed of the aim of the study in the preoperative visit and informed consent was obtained. Smokers or those receiving drugs were excluded and premedication was omitted. Patients were assigned randomly to one of four groups: thiopentone/normal saline, thiopentone/flumazenil, propofol/normal saline, and propofol/flumazenil.

After three minutes inhalation of 70% N₂O in O₂ via a Mapleson A anaesthetic system patients received randomly either flumazenil 0.5 mg or normal saline 5 mg iv. Two minutes later anaesthesia was induced with either thiopentone 7 mg · kg⁻¹ or propofol 3 mg · kg⁻¹ iv. The patient was placed in the lithotomy position, an oral airway was inserted, and anaesthesia was maintained with

Key words

ANAESTHETICS INTRAVENOUS: propofol, thiopentone;
ANTAGONISTS: benzodiazepines, flumazenil;
POTENCY: anaesthetic.

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TABLE I Age (yr) and body weight (kg) in each group of patients. Mean $\pm$ sd.

	Thio/NS n = 18	Thio/Flum n = 24	Prop/NS n = 21	Prop/Flum n = 21
Age (yr)	50.7 $\pm$ 9.9	45.2 $\pm$ 9.6	50.4 $\pm$ 10.6	50.9 $\pm$ 8.5
Weight (kg)	68.9 $\pm$ 9.7	65.4 $\pm$ 7.6	66.9 $\pm$ 8.8	67.6 $\pm$ 10.5

Thio - thiopentone, NS - saline, Flum - flumazenil.

TABLE II Time (min) between anaesthetic administration and (a) first movement and (b) cervical dilatation in each group. Mean $\pm$ SD.

Time (minutes)	Thio/NS n = 18	Thio/Flum n = 24	Prop/NS n = 21	Prop/Flum n = 21
To first movement	6.5 $\pm$ 1.6*	5.3 $\pm$ 2.4*	7.0 $\pm$ 2.2	7.1 $\pm$ 4.5
To cervical dilatation	4.4 $\pm$ 1.2	4.3 $\pm$ 1.7	4.8 $\pm$ 1.5	4.2 $\pm$ 1.0

* $P < 0.05$.

N₂O in O₂ via a face mask. Heart rate, ECG, and SaO₂ were monitored continuously and blood pressure was recorded automatically every five minutes (Cardicap, Datex).

The time that elapsed between the *iv* administration of the anaesthetic and (a) cervical dilation and (b) the patient's first movement, including attempts to reject the airway, were recorded. When movement occurred and the D & C had not been completed anaesthesia was supplemented either with isoflurane 1% or with an opioid (fentanyl 50 μ g), or both. Observations and recordings were made by an anaesthetist who was unaware of the pretreatment given and of the study design.

The age and body weight among the groups were analyzed using ANOVA. The times to first movement of the patient were analysed using the Mann-Whitney test. $P < 0.05$ was considered statistically significant.

Results

The four groups of patients did not differ with regard to age or body weight (Table I).

The time from administration of thiopentone to first movement was decreased by 18.5% in the thiopentone/flumazenil group compared with the thiopentone/normal saline group ($P < 0.05$) but there was no difference between the propofol/normal saline and propofol/flumazenil groups (Table II).

Supplemental anaesthesia-algesia was given to six patients in the thiopentone/normal saline group, to ten patients in the thiopentone/flumazenil group, to six patients in the propofol/saline group, and to four patients in the propofol/flumazenil group.

Discussion

Flumazenil in a dose of 0.5 mg reduced the duration of thiopentone anaesthesia but had no effect on the duration of propofol anaesthesia.

Flumazenil specifically antagonizes the effects of benzodiazepines which act on specific receptors in the brain, the GABA-and benzodiazepine receptor-chloride channel complex.¹⁻³ Alon *et al.* found a reduction in sedation and improvement in orientation and comprehension in women that received the specific antagonist after midazolam anaesthesia.⁴ Similar results have been reported by other investigators. Nilsson *et al.* reported that flumazenil administration improved performance after general anaesthesia induced with midazolam and alfentanil but re-sedation occurred.² With regard to the analgesic requirements when the antagonist is administered post-operatively to reverse benzodiazepine effects, studies are controversial; either an increase⁵ or no change² have been reported. The efficacy of flumazenil to antagonize sedation, disorientation, and lack of cooperation produced by midazolam administered to patients undergoing spinal anaesthesia has been compared with that of aminophylline. Aminophylline only partially reversed the effects of midazolam, while antagonism produced by flumazenil was rapid and complete.⁶

Flumazenil has not been shown to reverse reliably the effects of chloralhydrate⁷ and the action of ethanol.^{8,9} The drug failed to enhance or antagonize the anaesthetic effects of halothane in rats¹⁰ and of isoflurane, enflurane, or enflurane-fentanyl anaesthesia in dogs.¹¹ These results are in contrast with those of Schwartz *et al.* who reported a decrease in the MAC of isoflurane by flumazenil in dogs.¹²

An antagonizing effect of flumazenil on the action of intravenous anaesthetics may exist, since the GABA-receptor/chloride channel stimulation has been proposed as a possible molecular mechanism of general anaesthesia produced by intravenous anaesthetics.¹³ However, the GABA receptor is a part of a multimolecular membrane complex, which also contains the benzodiazepine receptor, the chloride ionophore, and possibly other molecular entities.¹⁴

It has been suggested that barbiturates increase the average open life time of chloride channel and the benzodiazepines increase the frequency of chloride channel opening.¹⁵ Despite the different mechanisms potentiating the GABA response, our results suggest some interaction between thiopentone and flumazenil. On the other hand the cellular actions of propofol are not well known. Propofol potentiates the surface depolarizations evoked by GABA, muscimol and 3-aminopropanesulphonic acid in the rat olfactory cortex slices.¹⁶

The large predetermined fixed doses of both thio-

pentone and propofol were chosen to obtain a satisfactory depth of anaesthesia in all patients. An argument may be that during D and C stimulation varies, with movement most likely to occur during cervical dilatation. Nonetheless, as the time from administration of the anaesthetic to cervical dilatation does not differ between the groups (thiopentone/normal saline vs thiopentone/flumazenil and propofol/normal saline vs propofol/flumazenil), the timing of this powerful stimulus is unlikely to override any effect due to flumazenil.

Nitrous oxide was given prior to the *iv* anaesthetics, so that the desired N₂O alveolar concentration was obtained before respiratory depression occurred due to the *iv* anaesthetic. The administration of N₂O in all groups might be a limitation regarding the flumazenil-*iv* anaesthetic interaction. Nonetheless, we did not omit analgesia produced by N₂O, even in such a short procedure for ethical reasons.

Another limitation of the study may be the lack of a dose response relationship. Higgit *et al.* showed that 100 mg *po* of flumazenil in healthy subjects produced benzodiazepine-like effects, while 30 mg *po* produced effects opposite to those of benzodiazepines.¹⁷ However, in our study the ampoules of flumazenil (0.5 mg in 5 ml volume, Anexate®, Roche) were appropriately covered by the Hospital Pharmacy in an identical manner with the 5 ml ampoules containing NaCl, so that the trial was conducted double-blind. This was the reason for not obtaining a dose response curve.

In conclusion, these results suggest that flumazenil may antagonize, to some degree, the anaesthetic effects of thiopentone but not of propofol. This antagonistic effect is far less pronounced than in the reversal of benzodiazepine sedation. Whether these findings are clinically important for thiopentone anaesthesia remains to be determined.

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