Midazolam coinduction does not delay discharge after very brief propofol anaesthesia

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Previous reports have demonstrated synergism of midazolam and propofol for induction of anaesthesia in humans. We tested the hypothesis that in the presence of alfentanil, the combination of midazolam with propofol for a very brief operative procedure would not affect the recovery phase. During pre-oxygenation, 64 outpatients scheduled for dilatation and curettage received placebo, or low-dose midazolam ($0.03 \text{ mg} \cdot \text{kg}^{-1}$), or high-dose midazolam ($0.06 \text{ mg} \cdot \text{kg}^{-1}$) iv, in a randomized double-blind manner. They then received alfentanil $10 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$ iv, followed by titrated doses of propofol iv for induction and maintenance of anaesthesia. Ventilation with 70% N_2O in O_2 by mask was controlled to achieve a PETCO_2 30–40 mmHg. Outcome measures were: propofol dose (induction and maintenance), time until eye-opening to command, and time to discharge-readiness. Propofol induction dose was decreased by increasing doses of midazolam ($P = 0.00005$). Midazolam delayed time to eye-opening ($P = 0.02$) but not time to discharge-readiness. This study had an 80% power to detect a 39 min difference in time to discharge-readiness. We conclude that midazolam propofol co-induction in the presence of alfentanil delays eye-opening, but does not delay discharge after anaesthesia.

Key words

ANAESTHETICS, INTRAVENOUS: propofol, midazolam, alfentanil;

INTERACTIONS, DRUG: propofol, midazolam;

RECOVERY: assessment;

SURGERY: ambulatory.

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Des rapports antérieurs ont montré pendant l'induction de l'anesthésie chez l'humain une synergie entre le midazolam et le propofol. Nous avons vérifié l'hypothèse selon laquelle, en présence d'alfentanil, l'association du midazolam au propofol, au cours d'interventions très courtes, pourrait ne pas affecter la phase de récupération. Pendant la pré-oxygénation, 64 patientes programmées pour dilatation et curetage reçoivent soit un placebo, soit une petite dose de midazolam ($0,03 \text{ mg} \cdot \text{kg}^{-1}$), soit une forte dose ($0,06 \text{ mg} \cdot \text{kg}^{-1}$) iv en double aveugle et au hasard. Elles reçoivent ensuite de l'alfentanil $10 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$ iv suivi par des doses titrées de propofol pour l'induction et l'entretien de l'anesthésie. La ventilation avec $\text{N}_2\text{O}/\text{O}_2$ à 70% au masque est contrôlée pour obtenir une PETCO_2 de 30–40 mmHg. Sont mesurés: la dose de propofol (induction et entretien), le temps mesuré jusqu'à l'ouverture des yeux sur commande et le temps mesuré jusqu'à l'accès au congé. La dose d'induction au propofol diminue lorsqu'on augmente la dose de midazolam ($P = 0,00005$). Le midazolam retarde l'ouverture des yeux ($P = 0,02$) mais ne retarde pas le congé. Cette étude a une puissance de 80% pour déceler une différence de 39 min pour le délai du congé. Nous concluons que l'association de midazolam et de propofol en présence d'alfentanil retarde l'ouverture des yeux mais ne retarde pas le congé de l'hôpital.

The pharmacokinetic behaviour of propofol makes it a popular anaesthetic for ambulatory surgery. Used as a single agent, recovery from propofol anaesthesia is more rapid than that after thiopentone,^{1–3} which is much more rapid than that after midazolam,^{4–7} even with flumazenil reversal.⁸

Midazolam and propofol are synergistic when used in combination for the induction of anaesthesia.^{9–11} This interaction may occur at a common site of action of these agents on the GABA receptor.¹² Alfentanil, in combination with midazolam and propofol, also contributes to this dose-reducing interaction.^{13,14}

The addition of midazolam to propofol might prolong recovery from anaesthesia particularly after very brief procedures. One study of this combination showed a

slight delay in eye-opening and orientation, but no delay in discharge.¹⁵ However, in that study the duration of surgery was one hour and the time to discharge was three hours. Therefore, we tested the hypothesis that the combination of midazolam and propofol for a very brief procedure would not affect the duration of recovery.

Methods

Patients

With institutional ethics board approval, ASA I and II elective outpatients scheduled for dilatation and curettage (D+C) were contacted by telephone.¹⁶ They gave written informed consent for a randomized double-blind study upon arrival in hospital. Patients were excluded if they were taking benzodiazepines, antidepressants or antiseizure medications, or if the anaesthetist chose to use tracheal intubation. (Indications for intubation were gastroesophageal reflux disease, and anticipated difficulty with airway maintenance during mask anaesthesia.) A random number table was used to prepare sealed envelopes for group assignment, and an assistant opened the envelope and prepared the study drug in five ml saline. The investigators were blinded to the group assignment of each patient.

Anaesthetic

Patients were not premedicated and did not have laminaria tents inserted. A freely flowing *iv* infusion was established in the hand or wrist for the administration of all medications. One of the investigators was present for all anaesthetics, and everyone present was blinded to group assignment.

During pre-oxygenation, patients received placebo (Group C), low-dose midazolam $0.03 \text{ mg} \cdot \text{kg}^{-1}$ (Group LM), or high-dose midazolam $0.06 \text{ mg} \cdot \text{kg}^{-1}$ (Group HM). One minute later, all patients received alfentanil $10 \mu\text{g} \cdot \text{kg}^{-1}$. Two minutes after the study drug was injected, patients received lidocaine 20 mg, followed by propofol 30 mg every ten seconds until loss of lash reflex. Anaesthesia was maintained with 70% N_2O in O_2 by mask, with ventilation controlled as needed to maintain end-tidal CO_2 30–40 mmHg. Patients received propofol 20–30 mg when movement was observed, but not when spontaneous ventilation occurred. Propofol 20–30 mg was also given for an increase in heart rate or systolic blood pressure to 120% of preoperative baseline. Vital signs were recorded every three minutes, and N_2O was discontinued upon completion of surgery. Patients remained on the operating table until they responded to a repeated command to open their eyes.

They were then transferred to the post-anaesthesia recovery room where they were allowed morphine 2 mg

TABLE I Patient demographics. Mean (SD), *P* values for analysis of variance

Group	<i>n</i>	Age (yr)	Weight (kg)	Duration (min)
C	21	45 (11)	74 (18)	7.8 (5.8)
LM	23	45 (12)	65 (14)	6.5 (4.2)
HM	20	46 (11)	73 (17)	7.3 (3.9)
<i>P</i>		0.95	0.13	0.65

iv and cyclizine 25 mg *iv* as required. After a minimum of 30 min, they were returned to the daycare surgery unit, where they were assessed by daycare nursing staff (unaware of group assignment) for discharge score¹⁷ every 15 min until a score of 9 out of 10 was achieved. The discharge score allotted 2 points each to systolic blood pressure (SBP, 2 if within 20% of pre-op, 1 if within 20–40%, otherwise 0), mental status (2 if fully oriented and steady gait, 1 if either, 0 if neither), pain and vomiting (2 if minimal, 1 if required treatment, 0 if severe), bleeding (2 if minimal, 1 if mild, 0 if severe), voiding and drinking (2 if both, 1 if either, 0 if neither). Outcome measures were propofol induction dose, maintenance dose (cumulative intraoperative doses divided by duration of surgery), duration of surgery, time to eye-opening and time from end of surgery to discharge-readiness.

Statistical analysis

All results are expressed (using two significant figures) as mean followed by standard deviation (SD). Propofol doses, and duration of surgery and recovery times were analyzed (Epi Info, Version 5. USD Inc. Stone Mountain Georgia, 1990 and Sigmaplot statistical analysis system, version 1.00. Jandel Corporation, San Rafael, California, 1992) by analysis of variance. Comparisons between individual groups were made using the Student-Neuman-Keuls test¹⁸ with log transformation of data as necessary to achieve normal distribution. Haemodynamic data were tabulated as preinduction baseline, and intraoperative maximum and minimum values, and were compared using a Kruskal-Wallis one way analysis of variance. This study had an 80% power¹⁹ to detect the following differences, for $\alpha = 0.05$: change in propofol maintenance dose of $0.08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, time to eye-opening of 1.9 min, time to discharge-readiness of 39 min.

Results

Seventy-eight of 266 consecutive eligible patients were approached for this study from January to December 1993, and 64 patients (five surgeons) completed the protocol. A hysteroscopy was done in 28% of patients. Exclusions were for psychotropic medications (seven), re-

TABLE II Induction and maintenance doses of propofol, and times to eye-opening and discharge-readiness. Mean $\pm$ SD

Group	Induction dose (mg $\cdot$ kg ⁻¹)	Maintenance dose (mg $\cdot$ kg ⁻¹ $\cdot$ min ⁻¹)	Eye-opening (min)	Discharge-readiness (min)
C	2.2 $\pm$ 0.78	0.12 $\pm$ 0.10	2.7 $\pm$ 1.7	120 $\pm$ 64
LM	1.6 $\pm$ 0.82*	0.14 $\pm$ 0.17	4.5 $\pm$ 2.9*	130 $\pm$ 57
HM	0.96 $\pm$ 0.67*†	0.080 $\pm$ 0.070	5.0 $\pm$ 3.4*	110 $\pm$ 50
P ANOVA	0.00005	0.59	0.02	0.58

* $P < 0.05$ vs Group C.

† $P < 0.05$ vs Group LM.

TABLE III Baseline and intraoperative maximum and minimum systolic (SBP) and diastolic (DBP) blood pressure (mmHg) and heart rate (HR beat $\cdot$ min⁻¹); Mean $\pm$ SD, P values for analysis of variance

	Group C	Group LM	Group HM	P
SBP baseline	142 $\pm$ 26	140 $\pm$ 20	134 $\pm$ 14	0.59
SBP maximum	150 $\pm$ 11	143 $\pm$ 19	144 $\pm$ 16	0.16
SBP minimum	110 $\pm$ 20	100 $\pm$ 15	110 $\pm$ 15	0.20
DBP baseline	82 $\pm$ 12	81 $\pm$ 14	80 $\pm$ 11	0.82
DBP maximum	90 $\pm$ 14	87 $\pm$ 11	87 $\pm$ 8	0.52
DBP minimum	61 $\pm$ 12	60 $\pm$ 10	62 $\pm$ 15	0.54
HR baseline	80 $\pm$ 17	82 $\pm$ 15	78 $\pm$ 12	0.67
HR maximum	83 $\pm$ 5	84 $\pm$ 4	83 $\pm$ 6	0.19
HR minimum	61 $\pm$ 10	62 $\pm$ 10	66 $\pm$ 9	0.46

fusal (three), intubation (two), ASA III status (one), and dose error (one).

Groups were similar in age, weight, and duration of surgery (Table I).

Midazolam produced a dose-related decrease in the induction dose of propofol. However, the maintenance dose of propofol was not altered by midazolam. Five patients in each group required no intraoperative supplementation with propofol. One patient in the study required supplementation for blood pressure increase, and none required supplementation for heart rate increase. Time to eye-opening to command was delayed in both the low-dose and high-dose midazolam groups when compared with control, but not delayed more with one dose of midazolam versus the other. Time to discharge-readiness was not altered by midazolam (Table II).

There were no differences among groups in either baseline or intraoperative maximum or minimum blood pressure and heart rate values (Table III). Spontaneous ventilation was present in 60–70% of patients at the conclusion of surgery, with no difference between groups ($P = 0.84$).

In the post-anaesthesia recovery room, two patients in Group C and two in Group HM received morphine. One patient in Group C and one in Group HM received cyclizine. No patient received both medications. No intra- or postoperative complications were observed.

Discussion

The propofol data show a highly significant dose-dependent interaction with midazolam at induction but no difference in propofol maintenance doses. There was a small difference in time to eye-opening that was not related to midazolam dose, and no difference was found in time to discharge-readiness between groups.

The agents in this study were given in a sequence and timing that resembles usual clinical practice. In previous studies, as in this study, midazolam has been given two to five minutes before propofol.^{9,10,14,15}

A confounder in any study of induction dose is the amount of drug that is still entering the circulation or has already been metabolized when the induction endpoint is reached.²⁰ Despite the large standard deviations, we have shown a highly significant difference between groups.

The reduction in propofol dose was greater in the present study than in the most comparable study, in which the propofol induction dose was decreased from 2.1 to 1.4 mg $\cdot$ kg⁻¹ by using midazolam 0.07 mg $\cdot$ kg⁻¹.¹⁵ Several differences between the two studies may account for this. The dose and timing of midazolam and opioid administration differed slightly, and synergistic interactions may be highly sensitive to such differences when short-acting drugs are involved. Furthermore, the more rapidly-acting opioid alfentanil was used in the present study.

When administered in dosage ratios (alfentanil:fentanyl) of 10:1, the EEG and respiratory depressant effects of alfentanil occur more rapidly than those of fentanyl.²¹ Lidocaine was used in the present study to prevent pain on injection of propofol, but it is unlikely that 0.3 mg · kg⁻¹ had a hypnotic effect.

Lack of difference in the dose of propofol for maintenance of anaesthesia among groups is consistent with a previous report,¹⁵ and may reflect both pharmacokinetic and pharmacodynamic factors. Redistribution of midazolam and alfentanil may have occurred during the maintenance phase, lessening the interaction with propofol. This might be particularly important for alfentanil which has a more prominent propofol-sparing effect for responses to noxious stimulation, such as cervical dilatation, than for hypnosis.¹⁴

The haemodynamic effect of midazolam-propofol coinduction has been inconsistent.^{9,10,15} This study produced no clinically important haemodynamic differences among groups.

The extra delay of two minutes to eye-opening in the presence of midazolam in this study is unlikely to be clinically relevant. Commonly, patients regain consciousness with the stimulation of being transferred from the operating table to a stretcher.

This study showed no delay in time to discharge-readiness. Times to discharge²² or discharge-readiness²³ typically have large standard deviations, even with very large patient numbers.²⁴ We chose to use a discharge scoring system that was designed specifically for ambulatory patients, rather than using hospital discharge time which can be delayed for non-medical scheduling reasons. This discharge scoring system has been used in over 30,000 patients,²⁵ and a validation of its use is in press.*

DeLucia and White¹⁵ showed delayed awakening and similar times to discharge with higher dose (5 mg) midazolam. The lack of difference in awakening time with low-dose midazolam (2 mg) versus placebo in that study could have resulted from redistribution or elimination of midazolam during surgery, since duration of surgery averaged an hour. The present study clarifies the role of midazolam on recovery after a much shorter anaesthetic.

We conclude that in the dosage range used, and in the presence of alfentanil, midazolam causes a slight delay in eye-opening, but does not delay time to discharge-readiness after anaesthesia for D+C.

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*Dr. F. Chung, personal communication.

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