Midazolam premedication and thiopental induction of anaesthesia: interactions at multiple end-points†

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We have studied the effects of midazolam premedication on multiple anaesthetic end-points (hypnotic, loss of verbal contact (LVC); motor, dropping an infusion flex or bag (DF); analgesic, loss of reaction to painful stimulation (LRP); and EEG, attainment of burst suppression (BUR)) during induction by slow thiopental infusion at a rate of 55 mg kg^{-1} h^{-1}. Patients received midazolam 0.05 mg kg^{-1} i.v. (group TM, $n=12$) or no midazolam (group T0, $n=13$). ED_{50} and ED_{95} values and group medians for times and doses at the end-points were measured. Midazolam premedication reduced significantly thiopental ED_{50} and ED_{95} values at all end-points (exception for ED_{95} for BUR). Potentiation was greatest for the motor end-point (dropping the infusion bag (DF)) (ED_{95} +52%, ED_{50} +23%, median +39%), and smallest for painful stimulation (LRP) (median +18%; ED_{50} +13%). For LRP and DF, premedication was associated with significant, non-parallel increases in the slope of the thiopental dose–response curves, resulting in marked potency ratio changes from ED_{50} to ED_{95} (LRP +31%, DF +29%). There were no such increases for LVC or BUR. The interaction between midazolam and thiopental varied with the anaesthetic end-point and may also depend on the dose of thiopental. Our data suggest that the mechanism of interaction between midazolam premedication and thiopental was different for motor effects or analgesia (DF, LRP) compared with hypnotic effects or cortical depression (LVC, BUR), in agreement with the different central nervous system substrates underlying these distinct anaesthetic end-points.

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The use of drug combinations is popular in clinical anaesthetic practice. Combinations can increase the spectrum of action of anaesthesia and reduce side effects by decreasing the required dose of individual drugs by synergism or additive effects. As anaesthesia results from the summation of multiple central nervous system effects, investigations of anaesthetic drug interactions should ideally include multiple end-points relevant to the anaesthetic state.

The majority of studies defining drug interactions for anaesthesia have involved i.v. bolus administration. Typically, they provide dose–effect relationships for a single clinical end-point, such as the hypnotic end-point of loss of verbal contact or the eyelash reflex, examined in a fixed time window. Such studies do not generally provide information on clinically important time elements or allow comparison of interactions at multiple end-points. Infusion induction titration models[1 2] may represent an interesting alternative for the study of drug interactions. They include the clinically important time element, allow easy evaluation and comparison of multiple end-points in one patient and session, and provide clinically relevant results applicable to bolus dosing.[2]

Midazolam, as an i.v. premedicant or co-inductant, has been shown to result in hypnotic synergism with thiopental[3 4] during induction of anaesthesia using bolus methodology. To our knowledge, this interaction has not been studied for

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multiple end-points relevant to anaesthesia. In this study, we have investigated the interaction between midazolam and thiopental at multiple anaesthetic end-points using an infusion induction titration model.

Patients and methods

After obtaining approval from the Institutional Scientific Review Board and Ethics Committee and written informed patient consent, we studied prospectively 23 ASA I–II patients undergoing herniated intervertebral disc surgery. Exclusion criteria included cardiovascular and neurological disease, diabetes mellitus, those receiving chronic hypnotic or analgesic medication, and abnormal body weight (more than 20% deviation from ideal). Patients were allocated by random table number to receive midazolam 0.05 mg kg^{-1} i.v. (group TM; n=12) or no midazolam (group T0; n=11) in the anaesthesia room, 20 min before induction of anaesthesia by someone not involved in the study. The investigators and those interpreting the electroencephalogram (EEG) were unaware of the presence or absence of premedication. After applying the monitoring devices and preoxygenation by face mask, anaesthesia was induced by continuous i.v. infusion of 2.5% thiopental by syringe pump (Perfusor, Braun Melsungen, Germany) at a rate of 55 mg kg^{-1} h^{-1} until the appearance of burst suppression in the EEG. From induction onwards, lung ventilation was assisted or controlled by face mask ($F_{I_{O_2}}$= 1; $S_{p_{O_2}}$ >95%; end-tidal carbon dioxide partial pressure= 4–5 kPa).

Continuous EEG recording (16-channel, Medilog, Oxford, UK) was started 5 min before i.v. premedication and continued until the study ended via a standard (10-20 system) 16-channel electrode montage. During the same period, arterial pressure and heart rate were measured at 1-min intervals. The following end-points were measured and marked on the EEG record: (1) hypnotic, loss of verbal contact (LVC), by questioning every 10 s 'please open your eyes'; (2) motor, drop flex (DF), time at which a 500-ml plastic infusion bag held in the hand was dropped; (3) analgesic, loss of reaction to pain (LRP), time at which purposeful somatic movement to transcutaneous constant current tetanic electric stimulation by a nerve stimulator ceased (nerve stimulator, Digistim; Biometer A/S, Copenhagen, DK). Stimulation was started after LVC and DF, applied via self-adhesive electrodes on the side of the index finger at 100 Hz, 40 mA and 0.2 ms, and avoided stimulating major nerves; and (4) electroencephalographic, burst suppression (BUR) (first occurrence of 3 s isoelectricity between bursts in the dominant side, frontoparietal channel).

Time, cumulative thiopental dose, arterial pressure and heart rate were noted at attainment of each end-point. When the patient ceased reacting to pain (LRP), vecuronium 0.1 mg kg^{-1} was given and the trachea intubated after achieving EEG burst suppression (BUR). Infusion of thiopental was discontinued, the study ended and anaesthesia continued at the discretion of the anaesthetist.

Statistical analysis

Based on the data of Naguib and Sari-Kouzel[5] for ED_{50} values, we estimated the group size necessary to detect a clinically relevant difference of 20% in ED_{50} values for loss of verbal contact to be 11 (alpha=0.05; beta=0.1; two-tailed). Because of the limited applicability of these data, we pre-planned *post hoc* power testing based on doses at LVC and BUR. For all statistical analysis, $P<0.05$ was considered significant, and multiple testing was Bonferroni-corrected, as appropriate. Haemodynamic data were compared using repeated measures ANOVA, followed by *post hoc* Tukey testing, as needed. Physical characteristics and median times and doses at the end-points were compared using the Mann–Whitney U test or Wilcoxon signed rank test, as appropriate. The ratios of the doses at DF, LRP and BUR compared with LVC were calculated (e.g. dose at LRP divided by dose at LVC) and medians compared between groups using non-parametric testing, as before. Dose–response relationships were studied by probit-transformation of the percentage response rate (percentage of patients attaining end-point) followed by multiple linear regression analysis of the resulting probit response–log dose curves.[6] ED_{50} and ED_{95} values were calculated and 95% confidence intervals estimated. For intra- and inter-group analysis, the significance of ED_{50} and ED_{95} differences was determined using a paired or unpaired Student's t test, as appropriate, as were comparisons of parallelism of regression curves via regression coefficients and the significances of parallel curve shifts via intercepts. $P<0.05$ was considered statistically significant. All testing was carried out using the Statistica for Windows software package (version 4.5; Statsoft Inc., Tulsa, OK, USA).

Results

There were no complications during the study. The groups were similar in age (group T0, mean 50 (range 21–78) yr; group TM 47 (26–74) yr), weight (group T0, mean 69 (SD 13); group TM, 78 (9) kg) and sex distribution (M:F: group T0, 7:4; group TM, 10:2). There were no differences between premedicated and unpremedicated patients for median times to the end-points, doses required to reach the end-points or mean haemodynamic values at the end-points (Table 1). Within groups, mean arterial pressure and heart rate were similar at all end-points, as were median times to and doses at the hypnotic (loss of verbal contact; LVC) and motor (dropping the infusion bag; DF) end-points. For both premedicated and unpremedicated patients, the analgesic end-point (loss of reaction to pain; LRP) differed significantly from the hypnotic (LVC) or EEG (attainment of burst suppression; BUR) end-points for median time and dose ($P<0.05$). Median potency ratio (i.e. median dose at a given end-point for premedicated patients divided by the

Table 1 Mean arterial pressure (MAP) and heart rate (HR), and median times and doses at the end-points. Data are mean (SD) (haemodynamic data) or median (95% confidence intervals) (times and doses) at the end-points LVC=loss of verbal contact, DF=drop flex, LRP=loss of response to pain and BUR=EEG burst suppression. T0=no midazolam premedication; TM=midazolam premedication. There were no significant differences between groups at the various end-points. *$P<0.05$ compared with LVC value, †$P<0.05$ compared with LRP value

Group	End-point	MAP (mm Hg)	HR (beat min^{-1})	Time (s)	Dose (mg kg^{-1})	Dose ratio (T0:TM)
T0	Control	104 (14)	82 (21)	0	0	—
TM	Control	94 (14)	83 (14)	0	0	
T0	LVC	98 (14)	81 (22)	280 (128–390)†	4.3 (2.0–6.0)†	1.26
TM	LVC	96 (11)	85 (11)	221 (120–427)†	3.4 (1.8–6.5)†	
T0	DF	99 (16)	83 (17)	282 (120–430)†	4.3 (1.8–6.6)†	1.39
TM	DF	95 (11)	86 (10)	204 (115–360)†	3.1 (1.8–5.5)†	
T0	LRP	99 (13)	85 (15)	480 (287–1063)*	7.3 (4.4–16.2)*	1.18
TM	LRP	103 (16)	89 (11)	409 (272–1408)*	6.2 (4.2–21.5)*	
T0	BUR	92 (12)	88 (15)	940 (442–1302)†	14.4 (6.8–19.9)†	1.25
TM	BUR	98 (17)	92 (13)	750 (256–1847)†	11.5 (3.9–28.2)†	

Table 2 Median end-point dose ratios compared with LVC. Results are medians of the ratio 'end-point dose divided by LVC dose' (95% confidence intervals). LVC=Loss of verbal contact, DF=drop flex, LRP=loss of response to pain and BUR=EEG burst suppression. T0=No midazolam premedication; TM=midazolam premedication. There were no significant differences between groups

Group	DF:LVC	LRP:LVC	BUR:LVC
T0	1.1 (0.5–1.3)	1.9 (1.3–3.4)	3.2 (2.5–6.3)
TM	0.9 (0.7–1.5)	1.9 (1.3–4.2)	4.2 (1.2–4.5)

median dose at the same end-point for unpremedicated patients) was lowest for LRP and greatest for DF. Median ratios of doses DF/LVC, LRP/LVC and BUR/LVC were similar in the presence or absence of midazolam (Table 2).

Thiopental ED_{50} and ED_{95} values derived from the probit response–log dose curves (Fig. 1) are given in Table 3. Midazolam premedication significantly potentiated thiopental ED_{50} and ED_{95} values at all end-points, except the ED_{95} for BUR which just failed to reach significance. In both groups, ED_{50} and ED_{95} values for the hypnotic (loss of verbal contact; LVC) and motor (dropping the infusion bag; DF) end-points were similar, whereas the ED_{50} and ED_{95} values for the analgesic end-point (loss of reaction to pain; LRP) were distinct from those for the hypnotic (LVC) and EEG (attainment of burst suppression; BUR) end-points. The potentiating effect of midazolam was greatest for the motor end-point (DF); the effect on ED_{50} (but not ED_{95}) was smallest for analgesia (LRP). Midazolam premedication caused significant non-parallel steepening of the thiopental dose–response curves for LRP and DF ($P<0.01$). For these end-points, there were large increases in potency ratios (i.e. end-point doses for premedicated divided by those for unpremedicated patients) of almost one-third from ED_{50} to ED_{95}. In contrast, for LVC and BUR, the dose–response curves remained parallel and without significant shift after midazolam, with only minor changes in potency ratios from ED_{50} to ED_{95}. The slopes of the LVC and DF dose–response curves were different for unpremedicated patients, becoming similar with midazolam premedication. In both groups, the slopes of the thiopental dose–response curves for LVC were similar to those for LRP and BUR.

Based on ED_{50} values for the hypnotic (loss of verbal contact; LVC) and EEG (attainment of burst suppression; BUR) end-points individually, the number of patients included (i.e. $n=11$ per group) gave the study a more than adequate power to detect changes of 10% in end-point dose at alpha=5% and beta=10% (two-tailed).

Discussion

Midazolam premedication potentiated thiopental at all anaesthesia end-points. Potentiation was greatest for the motor end-point (dropping the infusion bag; DF), and increased with thiopental dose for motor (DF) and analgesic (loss of reaction to pain; LRP) end-points, but not for the hypnotic (loss of verbal contact; LVC) or EEG (attainment of burst suppression; BUR) end-point. However, premedication did not affect the dose relationships of end-points relative to the hypnotic end-point (e.g. dose at LRP divided by dose at LVC). The interaction between midazolam premedication and thiopental was dependent on the anaesthetic end-point, but may also be affected by the dose of thiopental. We consider these differences to reflect different substrates inside (and perhaps outside) the central nervous system involved in attainment of motor, analgesic and hypnotic or electroencephalographic end-points in anaesthesia.

To our knowledge, the effect of midazolam premedication on multiple end-points during induction of anaesthesia by thiopental infusion has not been studied. Comparisons of induction of anaesthesia by thiopental infusion are available only for unpremedicated patients. The study of Avram and colleagues[1] of 30 males and 30 females, aged 18–83 yr, implied ED_{50} values (DF=4.0; BUR=11.5 mg kg^{-1}) close to the results of our study (DF=3.8; BUR=13.0 mg kg^{-1}), but with an infusion at approximately twice our rate (150 mg min^{-1}). Mehta, Bradley and Kissin,[7] studying 96 female patients, reported a higher induction dose of 5.3 mg kg^{-1} during a slower infusion (30 mg kg^{-1} h^{-1}). The differences reflect varying infusion rates and different study designs, including different definitions of, and methodologies for, detecting the end-points.

All other comparisons derive from thiopental bolus induction studies and are not directly comparable with the

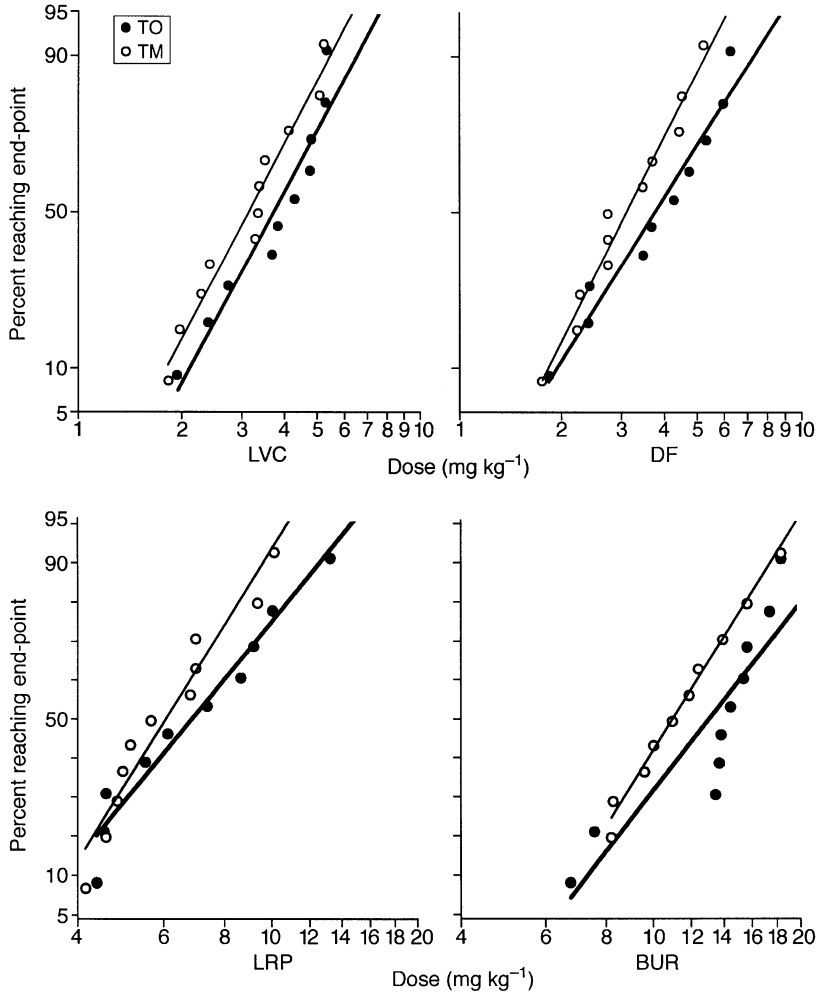

Fig 1 Multiple linear regression curves for log dose thiopental *vs* probit response at hypnotic (loss of verbal contact; LVC), motor (dropping of infusion bag; DF), analgesic (loss of reaction to pain; LRP) and EEG (attainment of burst suppression; BUR) end-points. T0=No midazolam premedication; TM= midazolam premedication. The characteristics of the curves are given in Table 3.

Table 3 Results of log dose *vs* probit response multiple linear regression analysis. Slopes and intercepts are mean (SD); ED_{50} and ED_{95} values are median (95% confidence intervals). T0=No midazolam premedication; TM= midazolam premedication. LVC=Loss of verbal contact; DF=drop flex; LRP=loss of response to pain; BUR=EEG burst suppression. To show the interaction between increasing dose of thiopental and midazolam premedication, potency ratios (T0:TM) for ED_{50} (RED_{50}) and ED_{95} (RED_{95}) values are included. *P* values refer to the fit of the curve. *Significantly different from TM value, †significantly different from LVC value ($P<0.05$). ‡T0 and TM curves were statistically parallel, no significant shift (intercept); §curves were not parallel

Group	End-point	*r*	r^2	*P*	Intercept	Slope	ED_{50}	RED_{50}	ED_{95}	RED_{95}
T0‡	LVC	0.96	0.91	0.00001	−3.0 (0.9)	2.3 (0.6)	3.7 (3.4–4.1)*	1.19	7.5 (6.7–10.0)*	1.14
TM	LVC	0.98	0.96	0.000000	−2.7 (0.7)	2.3 (0.7)	3.1 (3.0–3.3)		6.6 (5.5–7.2)	
T0§	DF	0.98	0.95	0.000001	−2.6 (0.6)	1.9 (0.3)†	3.8 (3.5–4.0)*	1.23	9.3 (7.4–11.0)*	1.52
TM	DF	0.99	0.97	0.000000	−2.7 (0.7)	2.4 (0.3)	3.1 (3.0–3.3)		6.1 (5.4–6.7)	
T0§	LRP	0.98	0.95	0.000001	−4.1 (0.9)	2.1 (0.6)	6.9 (6.4–7.4)*	1.13	15.4 (13.5–18.2)*	1.44
TM	LRP	0.97	0.94	0.000001	−5.0 (1.3)	2.8 (0.7)	6.1 (5.7–6.4)		10.7 (10.0–12.2)	
T0‡	BUR	0.89	0.80	0.0005	−5.7 (3.2)	2.2 (1.3)	13.0 (11.2–15.2)*	1.24	28.1 (22.2–44.7)	1.11
TM	BUR	0.94	0.88	0.000017	−4.5 (2.0)	1.9 (0.7)	10.5 (9.3–11.8)		25.3 (20.1–36.6)	

methodology used in our investigation. Using bolus study designs, Tverskoy and colleagues,[3] Short, Galletly and Plummer,[4] Naguib and colleagues,[5 8] van Hemelrijck and colleagues[9] and Kissin and Vinik[10] reported ED_{50} values for induction of anaesthesia in the range 2–3 mg kg^{-1} for thiopental alone, slightly lower than our values (LVC=3.7; DF=3.8 mg kg^{-1}). Short, Galletly and Plummer[4] quoted an 'anaesthetic' thiopental ED_{50} of 3.6 mg kg^{-1} (our LRP, 6.9 mg kg^{-1}), reduced by half to 1.8 mg kg^{-1} after premedication with midazolam 0.1 mg kg^{-1} (our LRP, 6.1 mg kg^{-1}; reduction of one-ninth with midazolam 0.05 mg kg^{-1}). Kissin and Vinik studied 50 patients and reported a reduction in the hypnotic ED_{50} of thiopental by one-third from 2.4 to 1.6 mg kg^{-1} after premedication with midazolam

0.02 mg kg^{-1},[10] while Short, Galletly and Plummer, investigating 300 patients,[4] found their thiopental–midazolam combination to be 1.8 times more potent than expected for the drugs administered individually. Kissin and Vinik[10] described hypnotic potentiation by midazolam to be greater at higher thiopental doses (e.g. ED_{95} *vs* ED_{50}),[10] in contrast with the results of Short, Galletly and Plummer[4] and ourselves which showed no change from ED_{50} to ED_{95} for hypnosis.

End-points in infusion models are determined during a running infusion, while bolus induction end-points are measured after application of a fixed dose. Thus infusion models are susceptible to overshoot and tend to report higher doses than bolus models.[2] Comparisons of the results of our study with those of bolus studies are complicated further by: (1) absence of information on the biophase drug concentrations achieved and (2) the fact that premedication, thiopental injection and the study end-points are further apart in our study than in the bolus studies quoted. In the bolus studies, midazolam effect-site concentrations are likely to still be increasing at the end-point under investigation, while in our study they are likely to be decreasing slowly during all end-points.[11–14] Thiopental effect-site concentrations, which are increasing for both designs, increase more slowly in an infusion model, but with smaller differences in plasma concentrations.[11–14]

We chose an infusion induction titration design because multiple end-points can be studied in the same patient and session, and because for thiopental, such a model is demonstrably efficient at deriving timing and bolus dose results relevant to clinical use.[2] The design allows conclusions about clinically important end-point timing not available from bolus administration studies (end-points sought in fixed time windows). A potential methodological problem with this design is the presence of infusion rate dependence. Our infusion rate for thiopental is midway in the range of rates (i.e. 40–150 mg min^{-1}) considered not to significantly affect median hypnotic doses.[11] Dependence of dose–response relationships on infusion rate has been reported for rates of 150–1200 mg min^{-1}.[11] The end-points loss of verbal contact (LVC) and dropping an infusion bag (DF) are well established as relevant to induction of anaesthesia,[1–5 7–10] and the end-point loss of reaction to pain (LRP), determined using loss of reaction to tetanic electrical stimulation, has been demonstrated to be a good surrogate measure for the presence of surgical anaesthesia.[5] The electroencephalographic end-point of attainment of burst suppression (BUR) is of particular interest in the intensive care setting.

Regarding clinical relevance, our results predict that, within each study group, thiopental doses for achieving hypnotic (LVC) and motor (DF) end-points during induction of anaesthesia are comparable. However, the doses of thiopental (and times) necessary to achieve adequate surgical anaesthesia (loss of reaction to pain; LRP)[15] are clearly distinct from, and about twice as high as, those necessary to attain loss of consciousness. This relationship is unaffected by midazolam premedication. Our results also suggest that in the presence of EEG burst suppression (BUR), patients can safely be assumed to be adequately analgesic for surgical and non-surgical nociception.

Barbiturates and benzodiazepines interact through their effects on the gamma-amino butyric acid (GABA) receptor,[16 17] with barbiturates allosterically enhancing benzodiazepine binding to the $GABA_A$ receptor.[18 19] The analgesic and motor (e.g. myorelaxant) effects of midazolam appear to have a mainly spinal $GABA_A$ receptor substrate, while hypnotic–sedative actions are more supraspinal in origin and may be mediated in part elsewhere than at the $GABA_A$ receptor.[20–24] The varying potentiating interaction of thiopental with midazolam premedication according to end-point and thiopental dose (i.e. ED_{50} *vs* ED_{95}) is most likely a result of the different CNS structures (e.g. cortical, subcortical, spinal) and hence biophases involved in these anaesthetic end-points. Each of these biophases has its own pharmacokinetic (biophase access) and pharmacodynamic (receptor populations) profile, thus leading to different patterns of drug interaction for the anaesthetic end-points studied. While hypnotic and EEG burst suppression end-points probably depend exclusively on cortical and higher subcortical structures, the analgesic and motor end-points are likely to involve major contributions from brainstem and spinal systems also. In this context, it is interesting to note that while the thiopental dose–response curves for end-points probably involving only supratentorial structures (hypnotic/LVC, EEG/BUR) remain parallel and unshifted with premedication (suggesting no change in the underlying mechanism), those likely to involve both supra- and infratentorial (i.e. brainstem, spinal cord) sites (motor/DF, analgesia/LRP) are significantly shifted in a non-parallel manner, suggesting a change in underlying pharmacological mechanisms.

In summary, midazolam premedication potentiated thiopental for multiple anaesthetic end-points during infusion for induction of anaesthesia. However, these effects varied according to the anaesthetic end-point and the thiopental dose chosen. Further investigations are needed to elucidate the mechanisms of anaesthetic drug interactions for multiple anaesthetic end-points involving different biophases.

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