Propofol infusion and the suppression of consciousness: dose requirements to induce loss of consciousness and to suppress response to noxious and non-noxious stimuli


SUMMARY
We have defined the infusion dose requirements of propofol to suppress consciousness and response to a variety of graded non-noxious and noxious stimuli in 84 unpremedicated patients aged 16-40 yr and 32 patients aged 41-65 yr. They were allocated to receive one of five loading dose-infusion schemes designed to establish stable conditions covering the range from wakefulness, through sedation, to loss of consciousness and anaesthesia. At 10 and 20 min after the loading dose, each patient’s response to a graded series of stimuli was recorded. Probit analysis was used to derive mean values (95% confidence interval) for the \( E_{50} \) and \( E_{95} \) (as final infusion rate) for loss of response to verbal command at 4.9 (4.7-5.1) mg kg\(^{-1}\) h\(^{-1}\) and 7.9 (7.3-8.8) mg kg\(^{-1}\) h\(^{-1}\), respectively, in the young group and 4.2 (4.0-4.4) mg kg\(^{-1}\) h\(^{-1}\) and 5.8 (5.4-6.4) mg kg\(^{-1}\) h\(^{-1}\), respectively, in the older group. In both groups the dose-response curves for suppression of proprioception, finger counting and perception of light touch in conscious patients were shifted to the left of the curves for loss of consciousness and eyelash reflex. Dose-response curves for noxious stimuli were shifted to the right of those for loss of consciousness. (Br. J. Anaesth. 1994; 72: 29-34)

KEY WORDS
Anaesthetics, i.v.; propofol.

Propofol has gained wide acceptance as a drug suitable for both induction and maintenance of anaesthesia. Previous studies have defined the dose requirements for infusions of propofol in combination with nitrous oxide in patients premedicated with morphine [1] or a benzodiazepine [2], or during total i.v. anaesthesia with alfentanil [3], using quantal somatic motor responses or visceral motor responses (lower oesophageal motility) [4] as indices of adequacy of anaesthesia. Several studies have shown that smaller infusion doses of propofol and other i.v. anaesthetics are required with increasing patient age [5], a finding supported also by studies of single doses of propofol for induction of anaesthesia [6].

Although these studies indicated the dose requirements to suppress movement in response to a surgical stimulus, they give no indication of the relative dose to suppress consciousness. Schuttler [7] compared four i.v. anaesthetics, including propofol, during infusion schemes designed to produce steadily increasing blood concentrations. These elegant studies allowed correlations to be made between drug infusion rate or blood concentration, and loss of consciousness and electroencephalographic indices, but only under conditions of rapidly changing blood concentrations of the i.v. anaesthetics.

We wished to determine the dose–response relationships for infusions of propofol alone to suppress consciousness under conditions of stable anaesthesia. We therefore used an infusion scheme [8] designed to achieve and maintain stable blood concentrations of propofol [4, 9], and determined the rate of propofol infusion required to suppress consciousness as defined by loss of response to a verbal command, suppression of the eyelash reflex, other responses and the effect of patient age on these relationships.

PATIENTS AND METHODS
We studied 84 patients (ASA grades I or II) scheduled to undergo a variety of minor surgical procedures. They gave informed consent to the study, which had been approved by the District Ethics Committee. No patient exceeded his/her ideal body mass index by more than 15%. Patients were allocated to one of two sets according to their age: a young set aged 16-40 yr and an older set aged 41-65 yr. Within these sets, we allocated sequentially 52 patients in the young set to one of five groups (A-E), and 32 patients in the older set to one of four groups (A-D). Each group within a set received a
different infusion scheme for propofol (table I) designed to achieve and maintain a stable predetermined blood concentration within 5 min [8]. As this scheme had been shown in four earlier studies [3, 4, 8, 9] to achieve and maintain stable blood propofol concentrations, we did not attempt to measure blood concentrations of propofol in the present study.

Patients were not premedicated. They were studied in the anaesthetic room before the commencement of their proposed anaesthesia. Heart rate (ECG), and oxyhaemoglobin saturation were monitored throughout the study. Arterial pressures were recorded before the infusion scheme was started and after the 20-min observations, but were not made in between, in order to avoid stimulating the patient at crucial periods of the study. An i.v. cannula was inserted under local anaesthesia. The predetermined loading dose of propofol was given and the first stage of the propofol infusion started using a 50-ml syringe in a calibrated IVAC 700 syringe driver. After 10 min the infusion rate was reduced (table I) and maintained at the new rate until just after the measurements made at 20 min. To facilitate comparisons with similar work published previously from the same department, and the paper accompanying this one [10], we have quoted final infusion rates as those which were used (table I) beyond 20 min, after the study had been completed. The rationale for this was based on the premise that the loading dose and first two infusion rates in each scheme are designed to increase the blood concentration to a predetermined value by filling the initial volume of distribution and compensating for the transfer of drug from this volume to peripheral tissues. After 20 min, the final infusion rate determines the blood concentration for a given whole body clearance of the relevant drug, and is therefore the most important marker of the infusion scheme.

At 10 and 20 min, patients were asked “Can you hear me?” A positive reply prompted more complex tasks or questions, detailed in table II (positive response). Joint position sense (proprioception) was tested in the index finger of the non-cannulated hand. If there was no response to command (negative response), the eyelash reflex was tested and then increasingly noxious stimuli applied and the corneal reflex tested.

All observations were made by one investigator to ensure consistency in the testing. After the tests at 20 min, the infusion of propofol was stepped down to the final infusion rate, and patients received additional supplementary general anaesthesia as appropriate for the planned surgery.

Probit analysis [11] (SAS for PC, version 6.04, SAS Institute, Cary NC, U.S.A.), was performed on each set of observations and used to estimate the “final” infusion rate to suppress the relevant response in 50% (ED$_{50}$) and 95% (ED$_{95}$) of subjects. The 95% confidence interval for each dose–response curve was also calculated. Mean differences for ED$_{50}$ and ED$_{95}$ were considered to be significantly different at the 5% level if the 95% confidence intervals did not overlap [12, 13].

RESULTS

There were no significant differences in age, weight or gender distribution between the groups within age-split sets, or in weight or gender distribution between sets. The mean age of the young set was 26.6 (SD 6.3) yr; that of the older set was 51.3 (7.6) yr ($P < 0.001$) (table III).

No patient in group D of the older set responded to command, so the greatest infusion rate scheme (group E) was not studied in this set. The final infusion rates, calculated by probit analysis, required to abolish the selected responses at 10 and 20 min in the two age sets are shown in table IV.

In the young set, the ED$_{50}$ values for suppression of proprioception and verbal response at 20 min were significantly smaller than those at 10 min, whereas the values for pinprick were not significantly different. There were no significant differences for ED$_{95}$ values at 10 and 20 min.

In the older set, the ED$_{50}$ values for suppression of verbal responses and pinprick at 20 min were
significantly smaller than those at 10 min, whereas the values for proprioception were not significantly different. There were no significant differences for ED₆₀ values at 10 and 20 min.

Table V shows the calculated final infusion rates required to abolish responses at 20 min for both age sets. In both young and old sets, there was a progressive increase in both ED₆₀ and ED₈₀ values from proprioception, through verbal response to painful stimuli. This indicates that the dose-response curves showed a generally parallel shift to the right. Thus less propofol was required to suppress proprioception and finger counting than for suppression of the response to verbal command. The propofol doses required to suppress light touch, response to command and eyelash reflex were not significantly different. Larger doses of propofol were required to suppress the painful modalities (pinprick and supraorbital pain). The corneal reflex was not suppressed in any patient in either young or older age set.

No patient was distressed in any way by the procedure and most had no clear explicit recall of the responses which they made, even though they were conscious at the time.

**DISCUSSION**

The aim of this study was to determine the doses (infusion rates) of propofol required to suppress consciousness and other sensory modalities (light touch, proprioception, ability to count fingers) related to the conscious state, under stable conditions covering the range from wakefulness, through sedation, to loss of consciousness and anaesthesia. Because suppression of the eyelash reflex appears to occur later than loss of consciousness during induction of anaesthesia with propofol [14], we also wished to determine if greater infusion rates of propofol were required to suppress the eyelash reflex than to suppress consciousness.

We have established the feasibility of measuring
quantal responses for loss of consciousness and other non-noxious stimuli during a period of 20 min of propofol infusion, in both this and the accompanying study [10]. The propofol infusion was, in effect, a prolonged induction phase, reaching a state of stability which altered very little, in terms of the patient's responses, between 10 and 20 min. Although the results of the present study do not enable us to be certain that no further changes would have occurred had the infusions been continued for a longer period, the results of the subsequent study [10], over 30-45 min under similar conditions, confirm this assumption.

Pharmacological effects must be related to the concentration of free drug in the biophase, the immediate extracellular environment of the appropriate cell. It is not currently feasible to measure directly such a concentration in the vicinity of those cells in the cerebral cortex, where one presumes the effects of anaesthetics such as propofol to be exerted [15]. To measure pharmacodynamic responses, therefore, one has to rely on achieving a quasi-steady state by maintaining a stable blood concentration of the relevant drug, based on the premise that there will be an equilibrium between the blood and biophase concentrations after some period of time, and that the responses of the brain will be determined by those concentrations. The stability of a response over a period of time can then be taken to imply a stability of the biophase concentration.

The foregoing argument was the premise upon which the studies by Tackley and colleagues [16] and Roberts and colleagues [8] were designed to develop infusion schemes to achieve a predetermined blood concentration within 2-5 min of the induction of anaesthesia, and maintain such a concentration stable over sufficient time (20-30 min) to allow measurement of dose-response curves. Apart from its initial validation [8], this stepped infusion scheme has been used in four subsequent studies [3, 4, 10, 17] in adults aged 18-65 yr and in children aged 3-12 yr [18]. Each of these studies has confirmed both the linearity of the relationship between final infusion rate and blood concentration of propofol and the stability of this relationship for periods up to 2 h. Nevertheless, we found evidence in both the young and older set of patients that ED₉₀ values for loss of verbal response were significantly smaller at 20 min than at 10 min, implying that we may not have achieved stable conditions during the first 10 min. As we consider the measurements made 20 min after the start of the infusion as more likely to be the most stable, we would not place too much emphasis on this finding. The only question which cannot be answered is whether or not there would have been a further change over the subsequent 10 min. In a subsequent study [10], we found reasonable evidence that blood concentrations were stable between 30 and 45 min, that the electroencephalogram was stable, and that the ED₉₀ for loss of verbal response was approximately the same as in the present study, despite the wider age range of patients.

We used the patient's loss of response to command as the primary end-point to determine the threshold for suppression of consciousness, the assumption being that response to command indicated consciousness or awareness, and that lack of response to command indicated unconsciousness. Although we can conceive of an order of degrees of consciousness implicit in the classification of varying degrees of sedation when i.v. [19-22] or volatile anaesthetics [21, 22] are administered under "stable" conditions in intensive therapy, there have been no previous studies during stable anaesthesia. Loss of consciousness is a threshold, or all-or-none phenomenon [23], which has greater importance for the patient than other reference points for the state, or degree, of anaesthesia. Patients may be conscious, as defined by appropriate response to question or command, yet have no subsequent explicit recall [24] of such events. The evidence for implicit recall, defined as an ability to recall events under the influence of hypnosis [25] or to identify "hidden commands" [26], is ambiguous. We did not test specifically for either explicit or implicit recall, although few of the patients who responded to command could remember having done so.

The concept of a minimum infusion rate (MIR, ED₉₀) of an i.v. anaesthetic, and its associated blood concentration (EC₉₀) under conditions of stable anaesthesia, required to suppress movement (somatic motor) in response to a surgical incision is well established as equivalent to the minimum alveolar concentration (MAC) of an inhalation anaesthetic [27, 28]. The values for ED₉₀, ED₉₀, EC₉₀ and EC₉₅ for propofol infusions to suppress somatic motor (movement) responses have been determined in combination with 67% nitrous oxide after various premedications [1, 2] and during total i.v. anaesthesia with alfentanil in adults [3] and children [18]. Although these dose and concentration requirements provide comparisons of equipotency comparable to MAC for inhalation anaesthetics, they give no indication of the relative values for propofol infusions required to suppress consciousness. The studies by Schuttler [7] referred to earlier were conducted under conditions of rapidly changing infusion rate, and cannot be compared with the present study in terms of dose requirement to suppress unconsciousness under conditions of stable infusion rates designed to establish stable blood and brain concentrations.

While the study has clearly defined the ED₉₀ and EDₐ values for loss of consciousness under propofol anaesthesia in patients from two separate age groups, there remain difficulties in making comparisons with other studies in which propofol has been combined with other agents such as nitrous oxide or alfentanil. For instance, it is difficult to predict how much less propofol might be needed to suppress consciousness in the presence of either of these other agents. There are no comparable data for inhalation anaesthetics.

The significant decrease in ED₉₀ for suppression of consciousness in the older set of patients, compared with the younger set, is in general agreement with all our previous studies in which the effect of age on dose requirement has been established for propofol [5] and for Althesin and methohexitone [29]. Although there seems to be a general decrease for all the measured responses in
We are grateful to Dr S. Raftery for his assistance with the statistical analysis.

Within each age set, there were clear and significant differences between the ED_{50} values for the responses of the conscious patients (propridation, finger counting) and that for loss of consciousness (verbal response) and eyelash reflex, and in the unconscious patients the responses to noxious stimuli (proprioception, orbital pain and pinprick) were markedly less steep than for all the other sensory modalities, a finding in keeping with those of the accompanying study [10].

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These indicate a progressive shift of the dose–response curves for each stimulus to the right with increasing final infusion rates of propofol, the effects being most marked at the mid-points (ED_{50}) of the dose–response curve, and least marked at the ED_{95} and greater (fig. 1).

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REFERENCES
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