Optimum rate of administration of propofol for induction of anaesthesia in rats

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Summary

Twenty rats received propofol 2.5, 5, 10 or 20 mg kg\(^{-1}\) min\(^{-1}\) i.v. Brain activity was monitored using the electroencephalogram (EEG). As the end-point for induction of anaesthesia we used a burst suppression period of 1 s or longer. At a fast (20 mg kg\(^{-1}\) min\(^{-1}\)) rate of administration, the induction dose was significantly larger compared with a slower rate (10 mg kg\(^{-1}\) min\(^{-1}\)). At a slow rate of administration (2.5 mg kg\(^{-1}\) min\(^{-1}\)), the induction dose was also significantly larger compared with a rate of 10 mg kg\(^{-1}\) min\(^{-1}\). In spite of different dose requirements at different rates of administration, duration of anaesthesia was not significantly different. (Br. J. Anaesth. 1994; 73: 692–694)

Key words

Anaesthetics i.v., propofol. Rat. Anaesthetic techniques, i.v.

The importance of injecting propofol slowly in order to avoid overdose and minimize cardiorespiratory depression is widely accepted. It has been shown that the induction dose of propofol is reduced at slow infusion rates compared with fast [1]. However, opposite results were obtained in mice when propofol was administered rapidly in the Cremophor EL formulation [2]. From this one might suspect that the speed of injection has different effects on induction dose depending on the choice of injection rates. The rate-dependency of the induction dose for other i.v. anaesthetics, such as thiopentone and hexobarbitone, has been investigated thoroughly showing that the rate of administration may be optimized [3].

The purpose of this study was to determine the rate-dependency of induction dose requirements of propofol, including very slow rates of administration.

Methods and results

After obtaining approval from the local Animal Research Committee, we studied 20 approximately 3-month-old, male Sprague–Dawley rats (MOL:SPDR Mollegaard, L1 Skensved, Denmark). The rats were housed three per cage and given food and water ad libitum. The rats were allocated randomly to receive propofol 2.5, 5, 10 or 20 mg kg\(^{-1}\) min\(^{-1}\) as a continuous infusion using a Sage 355 (Orion Research Inc.) syringe pump. Propofol was infused into a tail vein via a 25-gauge Venofix-S (B. Braun AG) infusion set while the rats were restrained in a perspex holder.

EEG signals were obtained from a pair of subcutaneous stainless steel sutures placed in a bifrontal configuration, with a crocodile clip attached to one of the external ears as a signal ground. A Mingograf EEG 10 (Siemens-Elema Ltd) was used to record the signals. To provide an end-point for induction of anaesthesia, we used a burst suppression period of 1 s or longer as described previously [3]. The infusion was stopped immediately after the end-point was observed and the required induction dose was calculated. The duration of anaesthesia was measured as the time without spontaneous return of the righting reflex with the rats housed individually in custom-built cages with recording beds [3]. One way analysis of variance (ANOVA) followed by the Bonferroni multiple comparison procedure was used to evaluate the effects of rate of administration on induction dose and duration of anaesthesia.

Anaesthesia was induced successfully in all rats using the described electroencephalographic end-point. The mean induction times were 602 (SD 69 (range 590–670)) s, 190 (21 (163–217)) s, 81 (8.7 (73–90)) s and 51 (6.0 (40–54)) s for the administration rates of propofol 2.5, 5, 10 and 20 mg kg\(^{-1}\) min\(^{-1}\), respectively. The corresponding induction doses of propofol were 25.1 (2.9 (21.2–27.9)), 15.8 (1.8 (13.6–18.1)), 13.4 (1.5 (12.2–15.0)) and 16.9 (2.0 (13.3–18.0)) mg kg\(^{-1}\); the dose–rate graph is shown in figure 1 A. The administration rate had a significant effect on induction dose [F(3, 16) = 29.0, P < 0.001]. The induction doses at the infusion rates 2.5 and 20 mg kg\(^{-1}\) min\(^{-1}\) were significantly (P < 0.001 and P < 0.05, respectively) larger compared with the dose at 10 mg kg\(^{-1}\) min\(^{-1}\). The slope of the dose–rate graph between 10 and 20 mg kg\(^{-1}\) min\(^{-1}\) was estimated to 0.34 (SE 0.11) min using the least squares method.

The corresponding mean durations of anaesthesia were not influenced significantly (F(3, 16) = 0.50) by the rate of administration (fig. 1 B).

Comment

Our results confirm the rate-dependency of induction dose requirements of propofol, as reported previously in animal and clinical studies [1, 2, 4]. We
have also shown that the rate of administration of propofol is a factor which may be optimized. The optimal rate of administration was found to be approximately 10 mg kg\(^{-1}\) min\(^{-1}\). The reason for an increase in dose requirements at very slow rates of administration is probably that propofol is metabolized or begins to distribute into poorly perfused tissues during induction. On the other hand, a fast rate of administration may not balance the distribution rate into the CNS, resulting in high concentrations in the central compartment instead. When the drug is injected as an infusion, this imbalance may result in a delayed onset of induction, resulting in a higher dose. Stokes and Hutton [1] commented that this phenomenon may be caused by the physicochemical properties of propofol. Propofol may require a finite transport time to reach the biophase because of these properties, and these authors call this a "biophase delay". Bolander, Wahlström and Norberg [3] have shown that the slope of the dose–rate graph for thiopentone above the optimal rate (i.e. the time constant at supraoptimal rates) exceeds the expected minimal slope that can be calculated from data of circulation time from the injection site to the CNS (33.0 vs 6.1 s). This indicates that thiopentone may have delayed penetration into the brain. In the present study the time constant was lower than that reported for thiopentone, but exceeded the expected minimal time constant reported by these authors (20.6 vs 6.1 s), indicating that factors other than circulation time may cause a biophase delay for propofol.

The duration of anaesthesia was not affected significantly by the different induction doses obtained by varying the administration rate (fig. 1B). The time constant at the supraoptimal part of the dose–rate graph reflected this. It has been shown [3] that the rate of administration does not substantially modify the duration of anaesthesia for hexobarbitone, which has a time constant comparable with that of propofol (20.4 s), while the duration of anaesthesia after thiopentone is greatly modified by the rate of administration. This indicates that a high level of biophase delay not caused by circulation time, that is blood–brain penetration barrier, may give rise to higher concentrations of anaesthetic in the central compartment which may continue to distribute into the CNS after induction of anaesthesia is discontinued. However, propofol has a fast blood–brain equilibration rate, most likely caused by its high lipid solubility.

We conclude that the administration rate of propofol may be optimized in order to identify the smallest effective dose for induction. Furthermore, dose–rate graphs are useful when comparing different anaesthetics and should be evaluated before estimating relative potencies. As anaesthetic potency, rate of administration and onset times are interrelated, as noted by Glen [5], effective doses of different anaesthetics may be compared when administered at their respective optimal administration rates. Underestimation of potency because of differences in onset times is then avoided.

It is important in anaesthetic practice to separate the effects of administered dose from administration rate. Using an optimal rate of administration may reveal the lowest effective dose for induction, which is important for reducing the incidence of side effects, but this does not necessarily have to imply that such a dose has to be administered at this slow rate [4]. Slow induction per se is more likely to produce excitatory side effects, and a combination of a low dose administered at a high rate with a longer period of observation may be more relevant. It would be useful to evaluate the dose–rate graph for propofol in a clinical study. Previous clinical studies have not shown an increased induction dose at the slowest infusion rate. This difference in response between patients and rats may also result from longer circulation and distribution times in humans, resulting in a linear response on induction dose to a wide range of infusion rates. A preliminary report by Gentry and colleagues [6] described induction of anaesthesia with an infusion of thiopentone. These authors proposed a parabolic dose–rate graph, using pharmacokinetic–pharmacodynamic simulation to estimate the suboptimal part of the graph. Such a technique may be useful as very slow rates of administration result in unacceptably long induction times in clinical investigations.

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Figure 1  A: Induction dose of propofol at different rates of administration (mean, SEM, \(n = 5\)). \(*** P < 0.001\), induction dose compared with induction dose at 10 mg kg\(^{-1}\) min\(^{-1}\). B: Duration of anaesthesia at different rates of administration (mean, SEM, \(n = 5\)).
Acknowledgements

This work was supported by the Swedish Medical Research Council and the Systembolaget Fund for Alcohol Research. We thank Zeneca Pharmaceuticals for supplying propofol.

References