Does tolerance develop to the anaesthetic effects of propofol in rats?

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SUMMARY
We have studied the development of tolerance to the anaesthetic effects of propofol in rats. In the first set of experiments, three groups of rats (A, B and C) received i.v. propofol 10 mg kg⁻¹, 15 mg kg⁻¹ and 20 mg kg⁻¹, respectively. The durations of anaesthesia were recorded, the rats were killed and blood was collected to measure the concentrations of propofol. In a second set of experiments, rats received propofol 10 mg kg⁻¹ i.v. repeated 24 h (group D), 48 h (group E) or 72 h (group F) later. Sleeping times were recorded after the first and the second administration and concentrations of propofol at awakening were measured after the second dose, when rats were killed. Sleeping times were significantly longer in groups B (22.4 min) and C (25.9 min) compared with group A (13.7 min) (P < 0.001 for both). Durations of anaesthesia in groups D, E and F were 14.7, 14.5 and 14.3 min, respectively, after the first dose of propofol and 11.6, 12.1, and 14.9 min respectively, after the second dose. The rats in groups D and E exhibited shorter sleeping times after the second dose of propofol than after the first (P < 0.01 for both). Concentrations of propofol at awakening did not differ between groups A, B and C or between groups D, E and F. The results suggest lack of changes in susceptibility of the CNS to the anaesthetic effects of propofol. (Br. J. Anaesth. 1994; 72: 127-128)

KEY WORDS
Anaesthetics, i.v.; propofol.

Development of tolerance to central nervous system depression has been reported for several anaesthetic agents [1]. Propofol has not been investigated for development of tolerance, except for the observations made in the course of two pharmacokinetic studies, one during continuous infusion of the drug in humans [2], the second during a bolus injection or a continuous infusion of propofol in dogs [3]. In this study, we have investigated possible development of tolerance to propofol in the rat.

METHODS AND RESULTS
Female Sprague–Dawley rats (IFA Gredor Laboratories) weighing 230–260 g and housed two per cage, had free access to water and rat purina chow. All animals were maintained, cared for, handled and killed in accordance with the regulations of the French Ministry of Agriculture.

In a first set of experiments groups (A, B and C) of 14 rats each received propofol (Diprivan) 10 mg kg⁻¹, 15 mg kg⁻¹ or 20 mg kg⁻¹, respectively into a tail vein over approximately 10 s and were tested for loss of righting reflex. The test was considered positive when the rat did not right itself within 30 s after being placed in supine position. On loss of righting reflex, the animal was placed in the centre of a 45 x 60-cm area outlined on the floor. As soon as the animal walked out of this area it was killed by decapitation and 1 ml of blood was collected and placed in tubes containing ammonium oxalate, for determination of blood concentrations of propofol.

In a second set of experiments, groups (D, E and F) of 14 rats each received i.v. propofol 10 mg kg⁻¹. When they recovered, the rats were returned to their cages and allowed free access to food and water. The same dose of propofol was repeated, 24 h later in group D, 48 h later in group E and 72 h later in group F. Sleeping times were determined as above. After the second recovery, the animals were killed and blood was collected for measurement of blood concentrations of propofol as in the first set of experiments.

During propofol anaesthesia, body temperature was not monitored, but all animals were treated in the same way and covered with aluminium foil to prevent heat loss. The room temperature was maintained at 22–24 °C. Rats of all groups were injected in random order. Duration of anaesthesia was defined as described previously [4]—time elapsed from loss of righting reflex to movement by the animal out of the rectangular area. In order to obtain comparable sleeping times produced by different doses of propofol, the duration of anaesthesia in groups A, B and C was divided by the dose of propofol given. Propofol concentrations were measured as described by Plummer [5].

Data were analysed statistically with ANOVA, Scheffe's test and two-tailed paired t tests where appropriate.

Durations of anaesthesia differed significantly between groups A, B and C (ANOVA F = 25.901, df = 2.39, P < 0.0001). Sleeping times in groups B and C (22.4 min and 25.9 min, respectively) were significantly longer than those in group A (P < 0.01 for
both comparisons). The duration of anaesthesia in group B rats did not differ significantly from that in group C (largest dose of propofol). The duration of anaesthesia normalized for dose of propofol administered and blood concentrations of propofol at wakening did not differ significantly between groups A, B and C (F = 2.0765, df = 2,39, P = 0.1390; F = 0.636, df = 2,39, P = 0.5349, respectively) (table 1).

Sleeping times in groups D, E and F were 14.7 min 14.5 min and 14.3 min (F = 0.063, df = 2,39, P = 0.938) and 11.6 min, 12.1 min and 14.9 min (F = 2.41, df = 2,39, P = 0.103) after the first and second doses, respectively. Intergroup comparisons showed no significant differences in durations of anaesthesia after the first or second dose of propofol (table 1). Durations of anaesthesia within groups D and E were significantly shorter after the second dose of propofol than after the first dose (P < 0.01 for both), but were similar in group F. Blood concentrations of propofol at wakening did not differ between groups D, E and F (F = 0.335, df = 2,39, P = 0.717) (table 1).

COMMENT

We have shown that reduction in sleeping times occurred when a second dose of propofol 10 mg kg\(^{-1}\) was administered 24 h or 48 h, but not 72 h, after a first dose. We chose a dose of 10 mg kg\(^{-1}\) for repeated administration because cumulation might occur with larger doses.

Acute tolerance has been reported for other i.v. anaesthetics, including thiopentone [1] although this was questioned when pharmacodynamic modelling was applied by means of power spectral analysis of the EEG [6]. In both dogs and humans, greater infusion rates of propofol were associated with greater wakening blood concentrations of the drug [2, 3]. This observation does not distinguish between pharmacokinetic and pharmacodynamic mechanisms, as peripheral venous concentrations of propofol are not necessarily a reliable index of central nervous system depression induced by anaesthetics.

Wakening blood concentrations of propofol were similar in all groups of rats, therefore greater or repeated doses of propofol are unlikely to be associated with changes in the sensitivity of the brain to propofol. Changes in the maximal EEG effect associated with changes in the sensitivity of the brain to propofol. However, for technical reasons we did not obtain EEG data.

Enhanced metabolism may be a possible explanation of the shorter sleeping times in groups D and E after the second dose of propofol. However, a different experimental design with a greater number of repeated administrations is required to confirm or refute this hypothesis.

We conclude that, in the circumstances examined, central tolerance to propofol did not develop with increasing propofol dose, or with repeated administration of the same dose.

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REFERENCES