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ORIGINAL ARTICLE

Severity and duration of mental deficiency symptoms after intravenous administration of propofol

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Abstract The severity and duration of cognitive performance capacity deficits after intravenous administration of propofol were determined using the validated psychological test procedure syndrome short test (SKT), a simple reaction test and original driving licence exam questions. The test battery was performed before, immediately after, as well as 1 and 2 h after propofol administration in 23 persons. Immediately after propofol anaesthesia, six individuals had a slight performance loss, and four subjects showed mild deficits, consistent with medium organic neuropsychologic disorder or dementia. The status of the subjects rapidly changed for the better, and 2 h after propofol anaesthesia, only one person (4%) showed slight deficits of memory and attention. Therefore, it is suggested that patients refrain from any participation in road traffic for at least 2 h after propofol anaesthesia. Driving a car should not be admitted until an interval of 6 h has elapsed.

Keywords Propofol · Narcotics · Deficiency symptoms · Memory · Attention · Driving ability

Introduction

Propofol (2,6-diisopropylphenol) is a global central nervous system depressant which is widely used for the induction and maintenance of anaesthesia and for sedation in intensive care units [12]. After a single bolus injection, propofol is rapidly distributed from the vascular space and therefore has a very short initial half-life of 2–7 min. Rapid conjugation of propofol in the liver leads to the formation of glucuronides and sulphates, and the inactive conjugates are excreted via the kidneys. As the terminal elimination half-life is dependent on sex, age, pre-existing illnesses, concomitant medication and the period of anaesthesia, it ranges from 60 min to 3 days [1, 13].

After a 2.5-mg/kg body-weight dose of propofol, consciousness is lost within 100 s. Duration of hypnosis is dose dependent and is 5–10 min after a 2.5-mg/kg dose [12]. Overly rapid infusion may cause fatal respiratory depression, and some cases of chronic propofol abuse with fatal outcome have been reported [4, 8].

As propofol needs a shorter mean time to sedation and offers a greater depth of sedation in comparison with benzodiazepines and opioids, i.e. midazolam and fentanyl, the use of intravenous propofol has increased over the last few years, especially in outpatient endoscopy [18]. In addition, patients with propofol anaesthesia reach full recovery earlier [9, 10, 16]. Sipe et al. [16] found a mean recovery time of 14.4 min for outpatient colonoscopy with propofol vs 33.0 min with midazolam/meperidine (pethidine). The patients who received propofol were discharged after a mean time of 40.5 min, whilst the midazolam/meperidine group had to stay on average for 71.1 min.

Only few of the studies have dealt with the driving ability of patients after propofol anaesthesia and the time needed to regain road traffic competence [14, 15, 17]. Whilst Sinclair et al. [15] found no impairment of simulator driving skills 2 h after 30 min of general anaesthesia with propofol (2.5 mg/kg body weight), desflurane and fentanyl, Sanou et al. [14] found a significant depression of cognitive

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functions for at least 3 h and a full recovery not until about 6 h after propofol anaesthesia. The ability to plan complex tasks was in particular impaired more than 3 h after propofol anaesthesia. Because of such controversial study results and due to the fact that the current recommendations are to refrain from driving for 24 h after general anaesthesia, many endoscopists feel alienated [15]. In the directions for use of propofol, it is stated that patients are not allowed to actively take part in road traffic or to run a machine after propofol anaesthesia. As no dates are given, the responsibility regarding the time factor is shifted to the endoscopist who has the individuality to decide on the required waiting period. To alleviate this decision, severity and duration of cognitive performance capacity deficits after intravenous administration of propofol were determined in this study using the validated psychological test procedure syndrome short test (SKT) [3, 5, 7, 11], a simple reaction test [2, 19] and original driving licence exam questions.

Materials and methods

Subjects

A total of 19 patients for gastroenterological surgery and four healthy volunteers (12 men and 11 women, age range 21–68 years, mean age 42.2 years, weight range 50–105 kg, mean weight 73.7 kg) participated in the study. Inclusion criteria were an age ≥18 years, a valid driving licence and, in the case of the patients, a medically indicated colonoscopy and/or gastroscopy with propofol anaesthesia. Four healthy subjects were included in this study to evaluate any influence on the test results by the medical intervention or the underlying disease. The history of alcohol and nicotine use of the subjects was none to heavy: the subjects consumed an average of 55 g of ethanol per week (range 0–340, four teetotalers) and smoked an average of seven cigarettes per day (range 0–30, 13 abstainers). This study was reviewed by the Ethics Committee of the Medical Faculty, Erlangen-Nuremberg University (Re.-No. 3200). Before their inclusion in the study, all subjects gave informed consent.

Experimental design

The patients were interviewed 1 day before the medical intervention. Subsequently, the tests described below were performed to obtain blank values without the influence of propofol. The next day, patients underwent colonoscopy and/or gastroscopy with the medically required propofol dosages (mean 2.4 mg/kg body weight, range 1.5–4.4). The duration of anaesthesia was on average 15 min (range 5–20 min). The four volunteers had a constant anaesthesia time of 15 min with a mean propofol dosage of 2.4 mg/kg body weight (range 2.1–2.7). Immediately after the intervention, a blood sample was taken, and the complete test battery was performed. This procedure was repeated 1 and 2 h after the intervention.

Test battery

The SKT is a short test for registration and quantification of memory and attention disorders [5, 11]. The test consists of nine subtests with a handling time of 60 s each. The raw values of the subtests are corrected with reference to age and intelligence using four age classes (17–44, 45–55, 55–64 and ≥65 years) and three intelligence levels (substandard, standard and above average). The sum of these corrected norm values allows an estimation of the degree of disorder, which is geared to clinical characterisations of slight, medium and severe organic neuropsychologic disorder or dementia. To avoid familiarisation and practice effects, the SKT exists in five parallel forms A–E with a reliability of r=0.86–0.88. In this study, the parallel test versions A–D were used in a constant order.

The staff-falling test [2, 19] is a simple reaction test for all age groups, which is integrated in many motor test batteries. The subject sits on a chair; the forearm is laid on the armrest, the hand is open and the fingers are stretched. The investigator suddenly drops a staff with a centimetre scale that was held at hand level before. The subject tries to close his hand and grab the staff as quickly as possible. The reaction time is estimated using the centimetre scale. The published reliability coefficients of this test range from 0.52 to 0.81.

Original driving licence exam questions as officially used in Germany had to be answered by each subject. An individual collection of comparable severity (six questions regarding traffic safety, three questions dealing with traffic signs and six questions about giving way) was compiled for each test cycle to avoid habituation effects. The results were given in error points.

Measurement of propofol concentrations

For the measurement of the serum propofol levels, two aliquots of 0.5 ml for each sample were analysed.

In a 2-ml plastic tube with 0.5 ml serum, 60 µl internal standard solution (5 µg/ml clomipramin-HCl in demineralised water), 0.5 ml buffer pH 6.0 (50.8 g $Na_2HPO_4 \times 2H_2O$ and 97.2 g KH_2PO_4 in 1 l) and 0.3 ml ethyl acetate were added. The mixture was vortexed for 1.5 min and centrifuged for 5 min at 10,000×g.

From the organic phase, 5 µl was injected directly without any concentration step into the GC–MS system. The MS was set on the single ion monitoring mode using

the fragments m/z=163 (target), 178 and 117 for the detection of propofol and 269 (target), 268 and 85 for the internal standard.

Quantification was carried out by a nine-step calibration (0, 20, 50, 100, 200, 500, 1,000, 2,000 and 5,000 ng/ml) showing a linearity with a correlation of 0.998 in this range. The determination of the analytical limits gave a limit of detection of 2.7 ng/ml and a limit of quantification of 10.4 ng/ml.

No influence by psychotropic agents other than propofol was found with immunological screening tests.

Data analysis

Statistical evaluation was performed using the PC program WinSTAT for Excel, release 2001.1. Spearman's correlation coefficient was calculated to evaluate the relationship between the variables obtained by the test battery. The significance of intragroup differences at various points in time was calculated by the Mann–Whitney U test.

Results

Propofol concentrations

Immediately after the intervention (0 h), serum propofol concentrations ranged from 772 to 4,655 ng/ml (median 1,650 ng/ml). One hour later (1h), there was a significant decrease with concentrations between 236 and 1,352 ng/ml (median 430 ng/ml), and after 2 h (2h), propofol concentrations were slightly lower, ranging between 108 and 785 ng/ml (median 253 ng/ml). The time course of the serum propofol concentrations is shown in Fig. 1.

SKT

The SKT results are given in Table 1 and Fig. 2. The intragroup differences between time points pre and 0h as well as between 0h, 1h and 2h are statistically significant (P<0.01, by Mann–Whitney U test). In contrast, there was no significant difference between time points pre and 1h or 2h. According to the SKT design, Spearman's rank correlation tests revealed no correlation between SKT results and age. Furthermore, no significant correlation existed between SKT results and propofol concentrations (0h: r=0.29, P>0.05; 1h: r=−0.39, P>0.01; 2h: r=−0.09, P>0.3 by Spearman's test).

Table 1 SKT results before (pre), immediately after (0h), 1 h (1h) and 2 h (2h) after propofol anaesthesia

SKT points	Deficits of memory and attention	pre	0h	1h	2h
0–4	No	19	5	18	16
5–8	Very slight	4	8	3	6
9–13	Slight	0	6	2	1
14–18	Medium	0	4	0	0
19–23	Heavy	0	0	0	0
24–27	Very heavy	0	0	0	0

Number of subjects (n=23)

Before propofol anaesthesia (pre), 19 subjects showed no deficits of memory and attention (0–4 points), and four subjects had very slight deficits (5–8 points). The majority of errors at this time point occurred by speed-oriented tasks. Immediately after propofol anaesthesia (0h), there remained only five subjects without and eight subjects with very slight deficits, whereas six persons had slight performance losses (9–13 points) and four subjects showed medium deficits (14–18 points), consistent with medium organic neuropsychologic disorder or dementia. At this time, errors in memory tasks increased remarkably, and only two subjects had exclusive errors in speed-oriented tasks. One of them (number 6) made memory errors in the SKT at time "pre", and the other person (number 20) had no error points at all in the first SKT.

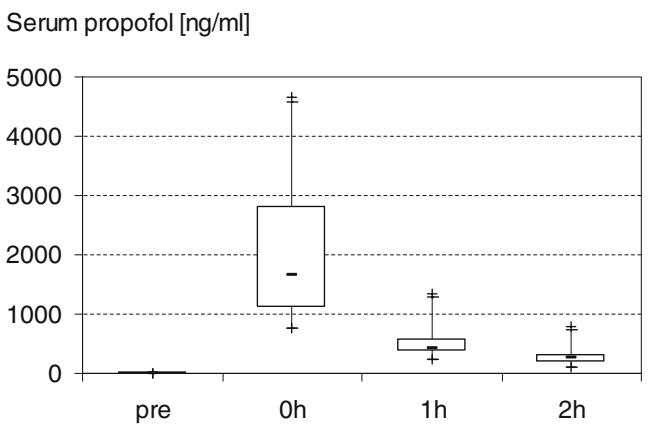

Fig. 1 Propofol concentrations before (*pre*), immediately after (*0h*), 1 h (*1h*) and 2 h (*2h*) after propofol anaesthesia (n=23). Fifty percent *boxes with medians*, 90% *span lines*, *minima* and *maxima*

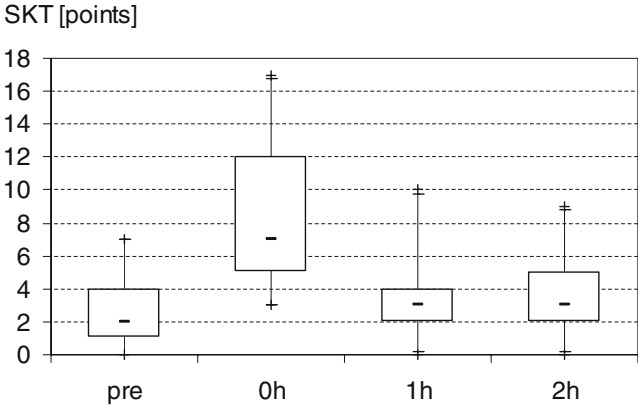

Fig. 2 SKT results (error points) before (*pre*), immediately after (*0h*), 1 h (*1h*) and 2 h (*2h*) after propofol anaesthesia (n=23). Fifty percent *boxes with medians*, 90% *span lines*, *minima* and *maxima*

Even 1 h after propofol anaesthesia, the vast majority (91%) of the subjects showed no or very slight deficits of memory and attention (Table 1), and in only two cases a slight impairment had remained. After 2 h (2h), the performance of these two persons had changed for the better, whilst one person (4%) had deteriorated and now showed slight deficits.

Staff-falling test

The results of the staff-falling test are given in Fig. 3. Although the reaction test tended to result in a deterioration of performance between time points pre and 0h, this difference was not significant ($P>0.5$, by Mann–Whitney U test). In contrast, the improvement between time points 0h and 1h/2h as well as between time points pre and 2h was statistically significant ($P<0.01$, by Mann–Whitney U test).

Driving licence test questions

The results of the driving licence test questions are given in Fig. 4. The slight differences between the points in time were all not statistically significant.

Discussions

The SKT revealed no relevant deficits of memory and attention before propofol anaesthesia. Immediately after narcosis, there was a significant decrease of cognitive functions. The deficits at this point in time were comparable with medium organic neuropsychologic disorder or dementia in four subjects and with slight disorder or dementia in six subjects. Severe dysfunctions as found after a therapeutic dosage of midazolam [7] did not occur under influence of propofol at all. The fact that the number of error points showed no correlation with propofol concentrations as well as the observation of five subjects without deficits at all (Table 1) can be interpreted as an individual degree of response.

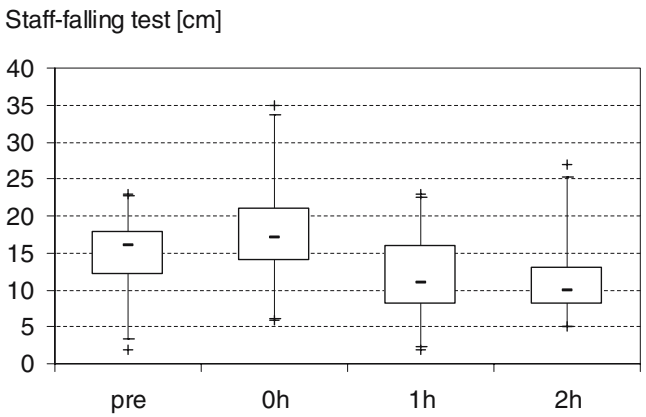

Fig. 3 Results of the staff-falling test (height of fall in centimeters) before (*pre*), immediately after (*0h*), 1 h (*1h*) and 2 h (*2h*) after propofol anaesthesia (n=23). Fifty percent *boxes with medians*, 90% *span lines*, *minima* and *maxima*

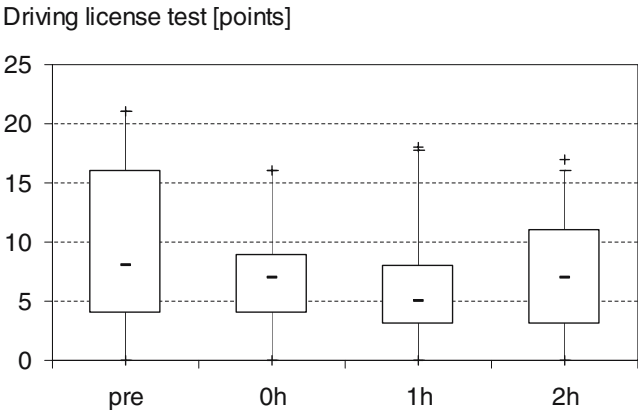

Fig. 4 Results of the driving licence test questions (error points) before (*pre*), immediately after (*0h*), 1 h (*1h*) and 2 h (*2h*) after propofol anaesthesia (n=23). Fifty percent *boxes with medians*, 90% *span lines*, *minima* and *maxima*

Whilst the majority of errors at time point pre was attributable to speed-oriented tasks, propofol led to a significant increase in memory deficits. This observation is in good accordance with SKT results of persons under the influence of alcohol [3]. In contrast, Thapar et al. [17] found no significant impairment of short-term memory under the influence of propofol. This discrepancy could be attributed either to the low propofol dosage of 1 mg/kg which was administered in the study of Thapar et al., or to the different memory test design. Whilst the SKT requires both an immediate and a delayed recapitulation of depicted items, Thapar et al. tested only the free recall of 15 words which were read out immediately before. Sanou et al. [14] also found a stronger impairment of long-term than of short-term memory.

Even 1 h after the intervention, the vast majority (91%) of subjects showed no or very slight deficits of memory and attention. This result underlines numerous reports of an early recovery after propofol anaesthesia [9, 10, 16]. Furthermore, the comparison with the results of Hausmann and Betz [7] proves a lower degree of impairment after propofol than after midazolam administration: 75 min after midazolam anaesthesia, 57% still showed slight, 19% medium and 4% severe neuropsychologic impairment.

Two hours after propofol anaesthesia, both the subjects with slight deficits at time point 1h changed for the better, whilst one person had deteriorated compared to the SKT 1 h before. The reason for deterioration in the last SKT (2h) which was not only observed at this subject but in a total of 11 persons (47.8%) remains unclear. Nobody showed an increase of serum propofol concentrations between the time points 1h and 2h, as one could assume due to a re-distribution of the lipophilic substance from fatty tissue.

Furthermore, there were no significant differences in propofol dosage, propofol concentration, age, weight, kind of intervention and duration of anaesthesia between the groups with and without deterioration in the last SKT (by Mann–Whitney *U* test, $P>0.5$). Therefore, some kind of exhaustion could have provoked deficits in concentration and memory performance.

The results of the staff-falling test seem to contradict this assumption. However, the fact that the enhancement of reaction between time points pre and 2h was significant ($P<0.01$, by Mann–Whitney *U* test) shows that a kind of practice effect process occurred. The same effect has been recorded in attention as well as in memory tests and demonstrates a well-known problem of repetitive tests [6, 14]. As these difficulties are normally restricted to tests which are available in just one version, the result of the driving licence test questions was absolutely surprising because it combines learning effects that blur a potential impairment by propofol with signs of exhaustion.

Altogether, the results of this study provide evidence for a relevant impairment in a small percentage of patients up to 2 h after propofol anaesthesia. Patients should therefore refrain from any participation in road traffic for at least 2 h after propofol narcosis. However, due to potential impairment in complex plan tasks which may last more than 3 h, driving a car should not be admitted until an interval of 6 h has elapsed.

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References

1. Baselt RC, Cravey RH (1995) Disposition of toxic drugs and chemicals in man. Chemical Toxicology Institute, Foster City, pp 656–657
2. Beuker F (1976) Leistungsprüfungen im Freizeit- und Erholungssport. Barth, Leipzig, pp 44–46, 63
3. Brückner K (1999) Kognitive Funktionsstörungen bei niedrigen Alkoholisierungsgraden. Thesis, University of Erlangen-Nuremberg
4. Cirimele V, Kintz P, Doray S, Ludes B (2002) Determination of chronic abuse of the anesthetic agents midazolam and propofol as demonstrated by hair analysis. Int J Legal Med 116:54–57
5. Erzigkeit H (1992) SKT: Ein Kurztest zur Erfassung von Gedächtnis- und Aufmerksamkeitsstörungen. Beltz, Weinheim
6. Grant SA, Murdoch J, Millar K, Kenny GNC (2000) Blood propofol concentration and psychomotor effects on driving skills. Br J Anaesth 85:396–400
7. Hausmann R, Betz P (1998) Schweregrad und Zeitdauer forensisch relevanter Wirkungen nach oraler Aufnahme von Midazolam. Rechtsmedizin 8:64–68
8. Iwersen-Bergmann S, Rösner P, Kühnau HC, Junge M, Schmoldt A (2001) Death after excessive propofol abuse. Int J Legal Med 114:248–251
9. Lazzaroni M, Porro GB (2005) Preparation, premedication, and surveillance. Endoscopy 37:101–109
10. Lazzaroni M, Bianchi Porro G (2003) Preparation, premedication, and surveillance. Endoscopy 35:103–111
11. Lehfeld H, Rudinger G, Rietz C et al. (1997) Evidence of the cross-cultural stability of the factor structure of the SKT short test for assessing deficits of memory and attention. Int Psychogeriatr 9:139–153
12. Marik PE (2004) Propofol: therapeutic indications and side-effects. Curr Pharm Des 10:3639–3649
13. Physicians' Desk Reference (1994) Medical economics. Montvale, New Jersey, pp 2328–2332
14. Sanou J, Ilboudo D, Goodall G, Bourdalle-Badie C, Erny P (1996) Évaluation des functions cognitives après anesthésie au propofol. Ann Fr Anesth Reanim 15:1155–1161
15. Sinclair DR, Chung F, Smiley A (2003) General anesthesia does not impair simulator driving skills in volunteers in the immediate recovery period—a pilot study. Can J Anaesth 50:238–245
16. Sipe BW, Rex DK, Latinovich D, Overley C, Kinser K, Bratcher L, Kareken D (2002) Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. Gastrointest Endosc 55:815–825
17. Thapar P, Zacny, JP, Thompson, W, Apfelbaum J (1995) Using alcohol as a standard to assess the degree of impairment induced by sedative and analgesic drugs used in ambulatory surgery. Anesthesiology 82:53–59
18. Ulmer BJ, Hansen JJ, Overley CA et al (2003) Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. Clin Gastroenterol Hepatol 1:425–432
19. Werle J, Zimber Z (1999) Sturzprophylaxe durch Bewegungssicherheit im Alter: Konzeption und Effektivitätsprüfung eines sensumotorischen Interventionsprogramms bei Osteoporose-Patientinnen. Z Gerontol Geriatr 32:348–357