Propofol and Spontaneous Movements: An EEG Study

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Materials and Methods

Twenty-one ASA Physical Status 1 children between 6 and 12 yr of age were included in the study after parents' informed consent and institutional ethical committee approval were obtained. Patients were scheduled for elective ears, nose, and throat procedures of short duration. Exclusion criteria included known allergy to trial drugs or their constituents and a history of previous adverse reaction to general anesthesia. Also excluded were patients with psychomotor retardation, epilepsy, a history of general anesthesia within the last 3 months, and evidence of baseline electroencephalographic abnormality.

All patients received atropine 0.04 mg·kg⁻¹ given orally 60 min before operation, and no sedatives were given before the induction of anesthesia. On arrival in the anesthetic room, the patient's heart rate and systolic and diastolic pressures were recorded with an automatic device (Cardiogap®, Datex, Helsinki, Finland). Other monitors included an electroencephalogram (EEG), a pulse-oximeter (Cardiogap®, Datex), a nerve stimulator (Dual Stim®, Live-Tech, Houston, TX), and a precordial stethoscope. A 19-, 20-, or 22-G catheter (Venflon®) was inserted into a vein on the dorsum of the hand or in the antecubital fossa.

Fourteen silver cup electrodes were placed according to the 10–20 international system. Electrode impedances measured less than 5 kOhm. A Nihon Khoden® transportable model 7314 F machine was used to record 14 channels. A high-frequency filter was set at 70 Hz; bipolar longitudinal montages were used. A baseline EEG was recorded in two montages during 10 min with the child awake and supine with the eyes closed and opened. An EEG was then recorded from the beginning of induction until 5 min after tracheal intubation. An ECG was also recorded on one channel.

Children were randomly allocated to group A (propofol 3 mg·kg⁻¹), group B (propofol 5 mg·kg⁻¹), or group C (thiopental 5–7 mg·kg⁻¹). Group A received a loading dose of propofol 3 mg·kg⁻¹ iv in 10 s, immediately followed by a continuous infusion of 0.1 mg·kg⁻¹·min⁻¹ with the use of an automatic pump (IVAC 711®, IVAC, San Diego, CA). In group B the same procedure was followed except the induction dose of propofol was 5 mg·kg⁻¹. Group C received a loading dose of thiopental 5–7 mg·kg⁻¹, and anesthesia was maintained with halothane (0.5–1%). Halothane was started only after the end of the EEG recording. Tracheal intubation was facilitated.

Spontaneous movements during induction of anesthesia with propofol were studied in 21 children aged 6–12 yr. The children were randomly assigned to group A (propofol 3 mg·kg⁻¹), B (propofol 5 mg·kg⁻¹), or C (thiopental 5–7 mg·kg⁻¹). A baseline electroencephalogram (EEG) was recorded during 10 min in children awake, supine with eyes closed and opened, and then from the beginning of induction until 5 min after tracheal intubation. Spontaneous movements were observed in all children in group A but only in 14% in groups B and C. The induction EEG sequences were similar for the three groups: after a mean latency of 12 s, the tracing showed an increase in frequency from 9 to 10 Hz (alpha waves) to more than 14 Hz (beta waves). This transition lasted approximately 2 s, followed by delta waves (2–3 Hz) that continued for 1–2 min. Finally, beta waves reappeared and progressively but incompletely replaced delta waves during the next 5 min. Neither spikes, spike-wave patterns, rhythmic theta waves, nor burst suppressions were observed. Spontaneous movements were recorded on videotape and analyzed after the completion of the study by a neurologist unaware of patient treatment. Videotape analysis of the periinduction period showed spontaneous movements to be dystonic and choreiform with flexion, twisting, or extension movements of all extremities. All movements occurred coincident with the appearance of delta waves on the EEG. Their dystonic nature and the absence of EEG abnormalities suggest a subcortical origin and argue against associated cortical epileptic activity. (Key words: Anesthetics, intravenous: propofol; thiopental. Complications: spontaneous movements. Measurement technique: electroencephalography.)

PROPONOL is the newest intravenous agent for induction and maintenance of anesthesia.¹ Common side effects observed during induction are pain on injection and spontaneous movements.²,³ Spontaneous movements have been observed during induction of anesthesia in adults⁴ and also in children, but with a higher incidence in the latter group.⁵ Until now no definitive explanation concerning their origin has been available. Although epileptic activity associated with propofol has been reported,⁶ other studies have not been able to demonstrate any convulsive effects.⁷ In view of the controversy surrounding the association between propofol and seizures, electroencephalographic tracings of healthy children were recorded during induction of anesthesia with propofol.

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with vecuronium 0.1 mg·kg\(^{-1}\) iv given 90 s after the administration of the anesthetic. A supplementary dose of vecuronium (a third of the initial dose) was given at the reappearance of more than two twitches of four (nerve stimulator). Manual ventilation with 100% oxygen was used in all patients until tracheal intubation; then a mixture of 33% oxygen and 66% nitrous oxide was administered. Hemoglobin saturation never decreased below 95%, and the end-tidal carbon dioxide tension (PET\(_{CO_2}\)) was kept between 35 and 40 mmHg (measured as soon as tracheal intubation was performed).

Anesthetic induction was recorded with a video camera (Newvicon\textsuperscript{®}, Panasonic). After completion of the study, the EEG tracings and the videotapes were reviewed by a neurologist blinded to the subjects’ group assignments. Spontaneous movements were graded as follows:

1. Movements limited to the hands or feet with or without internal rotation of the arm or leg.
2. Grade 1, plus flexion or extension of the arm or the leg.
3. Grades 2 and 3, plus internal or external rotation of the shoulder or the hip and a need to hold the arms to avoid displacement of the venous catheter.

Duration of spontaneous movements was classified as follows: a = less than 30 s; and b = between 30 and 50 s.

Pain on injection was considered present if patients complained or withdrew the forearm in which the venous catheter was inserted.

Statistical analysis was done with the Mantel-Haenszel chi-squared test (for multiple matched controls). \( P < 0.05 \) was considered significant. Demographic test data were evaluated with Students’\( t \) test.

**Results**

The age, weight, and sex were similar in the three groups and are shown in table 1. Mean arterial blood pressure decreased (with a maximum after 2 min) similarly in the three groups: 12, 15, and 11% for groups A, B, and C, respectively. Heart rate was unchanged or showed a slight decrease of between 8 and 14% of the preinduction values in group A and B, whereas an increase of between 10 and 15% was found in group C.

<table>
<thead>
<tr>
<th>Table 2. Side Effects during Induction</th>
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<tbody>
<tr>
<td><strong>A</strong> (n = 7)</td>
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<td>----------------</td>
</tr>
<tr>
<td>Spontaneous movements</td>
</tr>
<tr>
<td>Pain on injection</td>
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<tr>
<td>Erythema</td>
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<td>Hiccup</td>
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Data are number of patients.

\* \( P < 0.05 \).

Spontaneous movements appeared in all children in group A but in only one child each in groups B and C, respectively \( P < 0.05 \) (table 2); in group C one child was excluded from the study because some generalized theta bursts were detected on the baseline EEG tracing. Additional studies demonstrated this child had a seizure disorder.

Spontaneous movements were described by the neurologist (videotape reviewing) as dystonic and choreiform with flexion, twist, or extension of the arms or legs. They were most often bilateral but not strictly symmetric. They lasted between 10 and 50 s and appeared approximately 14–18 s after administration of the anesthetic. Clonic muscle activity was not observed. Movements occurring in children in groups B and C were briefer in duration and smaller in magnitude than those occurring in children in group A. In group A spontaneous movements were graded 3A in three children, 3b in one, 2a in three, and 1b in one, whereas those observed in groups B and C were 1a.

Electroencephalogram tracings were comparable in the three groups. All baseline EEG recordings were normal and similar. Latency between administration of the anesthetic and appearance of beta waves was 11–14 s for group A, 6–18 s for group B, and 10–13 s for group C. The sequence of the EEG pattern was similar for the three groups: after a mean latency of 12 s, the predominant frequency showed an increase from 9 to 10 Hz (alpha waves) to more than 14 Hz (beta waves). Then delta waves (2–3 Hz) appeared, lasting 1–2 min, followed by reappearance of beta waves mixed with delta waves; beta waves progressively but incompletely replaced the delta waves during the next 5 min (fig. 1). Neither spikes, spike-wave patterns, nor burst suppressions were observed. Moreover, there were no EEG asymmetries or distinct focal changes even in children in whom only one arm or leg exhibited spontaneous movements. All movements occurred coincident with the appearance of delta waves on the EEG.

Other side effects observed during induction were as follows: pain on injection, 28, 42%, and none in groups A, B, and C, respectively; hiccup, one child in group A; and transient erythema limited to the arm and the upper

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**Table 1. Characteristics of Patients**

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<tr>
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<th>A</th>
<th>B</th>
<th>C</th>
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<tr>
<td>( n )</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>8 ± 0.8</td>
<td>7 ± 0.8</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>26 ± 2.5</td>
<td>28 ± 3</td>
<td>28 ± 3.5</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>5/2</td>
<td>4/3</td>
<td>4/3</td>
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Mean ± SEM.
part of the thorax in two children in group A (28%) and one in group B (14%) (table 2).

Discussion

Spontaneous movements are a relatively common side effect during induction of anesthesia with propofol, especially in children. The loading dose of 3 mg · kg⁻¹ (group A) was chosen because Saint-Maurice and colleagues suggested inadequate anesthesia using 2–2.5 mg · kg⁻¹. Recently we observed a 75% incidence of spontaneous movements using 3 mg · kg⁻¹ for induction; therefore, a loading dose of 5 mg · kg⁻¹ was chosen in group B. Thiopental, whose anticonvulsive properties are well known, was chosen as a control anesthetic. Electroencephalographic tracings were similar in all groups despite the fact that spontaneous movements occurred in all children in group A but only in one child in groups B and C, respectively. The incidence of spontaneous movements observed in the thiopental-treated group is comparable to the one found by Purcell-Jones and colleagues. The induction EEG sequence was similar to that described by Saint-Maurice and colleagues using 2.5 mg · kg⁻¹ of propofol. The only detectable difference was a slight increase of slow, large delta waves in group B; also, no burst suppression was detected in children who received 5 mg · kg⁻¹ of propofol as a loading dose.

Spontaneous movements appeared exclusively during the early delta wave phase. During the occurrence of delta waves, neither spikes, spike-wave patterns, nor rhythmic theta waves were observed; also, no EEG asymmetries or distinct focal modifications were observed even in children in whom only one arm or leg exhibited spontaneous movements. These EEG recordings coupled with the type and quality of movements (essentially dystonic) argue against any cortical epileptiform activity resulting from propofol. However, the Committee on Safety of Medicines recently issued a warning concerning the possible risk of seizures after administration of propofol. Hodkinson and colleagues also described discharges of spikes, polyspikes, and slow wave complexes after propofol administration to patients having temporal lobectomy for intractable temporal epilepsy. Additional case reports also implicate propofol in causing possible epileptiform activity in patients with a personal or familial history of known epilepsy.

On the other hand, cortical EEG changes similar to those produced by thiopental were demonstrated after administration of propofol in patients without a history of seizure disorder. Also in accordance with the results of the current study, Lowson and colleagues showed that propofol has strong anticonvulsant properties in mice. Other studies, using the cerebral function monitor, have not demonstrated an epileptogenic effect of propofol. In two reports of patients having electroconvulsive therapy, the mean clinical seizure duration was reduced after propofol administration compared with that after methohexital. Moreover, propofol has been used successfully to treat status epilepticus refractory to combined diazepam, phenytoin, phenobarbital, and clomethiazole. It is interesting that Smith and colleagues also described seizure-like behavior in mice after an anesthetic dose of propofol, without any spike-wave activity. Subcortical seizures can sometimes be very difficult to detect with a conventional EEG. Although our recordings showed no signs of epileptic activity within deeper structures, this cannot be ruled out because neither sphenoidal nor transcortical electrodes were used in the current study.

The dystonic appearance of the movements makes a peripheral mechanism unlikely but points toward involvement of the deep brain structures. The cause of acute and transient dystonic reactions is unclear but could be related to the release of neurotransmitters in the central nervous system, in particular to the stimulation of dopaminergic subcortical sites. Dopaminergic cortical stimulation may also account for the euphoric mood sometimes observed during emergence from propofol anesthesia. It is interesting that dystonic movements,
hypomanic behavior, and hallucinations are well-known manifestations in patients with Parkinson’s disease receiving too much L-dopamine.  

The higher incidence of spontaneous movements in group A cannot be explained by an inadequate level of anesthesia; indeed, electroencephalographic tracings reflect sufficient anesthetic depth (delta waves) similar to that of the thiopental-treated group. The lower incidence of spontaneous movements in group B could be explained by postulating an additional inhibitory effect at higher tissue concentrations of propofol. This possibility, as well as the possibility that propofol may act as a central muscle relaxant at higher doses, deserves additional investigation.

Other side effects observed during induction, such as pain on injection, are similar to the results reported in the literature and also were closely related to the sizes of the catheter and the vein used. Transient erythema at the site of injection and of the arm or the upper part of the thorax suggests a local histamine release, although vecuronium could also be implicated in this reaction.

In conclusion, this study shows that spontaneous movements observed during induction with propofol are not associated with any cortical epileptic activity. These movements are dystonic and may be related to subcortical structures, but the possibility of noncortical seizure activity cannot be categorically ruled out. The incidence of spontaneous movements in children is significantly decreased both in magnitude and duration with a loading dose of 5 mg·kg⁻¹ as compared with 5 mg·kg⁻¹ of propofol. With the larger dose the induction was smoother, requiring fewer interventions to prevent displacement of the venous catheter. In no case was burst suppression observed during induction with 5 mg·kg⁻¹ of propofol. This, together with the absence of hypotension, argues against this dose being an overdose. Additional studies are needed to determine the precise biochemical or biophysical origin of the movements associated with induction of anesthesia with propofol.

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**References**