

Effects of Propofol on H-reflex in Humans

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Background: **Depression of spinal cord motoneuron excitability has been proposed to contribute to surgical immobility. The H-reflex, which measures α-motoneuron excitability, is depressed by volatile anesthetics, whereas the action of propofol is unknown. The objective of this study was to determine the effects of propofol anesthesia on the H-reflex.**

Methods: **In 13 patients (group 1), H-reflex was measured before (T_0), 3 min after (T_1), and 10 min after (T_2) a 2-mg/kg bolus dose of propofol, followed by an infusion of 10 mg · kg^{-1} · h^{-1}. Ten patients (group 2) were studied when propofol was given *via* a programmable pump set to a propofol blood concentration of 6 μg/ml, and 10 patients (group 3) were studied with the pump set to 9 μg/ml. Latencies and amplitudes of H-reflexes (H_0, H_1, H_2) and M-responses (M_0, M_1, M_2) of the soleus muscle were recorded, and H/M ratios (H_0/M_0, H_1/M_1, H_2/M_2) were calculated.**

Results: **In group 1, H-reflex amplitudes and the H/M ratio were diminished after induction with propofol (H_0 *vs.* H_1, $P = 0.033$; H_0/M_0 *vs.* H_1/M_1, $P = 0.042$). After 10 min of propofol infusion, the H_2/M_2 ratio was still decreased versus H_0/M_0 ($P = 0.031$). In group 2, no difference was detected. In group 3, propofol depressed H-reflex amplitudes at T_2 (H_0 *vs.* H_2, $P < 0.01$), and amplitudes were also lower at T_2 than at T_1 (H_1 *vs.* H_2, $P < 0.01$). In this group, the H/M ratio decreased from T_0 to T_2 (H_0/M_0 *vs.* H_2/M_2, $P < 0.002$).**

Conclusions: **During steady state conditions using propofol as the sole agent, a depression of the H-reflex is observed only at a high blood concentration of 9 μg/ml. The authors suggest that immobility during propofol anesthesia is not caused by a depression of spinal motoneuron circuit excitability.**

WALL[1] was one of the first investigators to speculate that general anesthetics might not only depress brain activity, but that the spinal cord could be involved as well. de Jong *et al.*[2] found muscular relaxation during general anesthesia correlated to suppression of spinal motoneuron excitability, as measured by H-reflexes. Recent studies have rejuvenated the concept of spinal cord as a site of anesthetic action.[3,4] The inhibition of H-reflexes and F-waves by isoflurane[4] suggests that anesthesia and surgical immobility might at least be caused in part by suppression of motoneuron excitability. Monitoring motoneuron excitability during anesthesia could serve as a tool to predict patient movements and might possibly be related to anesthetic depth. Furthermore, during spinal cord surgery[5] or surgery of spastic disorders, monitoring motoneuron excitability might be helpful for the operating surgeon to determine more precisely the extension of the surgical procedure.

The H-reflex was first described by Hoffmann in 1918.[6] It consists of electrical stimulation of the posterior tibial nerve generating Ia afferent input and activation of α-motoneurons in the spinal cord. Activation of these motoneurons induces a contraction of the soleus muscle that can be recorded by electromyography. The H-reflex can be considered as representative of excitability changes in the myotactic reflex arc and of motoneuron excitability[7,8]; however, it depends not only on excitability changes of the α-motoneuron, but also on afferent terminals, synaptic transmission, and interneurons.[8,9] Because the α-motoneuron is only the final pathway of transmission of motor responses and as such subjected to segmental and suprasegmental excitatory and inhibitory influences, no distinction can be made between direct spinal or supraspinal effects.

Most of the previous studies on motoneuron excitability referred exclusively to inhalational anesthetics (ether,[10,11] halothane,[11] methoxyflurane,[11] enflurane,[12] isoflurane[4]) or nitrous oxide.[4] To date, only two studies exist regarding the effects of intravenous anesthetics, ketamine and etomidate, respectively.[13,14] It was therefore interesting to investigate if propofol would also depress the H-reflex as inhalational anesthetics do.

To distinguish the effects of propofol on axonal conduction or the neuromuscular junction from effects on motoneuron excitability, M-responses were measured. The ratio of the peak H-amplitude to the peak M-amplitude (H/M ratio) was calculated. This ratio may indicate the activity of the motoneuron pool, as it represents the percentage of motoneurons firing at one given moment[15] and is considered a more precise indicator of motoneuron excitability than H-reflex alone.[16]

Methods and Materials

Subjects

After obtaining approval from the Institutional Review Board at Johannes Gutenberg University Hospital and written informed consent, 33 otherwise healthy patients in American Society of Anesthesiologists class I or II, scheduled for elective urologic, orthopedic, or transnasal surgery of nonfunctional pituitary tumors were chronologically divided into three groups. Group 1 consisted of 13 patients, and groups 2 and 3 consisted of 10 patients each. All patients were given 100 mg hydroxyzine orally 1 h before arriving at the operating

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room. No patient suffered from central or peripheral neurologic disorders.

Anesthesia Protocol

After the patient arrived at the operating room, an intravenous infusion of normal saline was started, and the study equipment was attached. All patients received preoxygenation for 3 min by face mask before anesthesia induction was begun.

In group 1, an initial propofol dose of 2 mg/kg over 1 min was given, immediately followed by propofol as a continuous infusion at a rate of 10 mg · kg^{-1} · h^{-1} (167 μg · kg^{-1} · min^{-1}). Electrophysiologic measurements were taken at baseline (preanesthesia = T_0), 3 min after induction (T_1), and 10 min after induction (T_2). The effect-site propofol concentration was calculated later with the IVA-SIM program using a three-compartment model (Version 3.01; Zeneca, Plankstadt, Germany).

In groups 2 and 3, propofol was injected with an Alaris IVAC TCI pump (Alaris Medical Systems, Hampshire, United Kingdom), indicating an estimate for the concentration in the blood and brain compartment. The TCI pump was programmed with patient age, weight, and the desired blood level. Targeted blood levels of 6 μg/ml in group 2 and 9 μg/ml in group 3 were achieved after 1 min as the pump was programmed for a three-step induction with a 20-s pause after each step. Electrophysiologic measurements were taken at baseline (preanesthesia = T_0) and 3 min after induction (T_1). To ensure sufficient equilibration between the blood and the effect site, the third measurement (T_2) was taken 10 min after the estimated effect-site concentration, as indicated at the TCI pump's display, corresponded to the preset blood target concentration of 6 or 9 μg/ml.

If spontaneous breathing ceased, controlled ventilation was initiated by a face mask to maintain an end-tidal carbon dioxide level of 33–40 mmHg (Capnomac Datex, Helsinki, Finland). Fraction of inspired oxygen was 1.0. No patient required supplementary propofol injections.

Electrophysiologic Protocol

H-reflexes and M-responses were evoked by stimulating the tibial nerve in the popliteal fossa using cutaneous surface electrodes, and electromyographic activity was recorded over the soleus muscle by means of two surface electrodes placed 2–3 cm apart from each other. Records were taken using a Nicolet Viking II (Nicolet, Offenbach, Germany) with a rectangular stimulus lasting 1 ms and intensities varying from 0 to 20 mA to elicit a maximal H-reflex amplitude. After having established the intensity that gave rise to a baseline maximal H-reflex amplitude, a series of eight (H-reflex) or four (M-response) stimuli was elicited at each time point (H_0, H_1, H_2; M_0, M_1, M_2). H-reflexes were distinguished from M-responses by their late occurrence and their elicitation by less intense stimuli. All subsequent stimulations were undertaken at the same intensity that had given rise to a maximal amplitude. At least 30 s was allowed to pass before a subsequent stimulation was performed. M-responses were evoked by supramaximal stimulation. Repetition of stimulation was performed using identical stimulus intensities as at T_0.

Table 1. Demographic Data of Study Group

Variable	Group 1	Group 2	Group 3
Number of patients	13	10	10
Age (yr)	53 ± 10.8	50.4 ± 11.8	46.6 ± 14.9
Sex (M/F)	6/7	3/7	7/3
Weight (kg)	76.4 ± 6.9	74 ± 10.9	80.1 ± 13
Height (cm)	170.7 ± 8	170.9 ± 9.5	175.9 ± 10.7

Values are mean ± SD.

The signals were stored on the system's hard disk. H- and M-amplitudes were measured offline from peak to peak using the cursor of the electromyograph apparatus. Latencies were also determined by use of the system's cursor. H/M ratios were calculated (H_0/M_0, H_1/M_1, H_2/M_2).

Statistical Analysis

Data collection was achieved and stored with the electromyograph apparatus, and the average amplitude of a series was taken into account. Demographic data and group comparisons were performed by chi-square analysis. Amplitudes were compared by a one-way analysis of variance for repeated measurements. When data were not normally distributed, a Friedman repeated-measures analysis of variance on ranks was used. All pairwise multiple comparison procedures were conducted with a Tukey test. Values for parametric data are represented as mean ± SD, and for nonparametric data they are given as median (interquartile range). A P value less than 0.05 was considered statistically significant. Statistical analyses were performed with an appropriate computer program (StatView 4.0, Abacus Concepts Inc., Berkeley, CA).

Results

There were no differences in demographic data between the three groups (table 1). No relevant changes of blood pressure (> 30% of baseline) were observed throughout the study period, nor was there any single recording of a mean arterial blood pressure less than 55 mmHg. In all groups, every patient had lost eyelash reflexes at T_1 and T_2.

H-reflex amplitudes for the three patient groups at baseline and at different calculated effect-site concentrations at T_2 are shown in figure 1.

In group 1, there was a decrease of H-reflex amplitudes and the H/M ratio after induction with propofol. The effect on H-reflex had disappeared 10 min later as there was no effect when H_0 measurements were compared

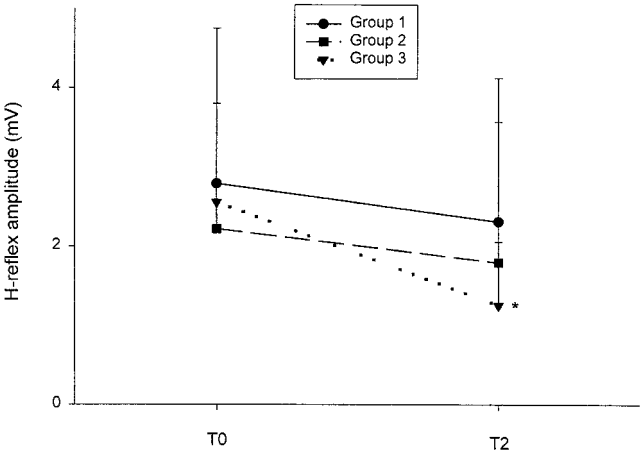

Fig. 1. H-reflex amplitudes after propofol infusion in three patient groups with different calculated effect-site concentrations of propofol (for further explanations, see text; *$P < 0.05$ *vs.* T_0). Error bars for groups 1 and 2 indicate SD, and for group 3 indicate the 95% confidence interval (nonparametric data).

with H_2 values. Depression of the H/M ratio still persisted at T_2 (table 2). The calculated effect-site propofol concentration 10 min after induction with 2 mg/kg propofol over 1 min and consecutive infusion of 10 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} at T_2 was 1.9 $\pm$ 0.2 μg/ml.

No difference was detected in group 2 (6 μg/ml propofol; table 3). However, one patient in group 2 showed complete loss of the H-reflex, whereas another showed a marked reduction of the H-reflex amplitude.

In group 3 (9 μg/ml propofol; table 4), propofol depressed amplitudes of H-reflexes. A multiple comparison analysis in this group revealed H-reflex amplitudes diminished at T_2 *versus* T_0 amplitudes (H_0 *vs.* H_2; $P < 0.01$), and T_2-amplitudes were lower than T_1 values (H_1 *vs.* H_2; $P < 0.01$). Values for the H/M ratio differed from T_0 to T_2.

The percentage of patients showing any signs of movement during the entire study period was 62% in group 1, 40% in group 2, and 0% in group 3 ($P = 0.009$, group 3 *vs.* group 1). H-reflex latencies remained unchanged throughout the study period in all groups. In no case did latencies exceed 35 ms.

Discussion

The results of our study demonstrate a concentration-dependent effect of propofol on spinal cord motoneuron excitability as measured by H-reflexes and the H/M ratio. No effect on axonal conduction or neuromuscular transmission could be detected, as the M-response remained unchanged throughout the experiment.

Previous studies of motoneuron excitability using H-reflexes or F-waves during general anesthesia found significant depression after administration of halothane,[11] enflurane,[12] isoflurane,[3,4,18] desflurane,[5] or nitrous oxide.[18–21] Only two studies in humans have assessed the effect of intravenous anesthetics on H-reflexes.[13,14] H-reflex amplitudes were found to be increased after administration of ketamine[13] and etomidate.[14] These two intravenous anesthetics are supposed to exert their effects at different receptor sites, ketamine on *N*-methyl-D-aspartate–type glutamate receptors[22] and etomidate, at least in part, on γ-aminobutyric acid$_A$ receptors.[23]

Depression of α-motoneuron excitability by volatile anesthetic agents has led to the conclusion that this effect would contribute to immobility during anesthesia and surgery.[3,4] Several researchers have exclusively studies F-waves[3] or both F-waves and H-reflexes,[4] as H-reflexes are affected by afferent terminals or interneurons, whereas F-waves can be considered as a pure indicator of motoneuron excitability. Those studying the effects of general anesthetics on H-reflexes found a 50% depression of H-reflex amplitudes from baseline values at relatively low isoflurane concentrations (0.6 minimum alveolar concentration). Further increase in isoflurane had

Table 2. Amplitudes (in mV) of H-Reflex, M-Response, and H/M Ratio in 13 Patients (Group 1) at Baseline (T0) and 3 min (T1) and 10 min (T2) after 2 mg/kg Propofol, followed by 10 mg $\cdot$ kg^{-1} $\cdot$ min^{-1}

	H-Reflex			M-Response			H/M Ratio		
Patients	T0	T1	T2	T0	T1	T2	T0	T1	T2
1	2.2	1.7	0.6	6.7	6.6	6.8	0.33	0.26	0.09
2	0.6	1	0.7	4.7	4.6	4.6	0.13	0.22	0.15
3	1.9	1.2	1.3	8.6	11.6	11.7	0.22	0.1	0.11
4	7.3	5.3	5.3	10.6	10.5	10	0.69	0.5	0.53
5	2.9	2.7	2.4	7.7	7.5	8.3	0.38	0.36	0.29
6	3.5	3.3	2.8	9.1	8.5	9	0.39	0.39	0.31
7	4.1	4.4	4.3	5.9	6.7	7.8	0.53	0.66	0.55
8	0.8	0.5	0.5	4	4	3.8	0.22	0.13	0.14
9	4.9	2.9	4.9	17.5	15.9	15	0.33	0.18	0.33
10	4.2	3.9	4.3	16.5	16.3	16.9	0.25	0.24	0.25
11	1.2	1.4	1.4	8.6	8.5	8.5	0.14	0.16	0.16
12	1.9	0.4	1.1	2.9	2.9	3.5	0.54	0.14	0.31
13	0.8	0.4	0.4	2.5	2.3	1.8	0.42	0.16	0.22
Mean $\pm$ SD	2.8 $\pm$ 2	2.2 $\pm$ 1.6*	2.3 $\pm$ 1.8	8.1 $\pm$ 4.7	8.2 $\pm$ 4.5	8.3 $\pm$ 4.4	0.35 $\pm$ 0.17	0.27 $\pm$ 0.17†	0.26 $\pm$ 0.15‡

* $P = 0.03$ *versus* T0. † $P = 0.042$ *versus* T0. ‡ $P = 0.031$ *versus* T0.

Table 3. Amplitudes (in mV) of H-Reflex, M-Response, and H/M Ratio in 10 Patients (Group 2) at Baseline (T0) and 3 min (T1) and 10 min (T2) after Reaching a Propofol Effect-site Concentration of 6 μg/ml

	H-Reflex			M-Response			H/M Ratio		
Patients	T0	T1	T2	T0	T1	T2	T0	T1	T2
1	3.7	1.7	0.6	2.6	2.5	2.3	1.42	0.68	0.26
2	1.2	0.7	0.7	8	8	8	0.15	0.09	0.09
3	1	1	1	15.3	14.1	14.7	0.07	0.07	0.07
4	0.5	0	0	5.7	2.3	3	0.09	0.01	0
5	1.9	3.5	2.3	12.2	10.1	11.2	0.16	0.35	0.21
6	5.1	6.1	5.9	8.2	9.4	9.4	0.62	0.65	0.63
7	2.8	3.1	3.1	2.9	3.5	3.6	0.97	0.89	0.86
8	3.6	3.2	2.4	10	10	9.4	0.36	0.32	0.26
9	0.2	0.1	0.2	8.2	10.6	10	0.03	0.01	0.02
10	2.2	1.6	1.8	1.5	1.3	1.3	1.47	1.23	1.38
Mean ± SD	2.2 ± 1.6	2.1 ± 1.9	1.8 ± 1.8	7.5 ± 4.4	7.2 ± 4.4	7.3 ± 4.5	0.53 ± 0.56	0.43 ± 0.42	0.38 ± 0.45

no significant effect on the amplitudes. When nitrous oxide was added at concentrations between 30% and 70% and isoflurane was reduced simultaneously to maintain 1 minimum alveolar concentration, H-reflex amplitudes decreased further to 34% of baseline at 30% nitric oxide. Further increase in nitric oxide, while isoflurane was reduced again, left amplitudes unchanged.[4] In our opinion, this would point to a drug-dependent effect in volatile anesthetics on motoneuron excitability. In contrast, and as our results show, the effect of the intravenous anesthetic agent propofol on motoneuron excitability appears to be concentration-dependent.

Loss of consciousness with propofol anesthesia occurs at blood concentrations of 3.5–5 μg/ml.[24] Plasma concentrations of 10.0 and 17.4 μg/ml propofol prevented movement in 50% of patients on skin incision and during intubation, respectively.[24] In our study, 62% of patients in group 1 and 40% in group 2 showed spontaneous movements, whereas this was the case in none of the patients in the group with 9 μg/ml of targeted propofol blood and estimated effect-site concentration ($P = 0.009$). As H-reflexes in group 3 showed a significant depression compared with baseline recordings, this immobility during pure propofol anesthesia could possibly be caused by an effect of propofol on spinal motoneuron excitability. Whether this immobility is caused by supraspinal action or is directly related to α-motoneuron depression remains to be clarified in a separate study.

The recommended propofol induction dose is 1.0–2.5 mg/kg, followed by an infusion of propofol 100–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$.[25] This corresponds to the dose used in group 1 of our study. Although only a relatively weak stimulus such as artificial ventilation by face mask was given during the study period, a majority of patients in this group showed spontaneous movements, but no eyelash reflex was observed. Because H-reflex amplitudes did not show prolonged depression, we assume that spinal motoneuron excitability is not persistently depressed when recommended clinical doses of propofol are given. On the other hand, 3 ng/ml of blood fentanyl reportedly decreases propofol requirements by approximately 50%.[24] We did not measure the association of propofol and fentanyl on its effect on H-reflexes, but our results possibly indicate that immobility during propofol anesthesia in recommended doses is not caused by a specific propofol action on motoneuron excitability, but rather by a synergistic effect of all drugs used. When propofol is the single anesthetic

Table 4. Amplitudes (in mV) of H-Reflex, M-Response, and H/M Ratio in 10 Patients (Group 3) at Baseline (T0) and 3 min (T1) and 10 min (T2) after Reaching a Propofol Effect-site Concentration of 9 μg/ml

	H-Reflex			M-Response			H/M Ratio		
Patients	T0	T1	T2	T0	T1	T2	T0	T1	T2
1	1.1	0.6	0	5.6	5.9	5.7	0.2	0.09	0
2	5.3	1.8	1.7	6.4	4.9	5.6	0.83	0.36	0.3
3	5	4.3	3.6	9.4	8.9	6.1	0.53	0.48	0.59
4	0.9	0.6	0.5	3.1	2.8	2.6	0.29	0.23	0.18
5	3.9	2.8	2.3	8.9	8.3	7.5	0.44	0.34	0.31
6	0.7	0.3	0.1	9.2	9.5	9.4	0.08	0.03	0.01
7	3.2	2.4	1.5	4.9	4.1	4	0.65	0.59	0.38
8	1.2	1.4	1	7.1	7.3	7.3	0.16	0.19	0.14
9	1.4	1.3	0.3	5.2	5.4	5	0.27	0.24	0.06
10	2.9	2.4	1.6	4.8	4.8	4.8	0.6	0.5	0.33
Median (interquartile range)	2.2 (1.1–3.9)	1.6 (0.64–2.4)	1.3* (0.3–1.7)	6 (4.9–8.9)	5.7 (4.8–7.3)	5.7 (4.8–7.3)	0.37 (0.2–0.6)	0.29 (0.19–0.48)	0.24† (0.06–0.33)

* $P < 0.01$ *versus* T0 and *versus* T1. † $P < 0.002$ *versus* T0

agent, very high blood levels are required to prevent motor responses. Turtle *et al.*[26] found that a propofol infusion of 350 $\mu g \cdot kg^{-1} \cdot min^{-1}$ prevented 95% of adults from moving in response to surgical stimulation when used together with nitrous oxide.

It is unclear why the injection of 2 mg/kg propofol over 1 min, followed by a propofol infusion of 10 $mg \cdot kg^{-1} \cdot h^{-1}$, diminished H-reflexes at T_1 *versus* baseline while there was no such reduction in group 2 or 3. The most likely explanation is probably very high transient propofol levels from the induction dose that were not reached when propofol was given *via* the TCI pump. Kalkman *et al.*[27] found that a single 2-mg/kg dose of propofol affected descending motor pathways in humans as it depressed evoked motor responses to transcranial stimulation. In that study, depression of motor evoked responses after administration of propofol even persisted for a much longer period than the effects on consciousness and was still detectable after 10 min, a time point when H-reflexes in our study no longer showed a difference compared with baseline. Motor evoked responses in the study by Kalkman *et al.* were also depressed for a 30-min period after midazolam 0.05 mg/kg, a dosage that produced only sedation but not loss of consciousness. In contrast, the concentration used in our study group 3 (9 μg/ml propofol) is sufficient as the sole agent to produce anesthesia in almost every patient. Therefore, it is conceivable that motor evoked response to transcranial stimulation is a very sensitive method of measuring motoneuron excitability, whereas H-reflex is more insensitive and perhaps could have some relation to the depth of surgical anesthesia. Therefore, measurements of H-reflexes would seem more appropriate for monitoring or predicting motor responses during anesthesia than motor evoked responses. However, this would be subject to further study.

Several studies have shown that there is significant potentiation of neuromuscular blocking agents by inhalational anesthetics but not by propofol.[28–30] Higher doses of muscle relaxants were required to provide adequate muscle paralysis when anesthesia was maintained with a continuous infusion of propofol as when anesthesia was maintained with inhalational halogenated agents.[29] The lack of motoneuron excitability depression by propofol in recommended doses in contrast to inhalational anesthetics could explain these differences.

In patients with spasticity associated with cerebral palsy, H-reflex monitoring has been proposed for identifying rootlets to be sectioned during selective posterior rhizotomy.[31] According to the results of this and the aforementioned studies, this monitoring technique can only be applied when the anesthetic drugs used exert no or minimal influence on electrophysiologic parameters. We therefore recommend avoiding the use of volatile anesthetics as well as the use of propofol at high dosages. However, the best anesthesia technique for this type of procedures still remains to be determined.

In summary, this study showed a concentration-dependent effect of propofol on spinal motoneuron circuit excitability as measured by H-reflexes and the H/M ratio. Recommended propofol doses for induction and maintenance only had a transient effect on the H-reflex and were no longer demonstrable after 10 min of propofol anesthesia. Propofol does not decrease axonal conduction or transmission at the neuromuscular junction, as M-responses remained unchanged. Immobility during propofol anesthesia at blood target and effect-site concentrations up to 6 μg/ml does not seem to be caused by a depression of spinal motoneuron circuit excitability.

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