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Propofol Requirement Is Decreased in Patients with Large Supratentorial Brain Tumor

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Background: **The anesthetic requirement is decreased in animals with head injury, but there are no data regarding the effect of intracranial tumor on the potency for intravenous anesthetics. The authors compared the quantal dose–response curves for propofol in patients having large (≥ 30 mm, mass effect) brain tumor with those having smaller (< 30 mm) lesions and with control patients undergoing noncranial surgery.**

Methods: **Sixty patients in each group were randomly assigned to receive one of the six doses of propofol (0.5, 0.7, 1.0, 1.3, 1.8, or 2.5 mg/kg) over 10 s. Two minutes after drug administration, patients were asked to open their eyes as a test for response to verbal command. Patients who failed to respond were given a 10-s, 50-Hz, 80-mA transcutaneous tetanic electrical current to the ulnar nerve as a test for response to painful stimulus. Purposeful movement indicated positive response. Log dose–response curves for loss of response to verbal command and tetanic stimulus were calculated after logit transformation.**

Results: **The median effective doses (ED_{50}s; 95% confidence interval) for suppressing response to verbal command and tetanic stimulus were 0.75 (0.65–0.86) mg/kg and 1.28 (1.11–1.49) mg/kg, respectively, in patients with large brain tumor. These values were significantly less than the corresponding ED_{50}s in patients with small tumor, 1.01 (0.88–1.15) mg/kg and 1.76 (1.51–2.07) mg/kg, or healthy control subjects, 0.98 (0.86–1.12) mg/kg and 1.89 (1.62–2.23) mg/kg.**

Conclusions: **The doses of propofol required to suppress response to verbal command and tetanic stimulus were 23% less and 32% less in patients with large brain tumor compared with control subjects. Small tumor did not affect potency of propofol. (Key words: Anesthesia; induction; intravenous; neurosurgery; potency.)**

THE anesthetic requirement for pentobarbital and the analgesic requirement for fentanyl and alfentanil were decreased by 28% and 25–26%, respectively, in male Sprague-Dawley rats with cryogenic brain injury.[1,2] However, it is not known whether other forms of brain lesion will also affect the potency of anesthetic agents. In particular, there are no data regarding the effect of intracranial tumor on anesthetic requirements. Clinically, patients with large brain tumor undergoing craniotomies for tumor excision are slower to emerge from anesthesia compared with patients undergoing noncranial surgery.[3] Although many surgical and anesthetic factors may delay emergence from anesthesia, we hypothesize that intracranial tumor increases brain responsiveness to anesthetics. Thus, anesthetic administration based on the dose requirements in healthy adults may result in drug overdose. This study set out to determine the change of anesthetic requirement associated with intracranial tumor. We compared the quantal dose–response curves of propofol for suppressing response to verbal command and tetanic stimulus in patients having large brain tumor with those of smaller lesions and control patients without brain pathology.

Materials and Methods

The study was approved by the local clinical research ethics committee. Written informed consent was obtained from all patients. Sixty patients were recruited for each group. All patients were classified as American Society of Anesthesiologists physical status I or II, aged 18–65 yr, weight within 20% of ideal, and had no known contraindication to the use of propofol. Exclusion criteria included current pregnancy and history of alcohol or opioid abuse. Patients were also excluded if they were disorientated or if the preoperative Observer's Assess-

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ment of Alertness/Sedation Scale score was less than 20.[4] Neurosurgical patients with supratentorial brain tumor were given dexamethasone, ranitidine, and valproate at least 1 week before surgery and were scheduled for elective craniotomy. Control patients were not taking any medication and were scheduled for minor gynecologic or peripheral orthopedic surgery. The size of the brain tumor was defined according to preoperative computed tomographic or magnetic resonance imaging appearance. Tumors were classified as large or small on the basis of Schubert's criteria.[3] A large brain tumor had a maximum diameter greater than or equal to 30 mm, with associated mass effect, whereas a small tumor was less than 30 mm in diameter. Evidence of mass effect included midline shift > 3 mm, significant cerebral edema, or ventricular compression.[5] Tumor volume was also measured using Cavalieri's direct estimator.[6] Location of the tumor was recorded as either frontal, parietal, temporal, or occipital.

Patients fasted from midnight before surgery, and no preanesthetic medication was prescribed. Patients in each group were randomly allocated to 6 sets of 10. Each set received a fixed dose of propofol. The six doses of propofol, 0.5, 0.7, 1.0, 1.3, 1.8, and 2.5 mg/kg, were derived from our previous data,[7–9] so that the logarithms of the doses were approximately equally spaced. Observers were blinded to the dose of propofol given. Although it was also intended that the observers were to be blinded to the study group, it was not always feasible because nearly all neurosurgical procedures were performed in one dedicated operating room. Therefore, patients studied in other rooms were more likely to belong to the control group. Nevertheless, the observers were blinded as to the size of the brain tumor in all neurosurgical patients.

Standard monitoring was applied, and patients were given oxygen, 6 l/min, for 5 min. Arterial pressure was recorded noninvasively by the automated module in a Narkomed 4E anesthetic machine (North American Dräger, Telford, PA). Propofol was injected over 10 s into a peripheral vein and was followed by a flush of 10 ml normal saline solution. The patient was undisturbed except for noninvasive measurement of arterial pressure. Heart rate and mean arterial pressure were recorded immediately before, at 1 min, and at 2 min after administration of propofol.

Two minutes after the start of the propofol injection, the patients were called by their names and were asked to open their eyes. Patients who did not open their eyes were recorded as "no response to verbal command." These patients were then given a standardized transcutaneous tetanic stimulus (10-s, 50-Hz, 80-mA) to the ulnar nerve at the wrist delivered by a constant current peripheral nerve stimulator (NS252, Fisher & Paykel Healthcare, Auckland, NZ). Any purposeful movement of the head, neck, or limbs apart from the stimulated arm within 30 s after the stimulus was considered a positive response. Absence of positive response was recorded as "no response to tetanic stimulus." Grimacing, bucking, swallowing, and hyperventilation were not positive responses.[10] Patients who respond to verbal command were not given the tetanic stimulus and were recorded as positive response to tetanic stimulus.

A 10-ml venous blood sample was taken before each study for the measurement of plasma valproate concentration using a fluorescence polarization immunoassay as previously described.[11] The inter- and intraassay coefficients of variation were 2.3% and 3.7%, respectively, at 5.4 μM, and the limit of detection was 0.1 μM (where 1 μM = 6.93 μg/ml).

Statistical analyses were performed with SPSS 7.5 for Windows (SPSS Ltd., Chicago, IL). Demographic data were compared among groups using analysis of variance or chi-square test as appropriate. Quantal log dose–response curves were calculated and were compared using the advanced statistics probit analysis module after logit transformation of data. The changes in mean arterial pressure and heart rate from 0 to 2 min were analyzed by multiple regression using log propofol dose and patient group as independent variables. Probability values less than 0.05 were considered significant.

Results

Patient characteristics are summarized in table 1. Age, weight, and height did not differ among groups. In patients with brain tumor, gliomas and meningiomas were the most common lesions and were found predominantly in the frontal and parietal regions. However, the distribution of lesion type or their locations were not different between groups. The median (range) duration of dexamethasone and valproate therapy before surgery in the large tumor group, 8 (7–12) days, was similar to that of the small tumor group, 8 (7–19) days. Plasma valproate concentrations taken immediately before each study did not differ between the two groups.

Figures 1 and 2 describe the probability relationship between the logarithm of the dose of propofol with loss of response to verbal command and tetanic stimulus,

Table 1. Patient Characteristics

	Large Tumor (n = 60)	Small Tumor (n = 60)	Controls (n = 60)
Age (yr)	41 ± 11	37 ± 10	38 ± 9
Gender			
Male (n)	27	27	28
Female (n)	33	33	32
Weight (kg)	60 ± 9	58 ± 9	59 ± 9
Height (cm)	159 ± 5	160 ± 3	159 ± 4
Tumor pathology			
Gliomas [n (%)]	32 (53)	37 (62)	—
Meningoma [n (%)]	20 (33)	17 (28)	—
Metastasis [n (%)]	3 (5)	2 (3)	—
Others [n (%)]	5 (8)	4 (7)	—
Tumor location			
Frontal [n (%)]	31 (52)	27 (45)	—
Temporal [n (%)]	8 (13)	10 (17)	—
Parietal [n (%)]	14 (23)	18 (30)	—
Occipital [n (%)]	7 (12)	5 (8)	—
Tumor volume (ml)	69.6 ± 27.1	5.0 ± 4.8*	—
Plasma valproate concentration (μM)†	466 ± 89	495 ± 88	—

Values are mean ± SD or n (%).

* $P < 0.001$ *versus* large tumor.

† Reference therapeutic ranges are 345–690 μM.

respectively. The fraction of patients who did not respond to verbal command and tetanic stimulus in each dose category is shown in table 2. The derived effective doses of propofol at which 50% (ED_{50}) and 95% (ED_{95}) of patients failed to respond at each of the endpoints are summarized in table 3. Compared with the control group, large brain tumor shifted the dose-response curves to the left and reduced the ED_{50}s of propofol at both endpoints ($P < 0.001$). However, small tumor did not change the dose requirement of propofol, and the dose-response curves overlapped with those of the control group. The large tumor-to-control relative median potency (95% CI) for loss of response to verbal command was 0.77 (0.55–0.95); for loss of response to tetanic stimulus, it was 0.68 (0.45–0.88). The corresponding large-to-small tumor relative median potencies (95% CI) were 0.74 (0.52–0.93) and 0.73 (0.51–0.92), respectively.

Baseline mean arterial pressure and heart rate did not differ among the three groups. Increasing propofol dose was associated with significant decrease in mean arterial pressure at 2 min compared with the baseline values ($P < 0.001$; table 4), but there was no significant regression between propofol dose and changes in heart rate

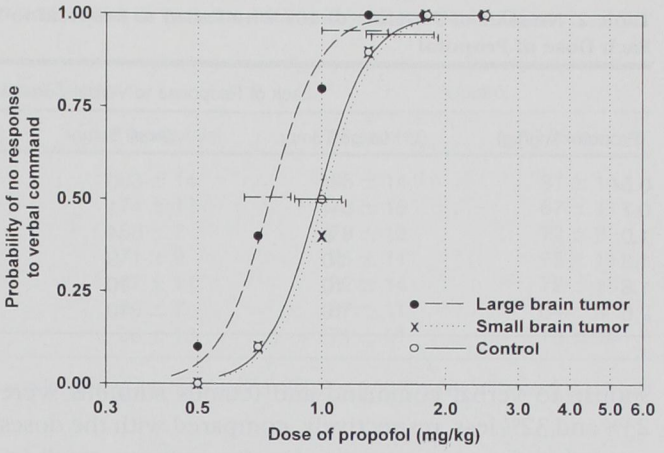

Fig. 1. Calculated dose–response curves (log dose scale) for loss of response to verbal command in patients with brain tumor and patients undergoing noncranial surgery. The 95% confidence intervals for the ED_{50}s and ED_{95}s are also displayed, slightly offset for clarity. Fraction of patients (of 10) who failed to respond to verbal command are shown as closed circles for patients with large brain tumor, as X for patients with small tumor, and as open circles for control patients.

($P = 0.07$). Changes in mean arterial pressure and heart rate were not different among groups.

Discussion

In patients with large (≥ 30 mm, mass effect) brain tumor, the doses of propofol required to abolish re-

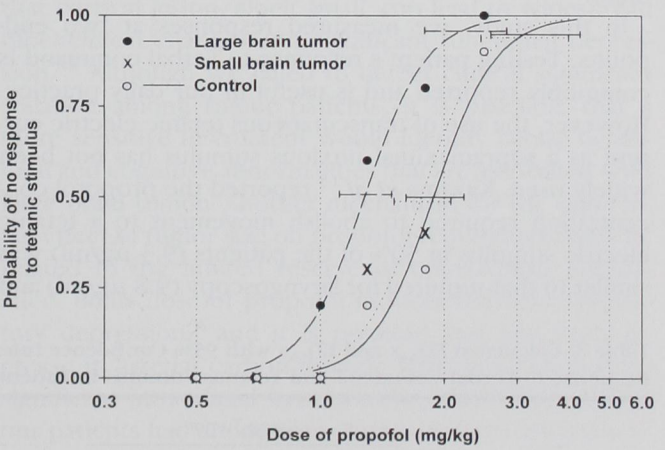

Fig. 2. Calculated dose–response curves (log dose scale) for loss of response to tetanic stimulus in patients with brain tumor and patients undergoing noncranial surgery. The 95% confidence intervals for the ED_{50}s and ED_{95}s are also displayed, slightly offset for clarity. Fraction of patients (of 10) who failed to respond to tetanic stimulus are shown as closed circles for patients with large brain tumor, as X for patients with small tumor, and as open circles for control patients.

Table 2. Number of Patients (of 10) Who Failed to Respond to Verbal Command and Tetanus Stimulus after Each Dose of Propofol

	Lack of Response to Verbal Command			Lack of Response to Tetanus Stimulus		
Propofol (mg/kg)	Large Tumor	Small Tumor	Control	Large Tumor	Small Tumor	Control
0.5	1	0	0	0	0	0
0.7	4	1	1	0	0	0
1.0	8	4	5	2	0	0
1.3	10	9	9	6	3	2
1.8	10	10	10	8	4	3
2.5	10	10	10	10	9	9

sponse to verbal command and tetanus stimulus were 23% and 32% less, respectively, compared with the doses needed in the control group. On the contrary, small (< 30 mm) lesions did not affect the potency of propofol. These data confirmed our hypothesis that patients with large brain tumor are more sensitive to propofol and that the increased response to anesthetics may contribute to the slower recovery in patients undergoing craniotomy for excision of large tumor.[3]

Our estimates of ED_{50} in the control patients at both endpoints are comparable to those reported previously from our institution using identical methodology.[7–9] The ED_{50} of propofol required to suppress verbal command (0.98 mg/kg) is also similar to those reported recently (1.11–1.16 mg/kg).[12–14] Any difference in ED_{50} can be attributed to the variation among studies in the method of determining the endpoint and the timing of assessment.

In this study, we measured responses at two endpoints. Testing patient's response to verbal command is commonly reported and is useful in our daily practice. However, the use of transcutaneous tetanic electric current as a supramaximal noxious stimulus has not been widely used. Kazama *et al.*[15] reported the propofol concentration required to abolish movement to a tetanic electric stimulus in 50% of the patients (9.3 μg/ml) was similar to that required for laryngoscopy (9.8 μg/ml) and standard skin incision (10 μg/ml). Their results suggested that the stimulus intensity of transcutaneous tetanic current is similar to skin incision. Nonetheless, tetanic stimuli are noninvasive, repeatable in each individual, and give reproducible results.

The ED_{95}s are less precise compared with ED_{50}s. The confidence intervals are wide, and the derived ED_{95}s for suppressing response to tetanus stimulus in the small tumor group and in the control group extended beyond the range of doses administered (2.94 and 3.14 mg/kg, respectively). Our analysis assumes that the propofol log concentration–response relationship is a sigmoid function, and this has been found appropriate in previous studies.[16,17] However, the ED_{95}s lie over the shoulder of the curves and result in large variation. Although the concept of ED_{95} is relevant and important in preventing paralyzed patients from unintentional recall, the wide confidence intervals reflect the limitations of these estimates.

We found the propofol requirement for suppressing response to verbal command and tetanic stimulus was reduced to a similar extent in patients with large brain tumor. These results are discrepant with the current belief that unresponsiveness to peripheral noxious stimuli during volatile anesthetics is independent to cortical structures.[18–20] On the other hand, cryogenic cortical brain injury reduces the anesthetic requirement for pen-

Table 3. Calculated ED_{50}s and ED_{95}s with 95% Confidence Intervals (CI) for Bolus Dose of Propofol Required for Suppressing Response to Verbal Command and Tetanus Stimulus in Patients with and without Brain Tumor

	Large Tumor		Small Tumor		Control	
	Dose (mg/kg)	95% CI	Dose (mg/kg)	95% CI	Dose (mg/kg)	95% CI
Verbal command						
ED_{50}	0.75	0.65–0.86	1.01	0.88–1.15	0.98	0.86–1.12
ED_{95}	1.14	1.00–1.45	1.53	1.32–1.93	1.48	1.28–1.88
Tetanus stimulus						
ED_{50}	1.28	1.11–1.49	1.76	1.51–2.07	1.89	1.62 ± 2.23
ED_{95}	2.14	1.79–2.84	2.94	2.44–3.97	3.14	2.60–4.27

Table 4. Heart Rate (HR) and Mean Arterial Pressure (MAP) at 0 min and 2 min in Patients with and without Brain Tumor Receiving Various Doses of Propofol

Propofol (mg/kg)	Large Tumor		Small Tumor		Control	
	MAP (mmHg)	HR (beats/min)	MAP (mmHg)	HR (beats/min)	MAP (mmHg)	HR (beats/min)
Baseline	92 ± 13	87 ± 13	89 ± 16	83 ± 14	86 ± 14	81 ± 14
0.5	76 ± 9	79 ± 9	80 ± 13	74 ± 13	73 ± 16	67 ± 11
0.7	76 ± 15	73 ± 12	72 ± 6	68 ± 7	79 ± 12	72 ± 9
1.0	73 ± 10	74 ± 11	77 ± 11	71 ± 9	75 ± 11	75 ± 11
1.3	70 ± 8	73 ± 8	70 ± 9	67 ± 11	72 ± 14	72 ± 18
1.8	77 ± 16	76 ± 11	68 ± 9	69 ± 7	67 ± 11	64 ± 8
2.5	70 ± 8	63 ± 11	74 ± 8	68 ± 13	71 ± 11	78 ± 14

Values are mean ± SD. Multiple regression showed a significant decrease in MAP with increasing log dose of propofol ($P < 0.001$) but no difference in HR with dose, and no difference among groups.

tobarbital by 28%.[3] We cannot speculate what the difference may be, although it is conceivable that the intrinsic mechanism of action may be different between intravenous and volatile anesthetics.

The change in propofol requirement may be a result of pharmacodynamic or pharmacokinetic differences between the tumor patients and the control subjects. Pharmacokinetic changes alter the effect site concentrations after a given dose of propofol; therefore, the cerebral effects may be markedly different between groups at the time of assessment. We are unaware of any data on the pharmacokinetic changes in patients with brain tumor. However, in a study evaluating the performance of a target-controlled infusion system for propofol during neurosurgical procedures, we found that a pharmacokinetic model derived from healthy adults predicted the blood concentrations of propofol accurately up to 12 h.[21] Other investigators have also confirmed our results, suggesting that the pharmacokinetics in neurosurgical patients is not much different from healthy adults.[22] We believe the lower propofol requirement in patients with large brain tumor is mainly a result of the greater drug effect that is associated with an increased sensitivity to propofol.

Interaction with concurrent drug administration may also affect the cerebral effects of propofol. All our patients with brain tumor received dexamethasone, valproate, and ranitidine as the standard practice in our neurosurgical unit. Although there are no data regarding the effect of dexamethasone and valporate on anesthetic requirement, recent evidence suggests that intravenous ranitidine produces abnormal behavior and emotion.[23] In this study, the preoperative drug therapy and plasma valproate concentration was similar among patients with brain tumor. Given the change of propofol requirement was limited to large brain tumor group, we concluded that the anesthetic-sparing effects of dexamethasone, valproate, and ranitidine, if any, are minimal.

Propofol decreased mean arterial pressure in all patients. Although the minimum alveolar concentration of halothane was reduced by 30% when arterial pressure was decreased by 40% for 1 h in mongrel dogs,[24] these results cannot be extrapolated to humans with brain tumor. In this study, the decrease in arterial pressure was modest (28%), transient, and was comparable among the groups. Therefore, we believe the observed differences in response to propofol could hardly be the results of hemodynamic changes.

We excluded patients who were somnolent preoperatively because baseline sedation would be expected to enhance the response to propofol. It is now established that cortical lesion, albeit small, can lead to widespread biochemical changes and significant functional depression.[25] Although we failed to detect clinical significant sedation among tumor patients, it is plausible that a more sensitive instrument would identify subtle behavioral and cognitive abnormalities that are associated with large brain tumor. Another mechanism for the differential effect of tumor size on propofol requirement may be related to the limited reserve of craniospinal compliance. Bolus dose of propofol induces transient respiratory depression,[9] and it is possible that any small increase in arterial carbon dioxide tension could lead to significant intracranial hypertension. However, none of our patients had an intraventricular catheter placed preoperatively, and the hypothesis cannot be confirmed.

In conclusion, the dose of propofol required to suppress response to verbal command was 23% less and that for tetanic stimulus was 32% less in patients having large brain tumor compared with control patients undergoing noncranial surgery. Small tumor did not affect the potency of propofol.

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