Children Undergoing Repeated Exposures for Radiation Therapy Do Not Develop Tolerance to Propofol

Clinical and Bispectral Index Data

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Background: The purpose of this study was to apply clinical criteria and Bispectral Index® monitor data for evaluating the development of tolerance to propofol in children undergoing repeated drug exposure.

Methods: Children undergoing multiple sessions of radiation therapy during anesthesia for various malignancies were given a predetermined dose of propofol at each session. Heart rate, blood pressure, oxygen saturation, respiratory rate, requirement of additional propofol, and time to emergence and discharge were recorded. The Bispectral Index was monitored continuously, and parameters were extracted and averaged for each week of therapy.

Results: Fifteen children (aged 2.5–10 yr) were treated for an average of 5 weeks (24 ± 6 sessions). There were no significant differences in physiologic parameters or requirements of additional propofol between the weeks of treatment. Bispectral Index data analysis showed that although a nonlinear change with time for each parameter could not be rejected, the differences between the first and last intervals were nonsignificant.

Conclusions: Overall changes with time resulted from random fluctuations without a consistent trend. Combined with clinical data, Bispectral Index parameters showed that tolerance to propofol does not develop in children undergoing repeated exposures to the drug during radiation therapy.

DEEP sedation or general anesthesia is frequently required for young patients with malignancies while they undergo daily radiation therapy. Treatment protocols dictate repeated daily anesthetics over a period of several weeks. Repeated exposure to some anesthetic drugs is associated with the development of tolerance, which is defined as reduced susceptibility to the effects of the drug because of its previous administration.[1,2] The development of tolerance to drugs that depress the central nervous system is a common finding. Pharmacologic tolerance develops with opioids,[3] nitrous oxide,[4] sedative–hypnotic drugs, and antianxiety agents.[2] Tolerance to ketamine has been reported in children sedated with it during radiation therapy[5] and after frequent dressings changes in burn patients.[6] Propofol is a hypnotic drug with unique pharmacologic properties, which make it attractive for short procedures that require deep seda-

tion or general anesthesia because of its fast onset, quick recovery time, and low incidence of nausea and vomiting. The data on tolerance to propofol are controversial. Early data suggested that tolerance to propofol develops both with repeated administrations necessitating increasing the doses of the drug or addition of other drugs over the course of treatment[7,8] and with prolonged infusion in the intensive care unit.[9] Later studies that used clinical parameters for depth of hypnosis failed to show tolerance in children undergoing repeated anesthetic procedures for radiation therapy[10] or in animal models.[11]

The Bispectral Index® (BIS®) monitor (Aspect Medical Systems, Natick, MA) uses a computer program to process an electroencephalogram to assess the hypnotic effects of anesthetic drugs. The device assigns a number from 0 (isoelectric) to 100 (awake state) based on the electroencephalographic waveform.[12] The BIS was reported to correlate or predict the level of sedation or hypnosis in patients or volunteers receiving anesthesia[13,14] and has been suggested as a means of assessing the depth of anesthesia in place of relying on physiologic parameters, such as heart rate and blood pressure.[15] BIS equipment and an algorithm have been defined for the adult, but the relation of BIS–propofol has not yet been studied in the pediatric population, although it seems to react the same way in a child. Data from a recent study showed a good correlation between BIS value and sevoflurane concentration in infants and children, and the authors suggested that the BIS equipment and algorithm may be applied to infants and children with unrestricted anesthesia.[16] Although the BIS was developed for intraoperative use, there is interest in applying this technology to assess the quality and depth of sedation outside the operating room, as well.[17,18] We hypothesized that if tolerance to propofol does develop over time, the BIS response to a predetermined fixed dose of propofol given to children for repeated anesthetic procedures for radiation therapy will change over time and reflect its development.

Materials and Methods

All children aged 16 yr or younger who underwent general anesthesia for radiation therapy at our institution during the 1-yr study period were eligible for the study. Institutional review board approval (Tel Aviv University, Tel Hashomer, Israel) and parental consent were obtained. No drugs other than antiemetics, steroids, or

antibiotics were given during the treatment period. Another eligibility criterion was that at least 18 treatment sessions with the use of general anesthetics were planned. Exclusion criteria were parental refusal and the requirement of any drugs other than propofol for sedation.

The study patients were anesthetized daily, with the exception of weekends and holidays. If treatment was stopped or delayed for more than 2 days, the patients were excluded from the study. All study children had chronic indwelling central venous catheters. All monitors were applied before induction. Patients were preoxygenated before induction and were breathing spontaneously throughout the procedure. Anesthesia was induced by a predetermined single bolus dose of propofol (5 mg/kg) followed by a continuous infusion of $150\ \mu g \cdot kg^{-1} \cdot min^{-1}$ *via* an infusion pump (Medfusion 2010i; Medexinc, Duluth, GA) into the intravenous tubing connected to the central venous catheter. Both clinical and BIS data were collected prospectively for each session. The addition of extra doses of propofol (1 mg/kg) was left to the discretion of the anesthesiologist in charge, who was blinded to the BIS results. The collected data included physiologic measurements (heart rate, blood pressure, respiratory rate) every 2.5 min and oxygen saturation. Movement or coughing during induction or maintenance and additional boluses of propofol given during the procedures were noted in the chart, as well.

The interval from the end of propofol infusion to emergence was also recorded. It was divided into an early emergence phase (withdrawal to jaw thrust) and a late emergence phase (spontaneous eye opening).

The Bispectral Index was measured on an Aspect Medical Systems Model A1050 electroencephalographic monitor by using commercially available disposable BisSensor® strips (Aspect Medical Systems) designed for use in adults. BIS values (BIS® version 3.3) were recorded continuously. The smoothing window was set at 15 s, and the update rate was set at 2 s. The continuously monitored BIS data were recorded at 1-min intervals by an observer who was not involved in the clinical care of the patient. The multiple measurements of BIS were summarized for each patient in each treatment as follows:

- *BIS awake*: before initiation of propofol administration
- *BIS nadir*: the lowest value after induction of anesthesia
- *BIS at 7 min after induction*
- *BIS 60*: the time from nadir to a BIS value of 60
- *BIS area under the curve*: the area under the curve of BIS *versus* the time for the first 12 min of anesthesia
- *BIS curve*: the slope of the regression line of a BIS value *versus* the time from nadir until BIS at 10 min
- *BIS emergence (early)*: the BIS value when the patient first responded to a painful stimulus (jaw thrust)
- *BIS emergence (late)*: the BIS value when the patient first opened his or her eyes

The other measured variables included the times from the end of propofol infusion until early and late emergence from anesthesia.

Statistical Analysis

The treatment period was divided into intervals of 5 days, with an overall number of six intervals (6 weeks). All parameters were averaged for each interval. To study the treatment effect along the designated intervals, an analysis of variance with repeated measures using the mixed model[19] was applied to each parameter. The time of examination was considered to be the fixed effect, and the subjects were the random effect. Because the

Table 1. BIS Parameters for Each Week of Therapy

BIS Variable	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
BIS area under the curve	691 ± 162	770 ± 132	711 ± 172	696 ± 228	733 ± 271	770 ± 201
BIS nadir	29 ± 11	26 ± 10	29 ± 8	20 ± 5	24 ± 10	20 ± 7
BIS at 7 min after induction	52 ± 7.5	48 ± 14	40 ± 6	53 ± 10	47 ± 7	58 ± 9
Time to BIS of 60, min	8.6 ± 4.6	8.1 ± 3.2	9.0 ± 3.6	8.9 ± 3.5	9.1 ± 3.4	9.3 ± 2.2
BIS emergence (early)	89 ± 3	79 ± 5	80 ± 5	81 ± 5	82 ± 6	83 ± 4
BIS emergence (late)	89 ± 3	88 ± 4	87 ± 3	86 ± 4	86 ± 4	89 ± 2
Time to emergence (early) min	9.7 ± 2.8	9.3 ± 5.1	13.3 ± 7.8	11.8 ± 6.8	13.3 ± 6.7	13.1 ± 5.0
Time to emergence (late) min	17 ± 5.4	17.3 ± 8.1	17.3 ± 8.1	18.0 ± 9.6	15.2 ± 8.2	17.7 ± 10.9
Regression curve slope	4.7 ± 3.1	5.5 ± 2.9	4.2 ± 2.3	5.1 ± 2.6	3.9 ± 1.4	4.8 ± 1.7
Additional dose of propofol per session, mg/kg	0.29 ± 0.26	0.25 ± 0.17	0.17 ± 0.21	0.18 ± 0.15	0.32 ± 0.22	0.17 ± 0.15

Data are presented as mean ± SD.
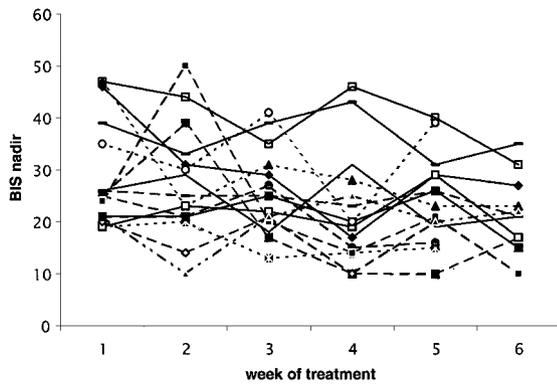
BIS = Bispectral Index.

Fig. 1. Bispectral Index (BIS) nadir *versus* time for each week of treatment (each *line* represents one patient).

number of treatments was not consistent for all of the patients (unbalanced design), the mixed model was chosen to account for incomplete data. To examine the shape of a time-related trend, linear and quadratic equations were applied to the data and tested by using contrast analysis. SAS PROC MIXED version 6.1 (SAS Institute, Cary, NC) was used to obtain restricted maximum likelihood estimates and to perform hypothesis tests. Statistical significance was set at $P = 0.05$.

Results

Fifteen children (seven boys and eight girls) were treated with radiation during the study period and fulfilled the inclusion criteria for this study. No patient was excluded after enrollment. Their age range was 2.5–10 yr (median, 4 yr). Seven patients were treated for infratentorial brain tumors, and the rest were treated for various non–central nervous system tumors (six for soft tissue sarcoma, one for lymphoma, one for nephroblastoma). The mean number of treatment sessions was 24 ± 5. A comparison of the hemodynamic variables, the respiratory variables, and the necessity for extra doses of propofol between the various intervals showed no statistically significant differences (table 1). Both early and late times to emergence did not change significantly over time (table 1). Other BIS parameters are summarized in table 1. Lines that represent the BIS nadir-*versus*-time

values for each week of treatment for the individual patients are illustrated in figure 1. The results of the analysis of variance using the mixed model are summarized in table 2. There was a significant overall change along the intervals in all of the studied parameters. The possibility of a linear trend was rejected for the following parameters: BIS nadir, time to BIS 60, and BIS emergence (early) (fig. 2). However, there was no evidence for rejecting a possible quadratic trend in all parameters. Contrast analysis was used to examine whether the overall significant trend in time was also expressed by a significant difference between the first and last intervals of treatment. The levels of each interval were compared with the level of the first interval for each parameter. None of the differences reached a level of significance (table 2), implying that the overall change along time for the various intervals was the result of random fluctuations along time and did not represent a consistent trend.

Discussion

Tolerance is defined as a decrease in the effect of a drug over time or the need to increase the dose to achieve the same effect.[1] The demonstration of tolerance relies primarily on the need to increase the amount of medication used to achieve the desired level of sedation, analgesia, or hypnosis. The amount of medication administered is titrated by means of bedside clinical assessment, physiologic parameters, or a scoring system that assesses the level of sedation.[17] Plasma concentrations of sedative–analgesic drugs are rarely, if ever, obtained, and their assessment is generally not available at most institutions.

The BIS proved to be an extraordinarily good predictor of hypnotic state, and it significantly outperformed the measured or targeted drug concentration. BIS monitoring has been used to demonstrate the development of tolerance to sedative drugs during sedation in the pediatric intensive care unit. During an ongoing, prospective study designed to evaluate the correlation between the BIS value and intensive care unit sedation scales, Tobias and Berkenbosch[18] noted the need to increase the doses

Table 2. Comparison of BIS Parameters between Different Time Intervals*

Parameter	Time-related Trend	Linear Trend	Quadratic Trend	Comparing Intervals 1 and 5	Comparing Intervals 1 and 6
BIS area under the curve	$P < 0.0001$	NS	NS	NS	NS
BIS nadir	$P < 0.0001$	$P = 0.0036$	NS	NS	$P = 0.06$
Time to BIS of 60, min	$P < 0.0001$	$P = 0.0263$	NS	NS	$P = 0.08$
BIS emergence (early)	$P < 0.0001$	$P = 0.0255$	NS	NS	$P = 0.06$
BIS emergence (late)	$P < 0.0001$	NS	$P = 0.0899$	NS	NS
Regression curve slope	$P < 0.0001$	NS	NS	NS	NS

* Analysis of variance with repeated measures using the mixed model.
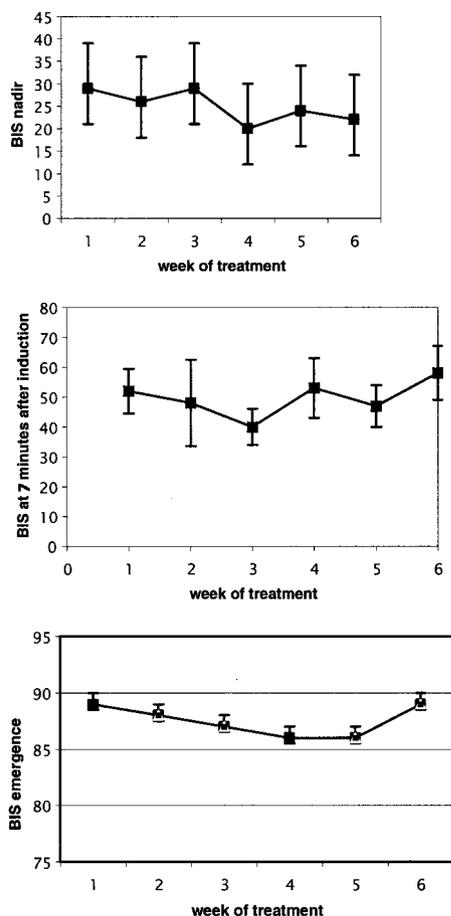
BIS = Bispectral Index; NS = not significant.

Fig. 2. Bispectral Index (BIS) parameters (BIS nadir, BIS 7 min after induction, and BIS emergence [early]) *versus* time for each week of treatment.

of fentanyl and midazolam administered to maintain the same BIS value. The issue of tolerance to propofol has been reported previously. Setlock *et al.*[10] showed that tolerance to an induction dose of propofol did not develop in children receiving propofol for high-voltage radiation therapy. There were daily variations in dosage, but they were not related to the number of treatments or pretreatment anxiety. In contrast, Deer and Rich[8] described a 2-yr-old boy undergoing radiation therapy who experienced extreme tolerance to the effects of an induction dose of propofol. In this child, the fourth induction dose of propofol was increased by 6-fold, and the nineteenth induction dose was increased by 16-fold compared with the first one. The authors suggested that the

tolerance was due to pharmacodynamic factors. Both reports[8,10] relied on clinical criteria alone, *i.e.*, tolerance to placement of monitors and mask and absence of movement. By using a fixed dose of propofol during the entire course of treatment, we could hypothesize that if tolerance had occurred, the BIS curve would change accordingly over time. Neither the clinical results nor the values derived from the measurements of the BIS parameters indicated that our study population developed tolerance to propofol after repeated exposures over time.

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