Tolerance to Propofol Generally Does Not Develop in Pediatric Patients Undergoing Radiation Therapy

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DEEP sedation or general anesthesia frequently is required for small children with malignancies undergoing daily high-voltage radiation therapy for several weeks. Propofol can be administered in small intravenous bolus doses for induction of anesthesia and continued as an infusion for maintenance of anesthesia during these procedures. However, it has been suggested that tolerance to propofol may develop with repeated administration and that increasing doses of the drug or addition of other drugs may be required over the course of treatment. †‡§# This is supported by a report from Deer and Rich. 2 They describe a single case of a 2-year-old girl who required increasing induction doses of propofol during a course of radiation therapy. Others, in retrospective and animal studies, have not found tolerance to be a problem. 3.4.** We previously reported a retrospective study of ten patients who received 134 radiation treatments and suggested that tolerance did not develop with repeated administration of propofol.** However this was a retrospective study, and drugs other than propofol were administered. In this study, we report a prospective evaluation of tolerance to an induction dose of propofol for all children requiring anesthesia for radiation therapy over a 2-year period at our institution.

Case Report

Methods

Subjects were children undergoing high-voltage radiation therapy for whom anesthesia/deep sedation had been requested by the radiation oncologist. Institutional review board approval and parental consent were obtained. All children had chronic indwelling central venous catheters, and no child had a history of allergy to eggs, soy, or propofol. Five staff anesthesiologists administered anesthesia. Patients were anesthetized daily with the exception of weekends and holidays. A preanesthetic evaluation was made, and anxiety level at the time of induction was noted using a four-point scale (1 = calm, 2 = mildly disturbed, 3 = crying but can be comforted, and 4 = uncontrolled crying). To induce anesthesia, an initial bolus dose of 1 mg/kg propofol was administered over an infusion pump (model AS40A, Baxter Healthcare, Deerfield, IL) into the intravenous tubing connected to the central venous catheter. Subsequent doses of 0.5 mg/kg propofol were given every 15-30 s by the staff anesthesiologist until the patient achieved the desired endpoint: a patient who tolerated placement of monitors and oxygen delivery device (nasal cannula or face mask) and who would remain motionless after positioning by the therapist. The total dose of propofol required to achieve this endpoint is defined as the induction dose. Patients were monitored by pulse oximetry (model N-100, Nellcor, Hayward, CA), electrocardiogram, and respiratory inductance (model 90604A, Spacelabs, Redmond, WA) and with automated blood pressure measurements (Dinamap vital signs monitor 1846, Critikon, Tampa, FL). For the procedure, patients received a propofol infusion of 1.5 mg·kg⁻¹·h⁻¹, and additional boluses were given as needed (i.e., after repositioning or stimulation by the technicians). Drug tolerance was evaluated by performing linear regression analysis for each patient with treatment number as the independent variable and propofol induction dose as the dependent variable (StatView, Abacus Concepts, Berkeley, CA). Regression slopes for all patients were pooled using the reciprocal of standard errors as weights. Drug tolerance was defined as pooled mean slope > 0.
The treatment period could not be standardized for comparison in the same manner as induction dose. The duration of these procedures and the required manipulation of the patients (e.g., repositioning, additional X-rays) were highly variable throughout the course of the treatment. Therefore, we did not examine total dose or additional boluses given during treatment, because this would be related to inconsistencies in the treatment procedure rather than tolerance to the drug.

Results

Six children (three girls and three boys) were anesthetized for a total of 150 treatments. Patients were aged 2.0 ± 1.2 yr (mean ± SD) and underwent 27 ± 8 treatments. The patients’ diagnoses were retinoblastoma, rhabdomyosarcoma, stage III Wilms tumor, medulloblastoma with spinal metastases, and recurrent posterior fossa ependymoma (two patients). Patients generally remained calm over the entire treatment course. Anxiety score was 1 (calm) for 90% of treatments, and no scores were greater than 2 (mildly disturbed). In five of six patients, the slopes relating induction dose to treatment number were negative (fig. 1). In one child (patient 5), the induction dose requirement had a slight increase of 0.2 mg/kg over 22 treatments. There was no correlation between induction dose and treatment number (regression coefficient, $r^2 = 0.004$) for this patient, and this change is clinically insignificant (fig. 1). For all patients, daily variation in induction dose occurred but was not related to treatment number as indicated by small regression coefficients (range 0.004–0.44; fig. 1). The pooled slope for all patients is $-0.03 ± 0.01$ mg/kg/treatment (mean ± SEM), and the 95% confidence interval for the pooled slope is $-0.04$ to $-0.01$ mg/kg/treatment. The hypothesis of the development of tolerance (slope > 0) is therefore rejected ($P < 0.05$). Patients did not require an increase in induction dose of propofol with repeated treatments, and therefore tolerance to an induction dose of propofol did not develop.

Discussion

Drug tolerance can be defined as a progressively diminished response to a drug with recurrent exposure. Development of tolerance to drugs that depress the central nervous system is common. Pharmacologic tolerance develops with opioids, nitrous oxide, ethanol, sedatives/hypnotics, and anxiolytics. Tolerance to the effects of ketamine has been reported in both human and radiotherapy patients after repeated exposures to the drug. Although a number of distinct mechanisms are involved in the development of tolerance, two types of pharmacologic tolerance are generally distinguished: pharmacokinetic and pharmacodynamic. Pharmacokinetic tolerance results from a change in the absorption, distribution, metabolism, or excretion of a drug that effectively reduces the concentration of the drug at its receptors. This type of tolerance usually produces no more than a threefold decrease in response to the drug. Pharmacodynamic tolerance results from adaptive changes within the organism so that the response to a given concentration of drug is reduced. This typically involves changes in drug receptor number or responsiveness (up-regulation), and the magnitude of the small changes to changes that occur with time. Tolerance is a complex phenomenon that may contribute to resistance to a given dose of drug.

In this study, tolerance to a single drug dose did not develop in children for high-voltage radiation therapy. The authors do not believe that this lack of tolerance was due to pharmacokinetics. Our patients required increasing doses of propofol over the course of their treatment. The authors believe that tolerance develops with repeated anesthesia, such as for a course of radiation therapy.

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Key words: Surgery, laparoscopy, cardiac trauma, dysrhythmia, metabolic agents.
CASE REPORTS

REFERENCES


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CARDIAC TRAUMA: AN UNUSUAL CAUSE OF DYSRHYTHMIAS AND ELECTROCARDIOGRAPHIC CHANGES DURING LAPAROSCOPIC NISSEN FUNDUPLICATION

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LAPAROSCOPIC surgery is undergoing a rapid expansion of applications from its long-time use in gynecologic surgery. Surgeons are using laparoscopic techniques for cholecystectomies, appendectomies, hernia repairs, exploratory abdominal procedures, varicocele repairs, nephrectomies, colostomy closures, and colectomies. The advantages of laparoscopic surgery include shorter hospital stays, greater patient acceptance, and decreased morbidity.1-4 However, laparoscopic procedures have unique risks, including organ damage, vascular injury, pneumothorax, and carbon dioxide embolism.4,5 The majority of these injuries result from

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