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Evaluation of propofol for repeated prolonged deep sedation in children undergoing proton radiation therapy

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Background. The aim of this study is to evaluate the safety and sufficiency of a fixed dose rate propofol infusion for repeated prolonged deep sedation in children for proton radiation therapy (PRT).

Methods. With ERB approval, we recorded anaesthesia monitoring data in children undergoing repeated prolonged propofol sedation for PRT. Sedation was introduced with a single bolus of i.v. midazolam 0.1 mg kg^{-1} followed by repeated small boluses of propofol until sufficient depth of sedation was obtained. Sedation was maintained with fixed dose rate propofol infusion of 10 mg kg^{-1} h^{-1} in all patients up to the end of the radiation procedure. Patient characteristics, number and duration of sedation, propofol induction dose, necessity to alter propofol infusion rate, and heart rate, mean arterial pressure, respiratory rate were noted at the end of the radiation procedure before cessation of the propofol infusion. Data are mean (SD) or range (median) as appropriate.

Results. Eighteen children aged from 1.4 to 4.2 yr (2.6 yr) had 27.6 (SD 2.0) (497 in total) radiation procedures within 44.1 (4.0) days lasting 55.7 (8.8) min. Propofol bolus dose for induction, monitoring, and positioning was 3.7 (1.0) mg kg^{-1}. Propofol bolus requirements were quite stable over the successive weeks of treatment and variability was larger between individuals than over time. In none of the children did propofol infusion rate need to be changed from the pre-set 10 mg kg^{-1} h^{-1} flow rate because of haemodynamic state, respiratory conditions or inadequate anaesthesia.

Conclusions. Repeated prolonged deep sedation over several weeks in very young children using a fixed rate propofol infusion was safe and adequate for all patients.

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Proton radiation therapy (PRT) is a highly conformal radiation technique offering the advantage of precisely depositing the energy within the target volume and sparing non-target tissues.[1] This reduces the risk of secondary cancer and normal tissue damage, being of particular interest in children.[2] Conformal radiation techniques require precise positioning of the patient, and additional positioning check-ups are performed before each radiation procedure. Therefore, PRT is a somewhat more time-consuming procedure than conventional radiotherapy, prolonging the time of sedation required.

During proton radiation, no personnel are allowed to be with the patient, and syringe pumps in the treatment room cannot be manipulated to adapt the hypnotic drug dose. Therefore, a safe and sufficient sedation technique for immobilization and stable cardio-respiratory conditions is required while the patient is observed by television cameras from a long distance. Repeated exposure to sedative drugs that depress the central nervous system is associated with the development of tolerance,[3 4] which may complicate appropriate dosing of sedative drugs under these challenging conditions.

Propofol is an interesting hypnotic drug to provide sedation for diagnostic procedures in young patients. It is increasingly used for children undergoing repeated

radiation procedures, since it provides reliable sedation, short recovery periods, and early hospital discharge.[5]

The aim of this study is to evaluate the safety and sufficiency of a fixed dose rate propofol infusion in spontaneously breathing children undergoing repeated prolonged deep propofol sedation for proton radiation over several weeks.

Methods

With hospital ethical committee approval (University Children's Hospital Zurich, Switzerland), we recorded anaesthesia monitoring data in children undergoing PRT under deep propofol sedation in the Division of Radiotherapy, Paul Scherrer Institut (PSI), Villigen, Switzerland. Patients receiving opioids or sedative drugs other than those suggested by the treatment protocol were excluded from the study.

The PSI is a Swiss National Physics Centre with a cyclotron providing high-energy protons for radiation therapy. The paediatric anaesthesia service in the PSI, located 50 km from the University Children's Hospital Zurich, is provided by four paediatric consultant anaesthetists of our department.

All patients had a permanent pre-existing indwelling central venous catheter or an implanted infusion system (Port-a-Cath) inserted. Patients had four radiation procedures a week with a break on Wednesday and during the weekend. Sedation was performed according to our standard institutional sedation protocol for immobilization of children for magnetic resonance imaging. Children were fasted for 4 h for solids and fluids and for 2 h for clear fluids, and did not receive premedication before induction. Sedation was introduced with a single bolus of i.v. midazolam 0.1 mg kg^{-1} followed by repeated small i.v. boluses of propofol ranging between 0.5 and 1 mg kg^{-1} until sufficient depth of sedation was obtained within 1–2 min for monitoring, including tolerance to nasal prongs, and to make the child motionless during positioning (about 5–10 min after induction) by the radio-therapist. Sedation was maintained with a fixed rate dose propofol infusion (10 mg kg^{-1} h^{-1}) in all patients up to the end of the radiation procedure. Sp_{O_2} monitoring was started before induction; ECG, non-invasive arterial pressure measurement, and nasal prongs for nasal CO_2 sampling and for application of oxygen were installed immediately after induction.

Deep sedation and monitoring was started in the anaesthesia induction room. Then the patients were transferred on a trolley to the imaging room. In the imaging room, the patients were positioned on the mobile treatment table in a whole body vacuum mould with bite block or mask immobilization of the head in either the supine or prone position. Additional positioning checks are performed at the PSI through imaging before each radiation procedure. After confirmation of proper agreement of actual with initial position, the patients were transferred on the treatment table to the proton therapy unit (proton gantry). Radiation therapy was performed without personnel in the proton gantry (Fig. 1). Patients were continuously monitored for arterial pressure at 5 min intervals, heart rate (HR) by ECG, and respiratory rate (RR) by means of E'_{CO_2} trace and Sp_{O_2}. Patients were observed by means of video cameras for inadvertent movements in the proton gantry and vital sign data were transmitted to a monitor screen in the control room, located 15 m away from the proton gantry. After radiation, patients were moved from the vacuum mould in their personal bed and brought into the recovery room.

Patient characteristics, number and duration (time from induction of sedation until cessation of propofol infusion) of sedation were noted. The total amount of propofol required for induction, application of monitoring and patient positioning was noted. RR, HR, systolic arterial pressure, diastolic arterial pressure were recorded at the end of the procedure before cessation of the continuous propofol infusion. Propofol induction bolus dose required and necessity to alter propofol infusion rate because of insufficient sedation or cardio-respiratory depression were noted; mean arterial pressure (MAP) was calculated from systolic and diastolic pressures for presentation and further calculations. Propofol bolus dose, MAP, HR, Sp_{O_2} and RR were averaged [mean (SD)] for each week of therapy. Data are mean (SD) or range (median) as appropriate.

Results

Eighteen children (13 girls and 5 boys) aged from 1.4 to 4.2 yr (median 2.6 yr) undergoing PRT at the PSI were included in the observational study. One girl with a

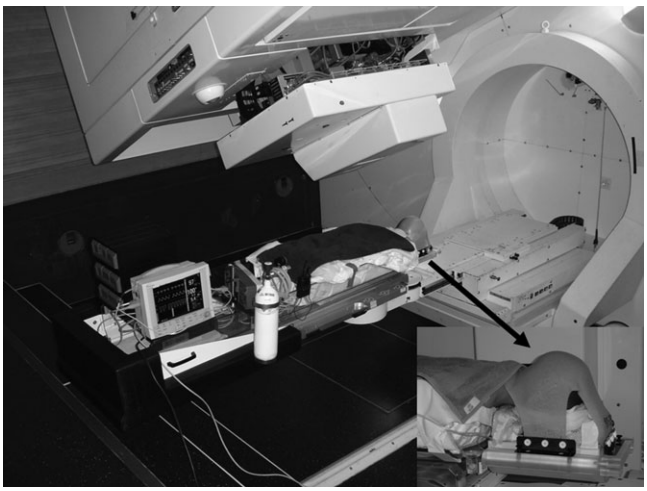

Fig 1 A 2.6-yr-old child under deep propofol sedation for proton therapy in the prone position placed in the whole body mould with the head immobilized by means of a head mask (arrow).

Table 1 Propofol bolus required for induction and final patient positioning, HR, MAP, and RR, measured at the end of the radiation procedure and duration of the sedation procedure. Data are mean (SD). (n=18 children, four sedations per week)

	Number of week						
	1	**2**	**3**	**4**	**5**	**6**	**7**
Propofol bolus (mg kg^{-1})	3.8 (1.2)	3.9 (1.1)	3.7 (0.9)	3.7 (0.9)	3.6 (0.9)	3.6 (0.9)	3.4 (1.2)
HR (beats min^{-1})	98.5 (15.8)	98.5 (11.7)	96.6 (10.8)	97.1 (10.7)	97.7 (11.7)	96.4 (11.0)	97.9 (11.6)
MAP (mm Hg)	54.2 (7.5)	54.6 (7.1)	53.5 (5.9)	52.8 (6.2)	53.7 (6.5)	54.0 (5.7)	53.8 (6.0)
RR (bpm)	25.3 (4.5)	25.2 (5.0)	25.2 (4.3)	25.4 (4.1)	25.9 (5.2)	25.9 (4.7)	26.0 (3.5)
Duration (min)	64.9 (21.4)	58.1 (13.6)	53.1 (12.6)	55.7 (16.8)	54.7 (16.3)	52.9 (18.2)	50.5 (12.6)

tracheostomy cannula had to be excluded from the study as she needed opioids because of coughing due to copious secretion. They had 27.6 (2.0) (497 in total) radiation procedures within 44.1 (4.0) days. Each period of sedation lasted 55.7 (8.8) min and total sedation time was 25.6 (4.4) h per patient.

The fixed rate dose propofol infusion of 10 mg kg^{-1} h^{-1} was sufficient in all patients to avoid inadvertent movements and to guarantee safe cardio-respiratory conditions. Sp_{O_2} values with 2 litres of oxygen at the nose ranged from 95% to 100% (median 99.3%). No additional propofol boluses were needed after final positioning until the end of the radiation procedure. The average propofol bolus dose for induction and patient positioning was 3.7 (1.0) mg kg^{-1}. Requirements of propofol induction dose were quite stable over the successive weeks of treatment (Table 1) and variability was larger between individuals than over time (Fig. 2). In none of the children did the propofol infusion rate need to be changed from the pre-set 10 mg kg^{-1} h^{-1} flow rate because of haemodynamic state, respiratory conditions or inadequate anaesthesia, although many of them suffered from local and systemic infections, weight loss, exhaustion, and intra-cerebral hypertension or received drug therapies and parenteral nutrition. Haemodynamic and respiratory variables measured at the end of the radiation procedure after at least 30 min of unchanged steady-state infusion of propofol demonstrated considerable inter-individual differences between different weeks of therapy, but on average they were stable over the treatment period of 7 weeks PRT (Fig. 3).

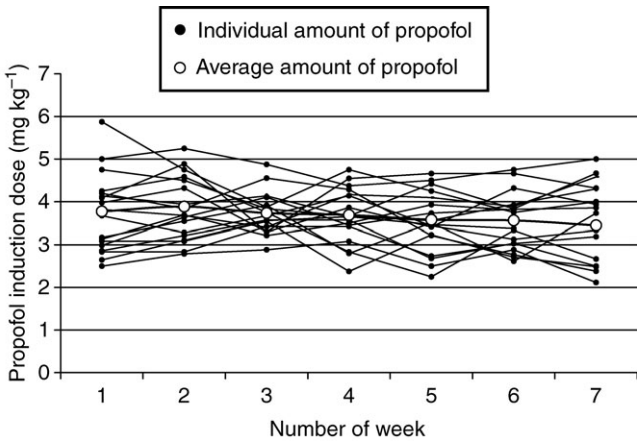

Fig 2 Individual and averaged amount of propofol (mg kg^{-1}) required for induction and patient positioning for each week of therapy (n patients=18; n procedures=497).

Discussion

Young children with malignancies requiring repeated radiation therapy usually need general anaesthesia or deep sedation. Because of its pharmacological profile, propofol is an excellent hypnotic drug for short procedures in young children. It allows reliable sedation and immobilization with spontaneous ventilation, and has been reported to be safe and appropriate for repeated conventional radiation procedures in children.[5–7]

In this study, we evaluated the safety and sufficiency of a fixed dose rate propofol infusion for repeated, prolonged propofol sedation in spontaneously breathing children undergoing PRT. The main finding was that a fix rate dose propofol infusion of 10 mg kg^{-1} h^{-1} was sufficient in all patients to provide safe cardio-respiratory conditions and to avoid inadvertent movements during the prolonged proton radiation procedure.

Propofol sedation in children is routinely used for diagnostic procedures such as magnetic resonance imaging or computed tomography and other imaging procedures. Normally, these procedures are short, not very often repeated and personal attendance or immediate access to the patient is possible in order to adapt depth of sedation or to provide cardio-respiratory support if needed. In this setting, the individual continuous infusion dose for propofol can be titrated to a desired level of sedation.

PRT is a time-consuming procedure similar to highly conformal or multiple-field radio-therapeutic procedures. Patient's induction, immobilization, the transportation to the imaging room and to the treatment room, patient positioning for control imaging before each radiation procedure, as used at the PSI, and the proton radiation itself resulted in a mean duration for sedation of almost 1 h and in a total sedation time of 25.6 h during 6–7 weeks. For PRT as a highly precise radiation technique, a sufficient level of deep sedation is required to avoid inadvertent

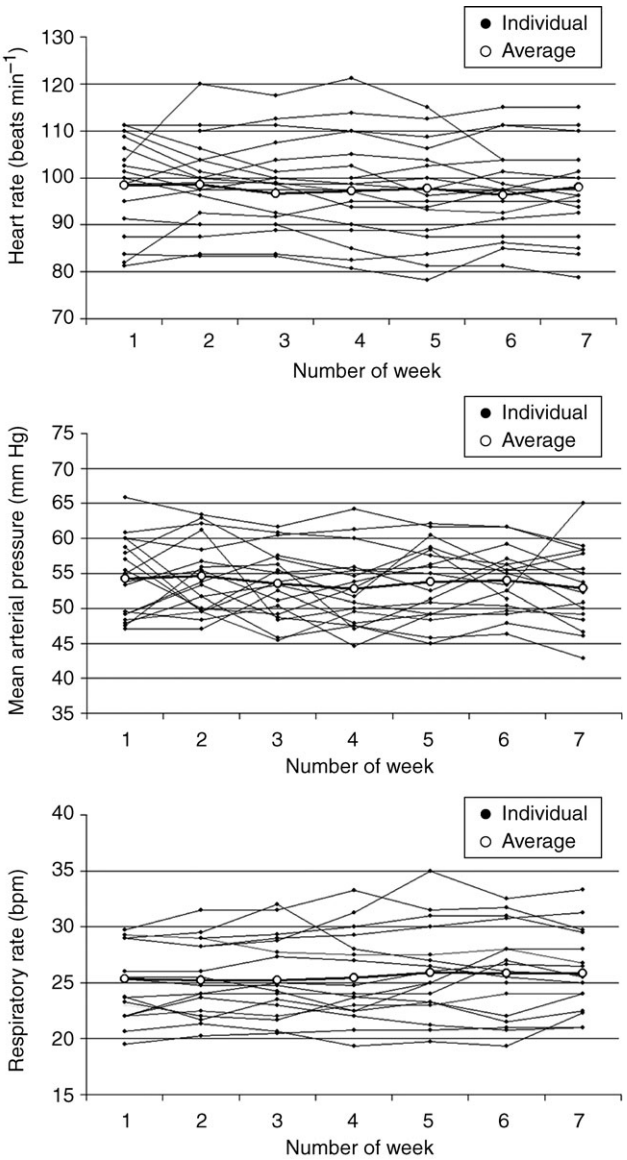

Fig 3 Individual and averaged HR, MAP, and RR noted at the end of each radiation procedure for each week of therapy (*n* patients=18; *n* procedures=497).

movement of the patient after positioning until the end of the radiation procedure since there is no access to the patient or to the infusion pump in the proton gantry without interruption of the radiation procedure. Any movements of the patient after the imaging procedure (transfer to the proton gantry or during proton radiation) would result in a break in the radiation procedure and would require re-confirmation of the correct patient positioning by imaging and restarting the radiation protocol. In addition, cardio-respiratory stability is another challenge, particularly in these children with weakened physical state (due to chemotherapeutic drugs, infections, sepsis, parenteral nutrition, exhaustion and loss of weight) and, on the other hand, in the child without a protected airway, the head restricted in a face mask and in the prone position (Fig. 1). Our data, obtained from 18 patients undergoing almost 500 prolonged sedation procedures, demonstrate that a fixed dose rate of propofol infusion of 10 mg kg^{-1} h^{-1} was able to provide a sufficient level of sedation and immobilization as well as stable conditions in all patients and procedures. Scheiber and colleagues[5] used a 10 mg kg^{-1} h^{-1} propofol infusion rate and then a reduced dose rate of 7.4 (2.2) mg kg^{-1} h^{-1} propofol was used, as allowed by immobilization. However, these procedures did not include highly conformal radiation techniques, were much shorter [18 (11) min], and easy access to the patient was guaranteed.

Overall, the induction dose in our study population was similar to that reported by Scheiber and colleagues.[5] In contrast to other authors using a fixed dose of propofol for induction,[8] with the presented technique the induction dose was titrated until sufficient depth of sedation was obtained. The rationale to titrate the propofol induction dose daily is to avoid propofol overdosage necessitating respiratory and haemodynamic support because of variations in tiredness, sedation and sometimes intracranial hypertension, other drug therapies and current infectious diseases, including sepsis requiring different induction doses (Fig. 2). Intra-individual variation in propofol requirements may additionally be related to various degrees of anxiety, previous puncture of the Port-a-Cath system, and differing reactions of the child to changing anaesthesia teams. The different physical and anxiety conditions may explain intra-individual weekly differences in recorded cardio-respiratory parameters with a fixed rate dose propofol infusion protocol over several weeks. It can be argued that monitoring the depth of anaesthesia would allow us to adapt propofol to a desired level of anaesthesia and to avoid a fixed rate dose propofol infusion. We did not use the bispectral index or another cerebral function monitor to give an objective measure of depth of sedation in our patients because of technical (mobility), positional (Fig. 1) and logistic barriers to using such monitors in the PRT setting and, as mentioned earlier, titration was not possible as the syringe pump could not be manipulated in the proton gantry.

To date, there are no clinical studies investigating tolerance to propofol in children undergoing repeated prolonged deep sedation. Usually, sedation for conventional radiation procedures lasts about 15–20 min, including monitoring and patient positioning. So far, no tolerance during induction for repeated propofol sedation in children was reported for repeated short-term propofol sedation,[5 8–10] except in one child requiring up to 16-fold the propofol dose compared with the first session, probably caused by pharmacodynamic tolerance.[11] In our study population, in none of the patients treated was an increase of induction dose or continuous propofol infusion required over time. Nevertheless, our data do not scientifically exclude the development of tolerance to propofol, since

preoperative anxiety and sedation scores and other factors such as intracranial pressure, infections, drug therapies, parenteral nutrition, and patient's exhaustion affect sensitivity to hypnotic drugs. Secondly, the therapeutic window for propofol is wide in children and, without using a cerebral function monitor, there is no way to be sure that half the dose or double the dose would not provide the same stability.

Recently, sevoflurane has been successfully used by different authors for sedation of small children undergoing magnetic resonance imaging.[12 13] This approach is excellent in children without venous access, since sedation is introduced and maintained simply by nasal insufflation. Awakening from sevoflurane sedation is rapid. However, transient excessive emergence agitation and vomiting have been described in up to 12% and 5%, respectively, of the patients, both of which are extremely rare after propofol sedation. Small children presenting for repeated radiation procedures usually have a central venous access implanted for i.v. induction, which is more comfortable than installation of a mask, a nasal tube or nasal prongs. Deepening anaesthesia for manipulation or positioning is easier and faster with i.v. boluses of propofol than by increasing sevoflurane concentration via the patient's nose. Secondly, environmental pollution of sevoflurane may become a problem in radiation theatres, where air conditioning is probably not always like that in an operating theatre. Thirdly, from a technical stand point, a syringe pump, in contrast to a sevoflurane vaporizer is easier to move with the patients through the different places during PRT and is a commercially provided stand-alone system without the need for an anaesthesia respirator. Finally, laboratory and clinical data are required for repeated daily sevoflurane applications before this approach is routinely used in paediatric radiation therapy.

In conclusion, repeated prolonged deep sedation for propofol radiation over several weeks in very young spontaneously breathing children using a small dose of midazolam and titrated propofol for induction followed by a fixed dose rate propofol infusion of 10 mg kg^{-1} h^{-1} for maintenance was safe and adequate. The presented sedation technique offered stable cardio-respiratory conditions and sufficient patient immobilization during repeated radiation procedures in the proton gantry.

References

1 Clair WH, Adams JA, Bues M, *et al*. Advantage of protons compared to conventional X-ray or IMRT in the treatment of pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2004; **58**: 727–34

2 Miralbell R, Lomax A, Cella L, Schneider U. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. *Int J Radiat Oncol Biol Phys* 2002; **54**: 824–9

3 Cronin MM, Bousfield JD, Hewitt EB, McLellan I. Ketamin anaesthesia for radiotherapy in small children. *Br J Anaesth* 1972; **27**: 135–42

4 Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Crit Care Med* 2000; **28**: 2122–32

5 Scheiber G, Ribeiro FC, Karpienski H, Strehl K. Deep sedation with propofol in preschool children undergoing radiation therapy. *Paediatr Anaesth* 1996; **6**: 209–13

6 Seiler G, Vol E de, Khafage Y, *et al*. Evaluation of the safety and efficacy of repeated sedations for radiotherapy of young children with cancer. A prospective study of 1033 consecutive sedations. *Int J Radiat Oncol Biol Phys* 2001; **49**: 771–83

7 Fortney JT, Halperin EC, Herz CM, Schulmann SR. Anesthesia for pediatric external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 1999; **444**: 587–91

8 Keidan I, Perel A, Shabtai EL, Pfeffer RM. Children undergoing repeated exposures for radiation therapy do not develop tolerance to propofol: clinical and bispectral index data. *Anesthesiology* 2004; **100**: 251–4

9 Setlock MA, Palmisano WB, Berences JR, Rosner RD, Troshynski TJ, Murray KJ. Tolerance to propofol generally does not develop in pediatric patients undergoing radiation therapy. *Anesthesiology* 1996; **85**: 207–9

10 Mayhew JF, Abouleish AE. Lack of tolerance of propofol. *Anesthesiology* 1996; **85**: 282–9

11 Deer TR, Rich GF. Propofol tolerance in a pediatric patient. *Anesthesiology* 1992; **77**: 282–9

12 Sury MR, Harker H, Thomas ML. Sevoflurane sedation in infants undergoing MRI: a preliminary report. *Paediatr Anaesth* 2005; **15:** 16–22

13 Sanabria Carretero P, Hajro M, Jimenez Mateos E, Altit E, Nodal Ramos A, Lahoz Ramon A. Sevoflurane anesthesia for magnetic resonance procedures in pediatrics. *Rev Esp Anestesiol Reanim* 2002; **49:** 184–90 (Spanish)