

Anaesthetic management of a three-month-old baby for cervical limited dorsal myeloschisis repair using propofol and alfentanil infusions guided by pharmacokinetic simulation software: A case report

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We present an uncommon case of limited dorsal myeloschisis in a 3-month-old infant requiring repair guided by intraoperative neuromonitoring (IONM) and therefore avoidance of volatile anaesthetic agents. The case presented challenges in positioning, airway management, a lack of age appropriate pharmacokinetic models in target-controlled infusion (TCI) syringe pumps and unavailability of remifentanyl, considered to be an essential drug in this setting. We overcame these challenges using manually controlled infusions of propofol and alfentanil guided by pharmacokinetic simulation software (Stelsim).

Keywords: cervical limited dorsal myeloschisis, intraoperative neuromonitoring (IONM), total intravenous anaesthesia (TIVA), target controlled infusion (TCI), paediatric anaesthesia

Introduction

Intraoperative neuromonitoring (IONM) has improved the safety of neurosurgical procedures but relies on avoiding volatile anaesthesia. Total intravenous anaesthesia (TIVA) for patients younger than one year is not possible using existing target-controlled infusion (TCI) devices. Applying the TCI pumps' pharmacokinetic (PK) models outside of their reference populations will lead to inaccurate dosing and is not recommended. PK models applicable for infants have been described and can be applied clinically using pharmacokinetic simulation software and advisory displays (e.g. Stelsim¹). The technique comprises tracking a manually controlled infusion regimen in real time while displaying the estimated blood and effect-site concentrations, thereby assisting the clinician to maintain stable drug concentrations and stable drug effect. The method also enables titration of drug dosage to the patient requirements and facilitates timely emergence and extubation. We call the technique "target guided infusion (TGI)".

Propofol and remifentanyl are the hypnotic and opioid of choice for TIVA in this age group for *inter alia* the rapidity of their onset and offset. We present a case requiring IONM and TIVA that involved an added challenge, namely unavailability of the opioid remifentanyl.

Case report

A 3.1 kg term male infant, born via normal vertex delivery, was referred to our institution for repair of a cervical limited dorsal myeloschisis. At the time of corrective surgery, the baby was 3 months old, weighed 5.2 kg with a height of 54 cm. Neurodevelopmental and growth parameters were appropriate. A soft, fluctuant mass was present over the upper thoracic and cervical vertebrae with intact overlying skin. Diagnosis of a



Figure 1. Magnetic resonance imaging of the cervical myeloschisis

A septated cystic lesion measuring 5.6 x 3.8 x 7.1 cm arising from the posterior central neck with tethered cord can be seen.

cervical limited dorsal myeloschisis was confirmed by magnetic resonance imaging (MRI) which revealed a septated cystic lesion measuring 5.6 x 3.8 x 7.1 cm arising from the posterior central neck (Figure 1). The cervical spinal cord at the level of C3/4 appeared to be tethered posteriorly with suspected cerebrospinal fluid (CSF) and cord connection into the mass.

Surgical resection with intraoperative neuromonitoring (IONM) was planned. Considering that remifentanyl was unavailable in our hospital at that time due to a nationwide shortage, a decision

Table I. Mammillary two and three-compartment model parameters for the three-month-old, 5.2 kg patient

Model parameter	"Elevedl" ² (propofol)	"Goresky" ³ (alfentanil)	Paedfusor ⁴ * (propofol)
V ₁ (L)	1.25	1.25	2.34
V ₂ (L)	3.26	1.05	9.50
V ₃ (L)	20.1		58.2
CL (L.min ⁻¹)	0.225	0.045	0.219
Q ₂ (L.min ⁻¹)	0.648	0.019	0.267
Q ₃ (L.min ⁻¹)	0.071		0.098
k ₁₀ (min ⁻¹)	0.180	0.036	0.794
k ₁₂ (min ⁻¹)	0.5184	0.015	0.114
k ₂₁ (min ⁻¹)	0.1988	0.018	0.055
k ₁₃ (min ⁻¹)	0.0568		0.0419
k ₃₁ (min ⁻¹)	0.00353		0.0033
k _{eo} (min ⁻¹)	0.280	2.20 †	0.910 †
t _{1/2} k _{eo} (min ⁻¹)	2.48	0.315 †	0.761 †

V₁-V₃ apparent volumes of distribution; CL total body clearance, Q₂-Q₃ intercompartmental clearances; k₁₀...k₃₁ micro rate constants; k_{eo} effect-site equilibration rate constant, t_{1/2} k_{eo} effect-site equilibration half-time.

* Propofol "Paedfusor" model parameters for one-year old infants, illustrating inappropriateness for infants younger than 1 year

† estimated using algorithms from Minto et al.⁵ assuming a time to peak effect of 2.2 minutes.

Table II. The precalculated dose regimens for the first ten minutes to be administered to a three-month-old, 5.2 kg infant

	Cumulative dose*	Initial loading dose†	Remainder of 10 min dose‡	Remainder infusion rate	Syringe Conc.	Pump rate (mL/hour)
Propofol (C _e 3 µg/mL)	25 mg (4.8 mg/kg)	16 mg (3 mg/kg)	9 mg (1.8 mg/kg)	180 µg/kg/min	10 mg/mL	5.6
Alfentanil (C _e 90 ng/mL)	166 µg (32 µg/kg)	104 µg (20 µg/kg)	62 µg (12 µg/kg)	1.2 µg/kg/min	25 µg/mL	15

C_e - targeted effect-site concentration

* Cumulative dose during the first 10 minutes as calculated by a Stelsim simulation for a three-month-old, 5.2 kg infant.

† Bolus dose given at initiation of TIVA

‡ Remaining dose = cumulative dose-bolus dose

was made to administer TIVA by TGI using propofol and alfentanil to facilitate IONM.

Because no appropriate pharmacokinetic (PK) models exist within currently available infusion pumps, we utilised Stelsim¹ (version 2.04, Revision 1, August 2012) pharmacokinetic simulation software to guide both infusions. We pre-planned an initial bolus-and-infusion regimen calculated to rapidly achieve and maintain propofol and alfentanil effect-site concentrations of 3 µg/mL and 90 ng/mL respectively, employing the pharmacokinetic parameter sets of Elevedl² for propofol and Goresky³ for alfentanil (Table I).

The dose regimens were planned as follows. Stelsim TCI simulations were conducted, targeting effect sites of 90 ng/mL for alfentanil and 3 µg/mL for propofol. From the simulations we obtained the initial loading doses to be administered, as well as the subsequent doses to be administered by infusion during the first ten minutes. The pre-calculated initial doses were thus administered to the patient manually, while the infusions were begun as indicated in Table II and the real-time Stelsim simulations were started. After the first ten minutes, the infusion rates were adjusted by observing the simulated effect-site concentrations and increasing or decreasing the infusion rates accordingly to maintain the Ce at the desired target. Anticipated

recovery concentrations were set to propofol 1.3 µg/mL and alfentanil 60 ng/mL.

The baby was positioned supine on an underbody forced air warming blanket with appropriate cushion support to avoid pressure on the myelomeningocele. After inhalational induction with sevoflurane, intravenous access was secured, sevoflurane was discontinued and propofol and alfentanil TGI were commenced using two Alaris[®] TIVA (model 1000LB1411 Iss 2) (Cardinal Health, 1180 Rollse, Switzerland) infusion pumps in manual control mode.



Figure 2. Patient ready for sterile cleaning and draping

Position prone with head resting on hollowed medium density foam block, ensuring no orbital pressure and adequate surgical access to the dorsal myeloschisis. IONM probes attached to scalp.

A grade 1 laryngoscopy view was obtained with a Macintosh 1 blade and the cords were topicalised with 2% lignocaine to facilitate intubation while avoiding muscle relaxation. Arterial and central venous lines and a urinary catheter were inserted. The baby was turned to the prone position with its face supported on its forehead, cheeks and chin in the centre of a hollow foam support used for intubation and all pressure points were addressed. Prior to each anticipated increase in surgical stimulus during surgery, an alfentanil bolus of between 5–20 $\mu\text{g}/\text{kg}$ was administered and recorded in Stelsim to maintain an accurate estimate of the predicted C_e . Infusion rates were adjusted according to clinical response (heart rate, blood pressure, effect on evoked potentials) to maintain appropriate C_e 's^{6,7} for surgical anaesthesia as predicted by Stelsim. Satisfactory somatosensory and motor-evoked potentials were achieved throughout the period of IONM.

Blood loss was approximately 100 mL. The lowest recorded haemoglobin concentration was 7.5 g/dL and 130 mL of cross-matched blood was transfused. At the conclusion of surgery, during closure of the subcutaneous layers, propofol and alfentanil C_e targets were lowered to 2.0 $\mu\text{g}/\text{mL}$ and 80 ng/mL respectively in order to decrease the time to recovery. This involved slowing/stopping the syringe pumps and restarting them at reduced infusion rates as the simulated effect-site drug concentrations approached the reduced targets. After application of wound dressings both infusions were stopped. Spontaneous breathing returned soon after repositioning in the supine position. Intravenous morphine 0.5 mg and clonidine 5

μg were administered, and the baby's trachea was extubated while on the operating table four minutes prior to the predicted recovery time.

He appeared comfortable with normal gross motor function noted in all four limbs and was transferred to the paediatric intensive care unit while receiving nasal prong oxygen. Total procedure time was 3 hours 45 minutes. Figure 3 portrays the pump rates and the simulated drug concentrations. Total doses administered were propofol 148 mg, alfentanil 1033 μg .

Discussion

Cervical limited dorsal myeloschisis (CLDM) is rare. There may be tethering to the spinal cord and 50% may involve neurological or orthopaedic anomalies, including hydrocephalus associated with Chiari II malformation⁸ and occult thoracolumbar spina bifida. The optimal timing for surgery is between six months and 1 year, unless neurological deterioration mandates earlier intervention. Surgery is performed in the prone position and involves laminectomy, intra-dural exploration and resection of septae and tethering bands. Intraoperative neuromonitoring (IONM) enhances surgical safety. IONM includes motor evoked potential (MEPs) monitoring, somatosensory evoked potential (SSEPs) monitoring and mapping of compound motor action potentials (CMAPs). Myelination is incomplete in children younger than three years, and it is important to avoid drugs that may impede signal conduction. Volatile anaesthetics and possibly dexmedetomidine^{9–12} may affect IONM, and therefore TIVA is the technique of choice.^{13–16} Muscle relaxants should be

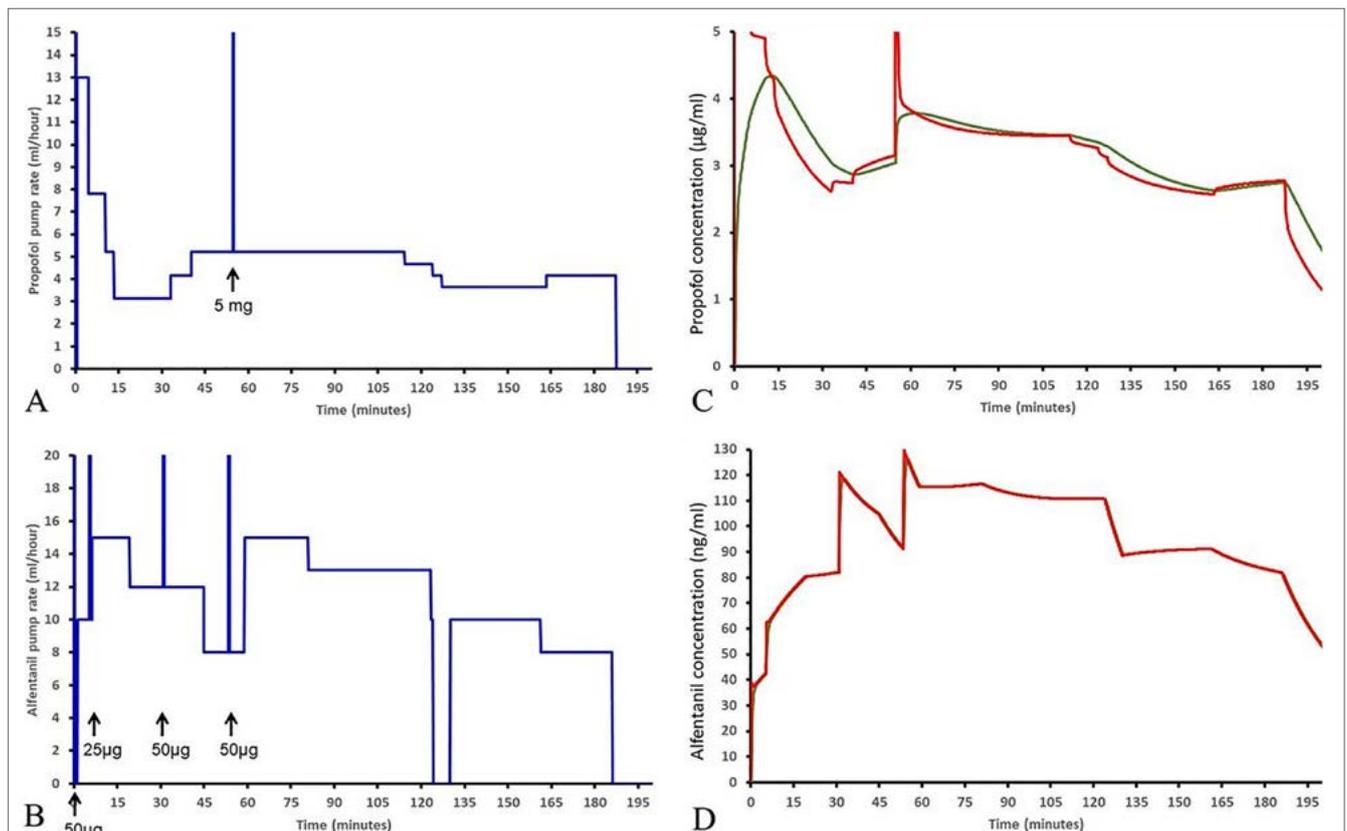


Figure 3. Syringe pump speeds and simulated blood and effect site concentrations over time

A and B: Syringe pump speeds over time. Arrows indicate supplementary bolus doses. **A** - Propofol; **B** - Alfentanil
C and D: Predicted blood (red) and effect site (green) concentrations. **C** - Propofol; **D** - Alfentanil

avoided during MEP monitoring. Blood pressure and temperature should be maintained within normal limits to facilitate accurate interpretation of IONM readings.¹⁷

The requirement for TIVA in this patient presented two challenges; unavailability of remifentanyl and TCI-pumps without age-appropriate PK models for sufentanyl or alfentanil. There are no sufentanyl PK studies available for infants aged less than one year undergoing non-cardiac surgery. The “Goresky” PK parameter-set for alfentanil³ is suitable for children aged between three months and 14 years. Stelsim simulations indicated that alfentanil would be suitable and that recovery would not be prolonged, even after prolonged infusions.

“Paedfusor”⁴ and “Kataria”¹⁸ paediatric propofol models used in commercially available TCI pumps have lower age limits of one and three years respectively. Using a PK model outside of its intended age group can result in significant dosage error¹⁹ (see Table I), as propofol pharmacokinetics vary significantly during the first 12 months.²⁰ We used the recently published “Eleveld” broad application model² which includes infant data. The model employs a maturation algorithm in addition to allometric scaling, thereby extending its lower age limit to infants and neonates below one year. The Eleveld model provides significant advantages over existing paediatric propofol models.

Similar to end-tidal volatile agent concentrations, advisory displays of expected plasma concentrations of infused intravenous drugs enable anaesthesiologists to fine-tune dosage according to patient requirements.²¹ Unlike end-tidal monitoring, patients’ real plasma concentrations of infused drug will always differ somewhat from the simulation’s display. Nevertheless, absolute prediction errors of 20% to 30% are clinically satisfactory.^{22–24} TCI and TGI dose regimens are based on pharmacokinetic principles that enable clinicians to establish patients’ drug concentrations within desired therapeutic windows and from there to titrate administration according to patient requirements. Useful guidelines for target concentrations have been published for individual drugs⁶ as well as for propofol-opioid combinations.⁷

Several other TGI advisory display systems with larger drug libraries and up-to-date PK models are available, for example TIVA Trainer (Windows), iTIVA and TIVA Manager (Android). We used Stelsim because users can utilise any combination of PK parameters for any drug, since Stelsim allows users to manually program the pharmacokinetic parameters of drugs not contained in the software’s original drug library. It is noteworthy that none of the newer models have been validated externally.

Recent developments include portrayal of drug-drug interactions based on response surface modelling.²⁵ Two systems are commercially available, the Smart Pilot View (Dräger, Lubeck, Germany) and the GE Navigator (GE Healthcare, Helsinki, Finland). Struys and co-workers provide a brief review of these advanced advisory display systems.²⁶

Conclusion

Unavailability of essential drugs is a reality in developing countries such as South Africa. Difficulties in providing TIVA

may be compounded by a non-availability of appropriate PK parameter-sets for patients at the extremes of age and size on TCI devices. This case illustrates how alternate drugs and advisory displays can be employed effectively. It also exemplifies the challenges of airway management and positioning of a small patient with a large CLDM.

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