Sedation With Midazolam After Cardiac Surgery in Children With and Without Down Syndrome: A Pharmacokinetic-Pharmacodynamic Study

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OBJECTIVES: To compare the pharmacokinetics and pharmacodynamics of IV midazolam after cardiac surgery between children with and without Down syndrome.

DESIGN: Prospective, single-center observational trial.

SETTING: PICU in a university-affiliated pediatric teaching hospital.

PATIENTS: Twenty-one children with Down syndrome and 17 without, 3–36 months, scheduled for cardiac surgery with cardiopulmonary bypass.

INTERVENTIONS: Postoperatively, nurses regularly assessed the children's pain and discomfort with the validated COMFORT-Behavioral scale and Numeric Rating Scale for pain. A loading dose of morphine (100 µg/kg) was administered after coming off bypass; thereafter, morphine infusion was commenced at 40 µg/kg/hr. Midazolam was started if COMFORT-Behavioral scale score of greater than 16 and Numeric Rating Scale score of less than 4 (suggestive of undersedation). Plasma midazolam and metabolite concentrations were measured for population pharmacokinetic- and pharmacodynamic analysis using nonlinear mixed effects modeling (NONMEM) (Version VI; GloboMax LLC, Hanover, MD) software.

MEASUREMENTS AND MAIN RESULTS: Twenty-six children (72%) required midazolam postoperatively (15 with Down syndrome and 11 without; $p = 1.00$). Neither the cumulative midazolam dose ($p = 0.61$) nor the time elapsed before additional sedation was initiated ($p = 0.71$), statistically significantly differed between children with and without Down syndrome. Population pharmacokinetic and pharmacodynamics analysis revealed no statistically significant differences between the children with and without Down syndrome. Bodyweight was a significant covariate for the clearance of 1-OH-midazolam to 1-OH-glucuronide ($p = 0.003$). Pharmacodynamic analysis revealed a marginal effect of the midazolam concentration on the COMFORT-Behavioral score.

CONCLUSIONS: The majority of children with and without Down syndrome required additional sedation after cardiac surgery. This pharmacokinetic and pharmacodynamic analysis does not provide evidence for different dosing of midazolam in children with Down syndrome after cardiac surgery.

KEY WORDS: cardiac surgical procedures; down syndrome; intensive care; midazolam; pharmacokinetics; sedation

DOI: 10.1097/PCC.0000000000002580

In 1887, John Langdon Down (1) was the first to describe the altered reaction to surgical procedures in individuals with Down syndrome. Later, chart review studies showed that intraoperative dosing of opioids did not

differ between children with and without Down syndrome (2) although those with Down syndrome more often received sedatives and muscle relaxants after cardiac surgery than children without Down syndrome (3). It has consistently been shown that the pharmacokinetics and pharmacodynamics of morphine are not different between children with and without Down syndrome after cardiac surgery (4, 5).

In the Republic of Ireland, the prevalence of Down syndrome is 1:546 live births (6). Approximately 54% of infants with Down syndrome have a congenital heart defect, often requiring cardiac surgery at a young age (7). To ensure their optimal postoperative treatment, it is highly relevant to study the pharmacokinetics and pharmacodynamics of the sedative agents employed. Midazolam is still the most used sedative agent in pediatric intensive care after cardiac surgery, despite wide variability in pharmacokinetics and the risk for delirium (8).

The aim of this study was to prospectively compare the pharmacokinetics of midazolam between children with and without Down syndrome after cardiac surgery and to link the midazolam concentrations to the pharmacodynamics by means of quantifiable distress assessments.

MATERIALS AND METHODS

Subjects and Setting

We performed an observational, prospective comparative cohort study at the Department of Anesthesia and Intensive Care Medicine of Our Lady's Children's Hospital, Dublin. The study protocol had been approved by the local medical ethics review board. Written informed consent for participation of their child in the study was obtained from the parents preoperatively. The analysis of the pharmacodynamics and pharmacokinetics of IV morphine in this cohort has been published previously (4).

Children between 3 and 36 months old, admitted to the ICU after cardiac surgery with cardiopulmonary bypass for atrial septal defect, ventricular septal defect, atrioventricular septal defect, or Tetralogy of Fallot repair, were eligible for participation in the study. The exclusion criteria were as follows: epilepsy, cerebral palsy, birth asphyxia, history of cardiothoracic surgery through sternotomy, preoperative mechanical ventilation, preoperative treatment with morphine or midazolam, and extracorporeal membrane oxygenation treatment after cardiopulmonary bypass.

Data were collected from the moment of the child's arrival in the operating theatre until one of the following events: a switch from IV to oral morphine, discharge to the ward, a procedure requiring general anesthesia, and reintubation for any reason other than oversedation.

General Anesthesia

Children received a standardized general anesthesic regimen without premedication as previously described (4). After discontinuation of cardiopulmonary bypass, a morphine loading dose (100 μg/kg) was administered, and a morphine infusion was commenced at 40 μg/kg/hr.

Postoperative Intensive Care Management

All patients received standardized postoperative pain and distress management titrated to pain. The first 24 hours after the surgery, the child's pain and distress were assessed every 2 hours using the COMFORT-Behavioral scale (COMFORT-B scale) and Numeric Rating Scale (NRS). Thereafter, scores were obtained every 4 hours and on indication (e.g., monitoring the effect of an intervention). Further information on the validity of these pain and distress assessment tools can be found in the original articles describing children with and without Down syndrome (9–13).

At arrival at the ICU, the morphine infusion was continued at 40 μg/kg/hr. Additional morphine was given (20–40 μg/kg bolus dose) if the COMFORT-B score was greater than or equal to 17 in combination with a NRS score greater than or equal to 4 (9)—indicating moderate to severe pain. Undersedation was defined as COMFORT-B score greater than 16 in combination with a NRS score less than 4 and considered as an indication to start midazolam. Midazolam boluses (50–100 μg/kg) were prescribed as needed with escalation to a midazolam infusion (1–2.5 μg/kg/min) if still further sedation was needed within 1 hour after the bolus administration.

All patients received three doses of IV acetaminophen for the first 24 hours (7.5 mg/kg for children < 10 kg and 15 mg/kg for children > 10 kg). At the discretion of the attending physician, rescue analgesics could be administered: either clonidine IV (1 μg/kg) or ibuprofen (10 mg/kg) as a suppository.

Samples for Pharmacokinetic Analysis

Arterial blood sampling was scheduled as follows: just before the first midazolam dose (t = 0) and next at t = 30–60 minutes, t = 4–8 hours, and t = 24 hours. Additional samples were obtained daily at 8.00 AM and once just before the end of the study. Blood samples (1.0 mL) were centrifuged, and plasma was stored at –80°C. Details on the analysis of the midazolam, 1-OH-midazolam, 4-OH-midazolam, 1-OH-midazolam-glucuronide levels using liquid chromatography with tandem mass spectroscopy can be found in the **supplementary material** (Supplemental Digital Content 1, http://links.lww.com/PCC/B533).

Population Pharmacokinetic Analysis

The population pharmacokinetic analysis was performed using nonlinear mixed effect modelling (NONMEM, Version VI; GloboMax LLC, Hanover, MD) by use of the first-order conditional estimation with η-ε interaction and ADVAN6 TOL5 (part of NONMEM software). The data were visualized using S-plus (Version 6.2; Insightful software, Seattle, WA). Model building was consisted of these four different steps: 1) selection of the structural model (one-, two-, or three-compartment model), 2) choice of the statistical model, 3) covariate analysis, and 4) model evaluation. Discrimination between different models was made by comparison of the objective function. A value of p less than 0.01, representing a decrease of 6.63 points in the objective function, was considered statistically significant. For more details, we refer to the supplementary material (Supplemental Digital Content 1, http://links.lww.com/PCC/B533).

Covariate Analysis

To visualize potential relationships, the covariates bodyweight, age, sex, Down syndrome, aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, C-reactive protein (CRP), and creatinine were plotted subsequently against the individual post hoc variable estimates and the weighted residuals. On the basis of these plots, covariates were tested for their influence. Starting from the basic model without covariates, the covariate model was first built up using forward inclusion ($p < 0.005$ representing a decrease of 7.88 points in objective function). Finally, after forward inclusion, a backward exclusion procedure was applied to justify the inclusion of a covariate ($p < 0.005$).

Model Validation

The internal validity of the population pharmacokinetic model was assessed by the bootstrap resampling method, that is, repeated random sampling to produce another dataset of the same size but with a different combination of individuals. Variables obtained with the bootstrap replicates (500 times) were compared to the estimates obtained from the original dataset.

Simulations

To compare the pharmacokinetic results from the current study with those of other pharmacokinetic models on midazolam in children, simulations were performed using the final modal and these two population pharmacokinetic models from the literature. One of these other studies reported midazolam pharmacokinetics in critically ill children (0–18 yr old; median age 5.1 mo) (14); the other reported this for nonventilated otherwise healthy children after craniofacial surgery (3–24 mo old) (15).

Pharmacodynamic Analysis

Input for the pharmacodynamic model consisted of the COMFORT-B scores at start of the midazolam infusion, routine scores, and scores obtained directly after an intervention. The COMFORT-B scores were modelled as ordered categorical data with three levels: undersedation (COMFORT-B score > 16), adequate sedation (COMFORT-B score between 11 and 16), and oversedation (COMFORT-B score below 11). Model estimation was performed using the Laplace estimation method in NONMEM. Details on this population pharmacodynamic analysis are presented in the supplementary material (Supplemental Digital Content 1, http://links.lww.com/PCC/B533).

Statistical Analysis

Univariate data were analyzed using SPSS version 23.0 (IBM, Chicago, IL). Nominal data were compared using the chi-square test (or Fisher exact test in the case of low predicted cell counts). Continuous data are presented as median (interquartile range [IQR]), and data for the children with and without Down

syndrome were compared with the Mann-Whitney *U* test. All *p* values are two sided, and a value of less than 0.05 is considered statistically significant.

RESULTS

Thirty-eight children participated (**Supplementary Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/B533) that is, 21 with Down syndrome and 17 without (**Table 1**). Parents of one child with Down syndrome did not give consent for the pharmacokinetic blood samples. Data of two children without Down syndrome were excluded from the analysis (one could not be weaned off cardiopulmonary bypass and was commenced on extracorporeal membrane oxygenation, the other because of inadvertent disconnection of the IV catheter for an unknown period during transport from theatre to the PICU).

Twenty-six subjects (72%), 15 with Down syndrome and 11 without, received midazolam postoperatively. The median (IQR) time from arrival in the PICU to administration of the first dose was 6 hours (5–14 hr) for the children without Down syndrome and 10 hours (5–15 hr) for children with Down syndrome ($p = 0.71$). The median number of midazolam boluses per patient was 5 (IQR 0–7) for the children without Down syndrome and 2 (IQR 0–9) for the children with Down syndrome ($p = 0.68$). A midazolam infusion was administered to seven children (33%) with Down syndrome and seven children (47%) without Down syndrome, *p* equals to 0.42. The median cumulative dose of midazolam per patient was 1,037 (IQR 101–2,516) microgram per kilogram during a median intensive care admission of 4 days (IQR 3–7 d). The cumulative midazolam dose did not statistically significantly differ between children with and without Down syndrome ($p = 0.61$). In two subjects without Down syndrome, midazolam infusion was stopped shortly after extubation. In one subject with Down syndrome and one without, a midazolam bolus was given after extubation.

The children who needed midazolam postoperatively had longer cardiopulmonary bypass times during surgery compared with those who did not require midazolam (median 119 min [IQR 100–136 min] vs 80 min [IQR 66–120 min]; $p = 0.04$). The children who received midazolam stayed longer in the PICU—with a median (IQR) duration of 4 days (3–7 d) days versus 2 days (1–3 d) for those who did not receive midazolam ($p = 0.01$).

Pharmacokinetics of Midazolam

Serum concentrations of midazolam, 1-OH-midazolam, 4-OH-midazolam, and 1-OH-midazolam-glucuronide exceeded lower limit of quantification (LLQ) in 147, 141, 81, 156 samples and were below LLQ in respectively 10.4%, 14%, 50.9%, and 6.0% of the samples. The pharmacokinetic model used is schematically depicted in **Supplementary Figure 2** (Supplemental Digital Content 1, http://links.lww.com/PCC/B533). Log transformed midazolam data were best described with a two-compartment model, parameterized in terms of the volume of the central compartment (V1), intercompartmental clearance between central and peripheral volume (Q), peripheral volume (V2), clearance to 1-OH-midazolam (CL1), and clearance to 4-OH-midazolam (CL4). The metabolites 1-OH-midazolam and 4-OH-midazolam were best described with a one-compartment model, whereas 1-OH-midazolam-glucuronide was best described with a two-compartment model. The residual errors were described with a proportional error model.

Table 2 lists the pharmacokinetic variable estimates and the results from the bootstrap analysis of the final model. The goodness of fit plots of the final model indicated a successful characterization of the data (**Supplementary Fig. 3**, Supplemental Digital Content 1, http://links.lww.com/PCC/B533). Bodyweight was a significant covariate for the clearance of 1-OH-midazolam to 1-OH-glucuronide (CL2)—implemented as a linear function (decrease in objective function of 8.77 points, $p = 0.003$). **Supplementary Figure 4** (Supplemental Digital Content 1, http://links.lww.com/PCC/B533) shows the relationship between bodyweight and CL2. Bodyweight as a covariate for peripheral volume of midazolam was rejected because the volumes of distribution of 1-OH-glucuronide could not be estimated anymore with adequate precision. Age was a significant covariate for the central volume of midazolam (decrease in objective function [ΔOF] = 9.71, $p = 0.002$), but incorporation of bodyweight on CL2 and age on V1 gave unstable results for the bootstrap analysis. Down syndrome was not a significant covariate on any of the pharmacokinetic variables. Furthermore, sex as well as markers of inflammation

TABLE 1.
Patient Characteristics

Patient Characteristics	Down Syndrome ($n = 21$)	Controls ($n = 15$)	p
Male sex, *n* (%)	7 (33)	8 (53)	0.23
Postnatal age, d, median (IQR)	175 (127–272)	204 (123–235)	0.50
Procedure, *n*			< 0.001[a]
Atrial septal defect	1	0	
Ventricular septal defect	4	5	
Atrioventricular septal defect	15	1	
Tetralogy of Fallot	0	9	
Atrioventricular septal defect and tetralogy of fallot	1	0	
Cardiopulmonary bypass time, min, median (IQR)	115 (80–127)	111 (72–134)	0.92[b]
Risk Adjustment for Surgery for Congenital Heart Disease-1 score 3, *n* (%)	16 (76)	1 (7)	< 0.001[a]
Morphine cumulative dose on day 1 in µg, median (IQR)	936 (705–1,076)	956 (845–1,074)	0.55
Pediatric Logistic Organ Dysfunction score day 1, median (IQR)	1.15 (0.1–1.3)	1.3 (0.1–1.3)	0.78
Duration of postoperative mechanical ventilation, hr, median (IQR)	26 (19–29)	26 (17–50)	0.82
Duration of intensive care admission, d, median (IQR)	4 (2–7)	4 (2–6)	0.92

IQR = interquartile range.
[a]*p* values are two-sided. A value of < 0.05 is considered statistically significant.

(CRP), liver tests (AST, ALT, bilirubin), and kidney function (creatinine) could not be identified as significant covariates.

The midazolam concentrations established in the current study compared better with those reported by Vet et al (14) than those reported by Peeters et al (15) (**Fig. 1**).

Pharmacodynamics

A total of 609 COMFORT-B and NRS scores were collected. The median COMFORT-B score was 13 (IQR 12–16) for the children with Down syndrome and 14 (IQR 12–24) for the children without Down syndrome ($p = 0.78$). The median NRS was 2 (IQR 0–2) for the children with Down syndrome and 2 (IQR 0–2) for the children without ($p = 0.57$).

Immediately before the first midazolam administration, the median COMFORT-B score was 18 (IQR 17–19). There were no differences in individually predicted midazolam levels and COMFORT-B scores between the children with and without Down syndrome (**Supplementary Fig. 5**, Supplemental Digital Content 1, http://links.lww.com/PCC/B533).

To demonstrate the pharmacodynamic effect, that is, the sedative effect of midazolam, on COMFORT-B scores, we developed an ordinal logistic regression model (**Table 3**). We tested the relation between midazolam concentrations and the probability of the categorized COMFORT-B scores, that is, undersedation (COMFORT-B < 11), adequately sedated (COMFORT-B 11–16), or oversedation (COMFORT-B > 16).

Down syndrome was not a significant covariate, since the OF remained 560 after testing this covariate. Including the effect of NRS in the model led to a decrease in OF (ΔOF 20; $p < 0.001$) (**Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/B533). This implies especially for children who have a NRS for pain greater than or equal

TABLE 2.

Population Pharmacokinetic Variables of Pharmacokinetic Model for Midazolam in Children and Results of Bootstrap Analysis

Variables	Values Based on Simple Model (CV in %)	Values Based on Final Model (CV in %)	Mean Bootstrap Value (CV in %)
Midazolam			
CL_1 (L/min)	0.020 (17.7)	0.019 (16.3)	0.019 (19.2)
CL_4 (L/min)	0.0015 (14.9)	0.0015 (20.5)	0.0015 (24.9)
$V_{1, central}$ (L)	1.55 (13.6)	1.51 (15.6)	1.52 (18.7)
$V_{2, peripheral}$ (L)	12.9 (25.9)	16.4 (24.5)	18.1 (35.7)
Q (L/min)	0.07 (15.5)	0.06 (15.4)	0.06 (16.1)
1-OH-midazolam			
CL_2 (L/min)	0.093 (17.3)	0.095 (14.9) + 0.019 (23.5) × (BW−6.5)	0.092 (20.5) + 0.017 (36.3) × (BW−6.5)
MF (in $V_3 = V_{1,central} \times MF$)	0.9 fixed	0.9 fixed	0.9 fixed
1-OH-midazolam-glucuronide			
$V_{4, 1\text{-OHG central}} = V_{5\text{-OHG peripheral}}$ (L)	0.13 (32.9)	0.12 (29.7)	0.11 (31.8)
Q_1 (L/min)	0.0036 (43.7)	0.0032 (37.9)	0.0033 (39.7)
CL_3 (L/min)	0.0086 (18.3)	0.0081 (16.9)	0.0079 (19.7)
4-OH-midazolam			
$V_6 = V_3$ (L)			
CL_5 (L/min)	0.039 (18.4)	0.038 (24.5)	0.039 (29.5)
Interindividual variability			
ωCL_1^2	0.34 (37.0)	0.24 (36.0)	0.24 (45.6)
$\omega V_{1, central}^2$	1.13 (29.3)	1.15 (28.3)	1.15 (39.4)
$\omega V_{2, peripheral}^2$	1.29 (34.0)	1.29 (33.7)	1.39 (38.5)
ωCL_2^2	0.29 (30.0)	0.11 (29.0)	0.12 (42.9)
ωCL_3^2	0.37 (33.9)	0.30 (45.2)	0.28 (52.4)
$\omega CL_1 CL_3^2$	0.27 (34.9)	0.19 (43.7)	0.17 (60.1)
Residual variability			
$\sigma^2_{(midazolam)}$	0.37 (22.8)	0.37 (23.2)	0.35 (23.7)
$\sigma^2_{(1\text{-OH})}$	0.20 (24.3)	0.21 (24.3)	0.20 (25.3)
$\sigma^2_{(1\text{-OHG})}$	0.17 (17.2)	0.18 (17.8)	0.18 (19.9)
$\sigma^2_{(4\text{-OH})}$	0.17 (16.1)	0.19 (16.5)	0.18 (19.0)
OF (-2LL)	0.7	−8.069	

BW = bodyweight, CL1= clearance of midazolam to 1-OH-midazolam, CL2 = clearance of 1-OH-midazolam to 1-OH-midazolam-glucuronide, CL3 = clearance of 1-OH-midazolam-glucuronide, CL4 = clearance of midazolam to 4-OH-midazolam, CL5 = clearance of 4-OH-midazolam, CV = coefficient of variation, MF = multiplication factor, Q = intercompartmental clearance of midazolam, Q1 = intercompartmental clearance of 1-OH-midazolam-glucuronide, V = volumes of distribution, ω2 = variance, the square root of the exponential variance of η−1 is the percentage of interindividual variability in the variables, σ2 = proportional intraindividual variance, OF (-2LL) = objective function, 1-OH = 1-OH- midazolam, 1-OHG = 1-OH-midazolam-glucuronide.

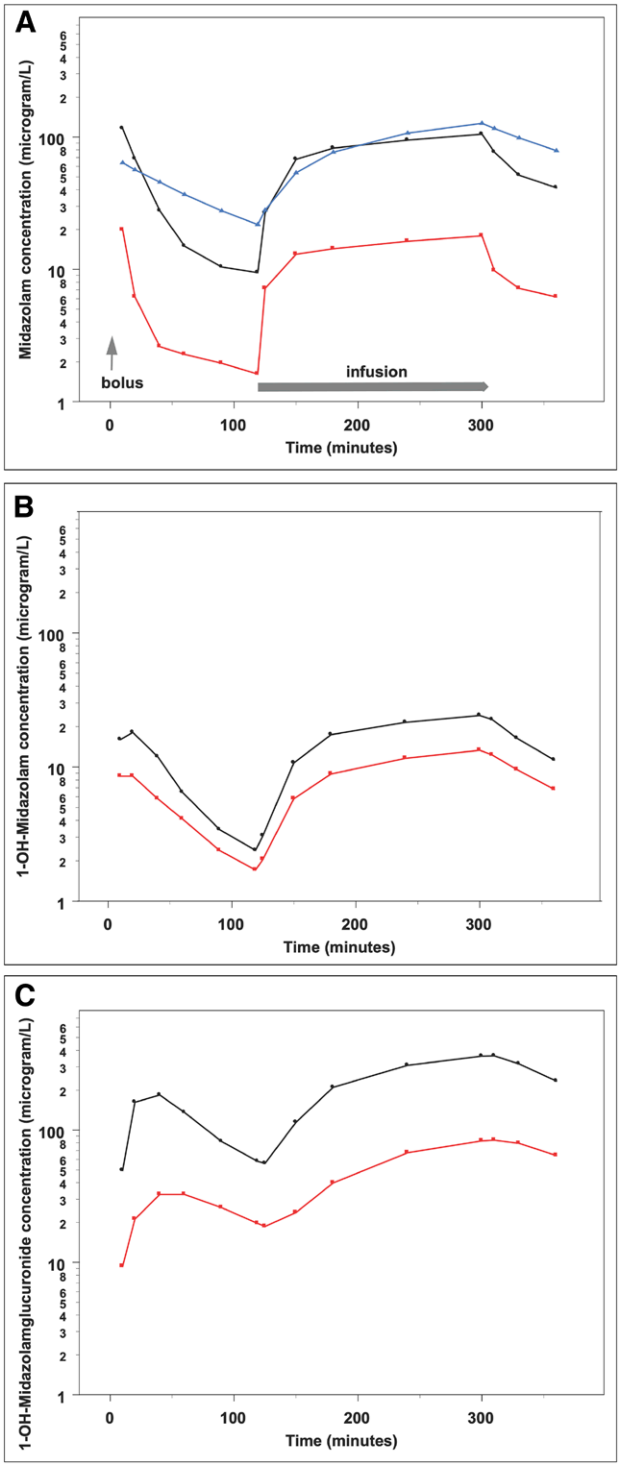

Figure 1. Midazolam (**A**) and metabolite (**B**, **C**) concentration versus time in children with a bodyweight of 6 kg after a bolus dose of 0.05 mg/kg followed by a continuous infusion that was started 2 hr after the bolus dose at a rate of the starting dose 0.06 mg/kg/hr during 3 hr. The simulations were based on the current study for children after cardiac surgery (*circles* and *black line*), for the published study of Vet et al (14), for critically ill children with C-reactive protein 35 mg/L and one failing organ (*triangles* and *blue line*), and for the study of Peeters et al (15) for nonventilated children after craniofacial surgery (*squares* and *red line*). Vet et al (14) did not determine metabolite concentrations.

to 4, there is a higher probability of undersedation at lower midazolam concentrations (**Fig. 2*B***). In children with a NRS score less than 4, we did not observe this effect of midazolam concentrations on the probability of undersedation (**Fig. 2***A*).

DISCUSSION

Sedation With Midazolam in Children With and Without Down Syndrome

This study shows that the dosing of midazolam does not need to be adjusted for children with Down syndrome. We found that neither the time before additional sedation was required nor the cumulative midazolam dose did statistically significantly differ between children with and without Down syndrome. We developed a population pharmacokinetic model that describes the distribution and clearance of midazolam and its metabolites 1-OH-midazolam, 4-OH-midazolam and 1-OH-midazolam-glucuronide. Down syndrome was not a significant covariate on the pharmacokinetics of midazolam.

Furthermore, the pharmacodynamic analysis showed no difference for the sedative effect of midazolam between children with and without Down syndrome.

Pharmacokinetics of Midazolam After Cardiac Surgery

In the present study, the concentrations of midazolam and its metabolites compared well with those in the previously published model by Vet et al (14) for children of different ages and different underlying diseases admitted to the ICU.

Vet et al (14) found that disease severity, expressed as number of failing organs, as well as CRP as a marker of inflammation, significantly affect critically ill children's midazolam clearance. In that study, the median CRP was 32 mg/L (IQR 0.3–385 mg/L). The median postoperative CRP value in our study was 34 mg/L, but CRP was not a significant covariate in the population pharmacokinetic analysis. Nguyen et al (16) reported that elevated levels of proinflammatory cytokines associated with infection and inflammation can modulate cytochrome P450 enzymes; interleukin-6 exposure up-regulated acute phase proteins (CRP, alpha-1-acid glycoprotein) and down-regulated CYP3A4. The proposed mechanism mediating cytochrome suppression

TABLE 3.

Population Pharmacodynamic Variables for the Basic and Final Model With Numeric Rating Scale Less Than 4 and Numeric Rating Scale Greater Than or Equal to 4 as Covariate Based on the COMFORT-Behavioral Score Categorized

Variables	Basic COMFORT-B Categorized, Mean (CV%)	Final COMFORT-B Categorized, Mean (CV%)
Fixed effects		
θ_1	1.2 (22.5)	1.5 (17.4)
θ_2	−4.0 (−8.0)	−4.2 (−7.9)
θ_3 (midazolam); θ4 (when Numeric Rating Scale ≥ 4)	0.0020 (52.9)	0.0019 (58.2); −1.8 (−30.6)
Interindividual variability		
ω^2	1.22 (39.8)	1.45 (40.9)
Performance measures		
-2LL	560.69	540.411

COMFORT-B = COMFORT-Behavioral, CV = coefficient of variation, -2LL = objective function, θ1, θ2 = cut-off points, θ3 = magnitude of the midazolam effect, θ4 = magnitude of the Numeric Rating Scale (NRS) effect (with 0 = NRS < 4 and 1 = NRS ≥ 4), ω2 = variance of the interindividual variability.

is most likely a result of direct interaction with cell surface receptors. As cardiopulmonary bypass is a potent trigger for a systemic inflammatory response, in our study, such an effect did not come unsuspectedly (17). Possible explanations for a lack of influence of CRP as a covariate in our study are the small range in CRP values, delayed modulation of the cytochrome P450 enzymes, and the fact that midazolam was started directly after the hit (cardiopulmonary bypass), during a relatively short study period (< 72 hr). The estimated degradation half-life of CYP3A4 is between 26 and 144 hours (18).

The majority of the 4-OH-midazolam concentrations were below the LLQ (2 ng/mL). The reported metabolic conversion fraction of midazolam to 4-OH-midazolam is 0.03 (19). It is understandable; therefore, that in view of the relatively low midazolam doses in this study, most of the 4-OH-midazolam concentrations were below the LLQ.

We identified bodyweight as a significant covariate on the glucuronidation clearance of 1-OH-midazolam. The glucuronidation of 1-OH-midazolam is mediated by UGT2B4, 2B7, and 1A4. Activity of these enzymes reaches adult levels within the first 1–2 years after birth. This would imply that bodyweight may be a surrogate descriptor for the ontogeny of drug glucuronidation in this population (20).

Pharmacodynamics of Midazolam After Cardiac Surgery

We found that the presence of Down syndrome had no influence on the pharmacodynamics of midazolam. In addition, a therapeutic effect of midazolam on COMFORT-B scores was hard to detect. We have compared all the scores before and after starting midazolam, looked at the individual plots displaying the COMFORT-B scores and midazolam levels over time (Supplementary Fig. 5, Supplemental Digital Content 1, http://links.lww.com/PCC/B533), and the probability for a particular COMFORT-B score to be a function of the midazolam concentration (Fig. 2). These concerted efforts revealed only a marginal effect of midazolam concentrations on the COMFORT-B scores. The pharmacodynamic model showed a lower probability for undersedation at higher midazolam concentrations. The probability of undersedation was higher when the NRS score was greater than or equal to 4 (Fig. 2*B*).

Why did we find only a marginal therapeutic effect of midazolam on COMFORT-B scores in this study? First, this may be due to the relatively low dosing of midazolam. Given that all subjects were receiving a morphine infusion as well, and in most cases the midazolam was administered as a bolus, a steady, therapeutic midazolam level may not have been indicated. Since undersedation was more common if NRS was greater than or equal to 4 (Fig. 2*B*) compared with NRS score of less than 4 (Fig. 2*A*), this confirms the overlap between the emotional states of pain and distress in these postoperative children. Second, little is known on the duration of the effect of midazolam on the pharmacodynamic outcome variable: the COMFORT-B scores. It may well be that, in the interval between administration of additional sedation and scoring, the stimulus for the additional sedative requirement (i.e., mechanical ventilation) had been removed. In theory, continuous monitoring of pain and distress levels would be preferable over nurses' assessments every 4–6

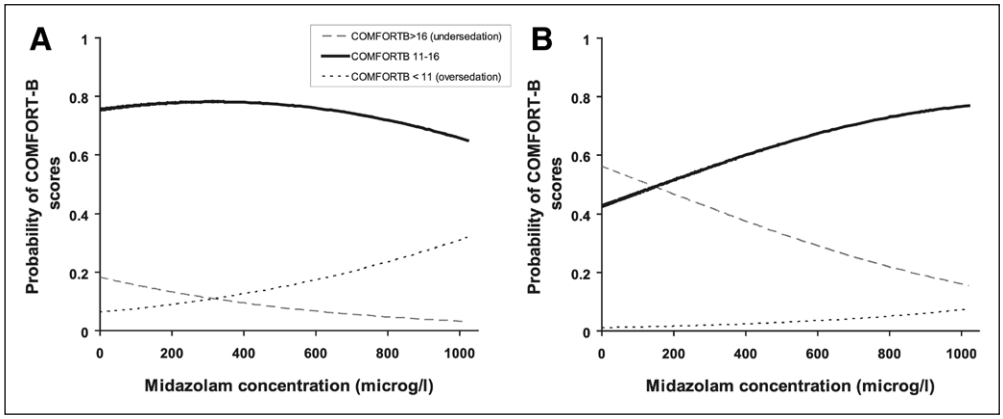

Figure 2. Probability of COMFORT-behavioral (COMFORT-B) score categorized as undersedation (COMFORT-B < 11), adequately sedated (COMFORT-B 11–16), or oversedation COMFORT B > 16), as a function of midazolam concentration (μg/L). **A**, Shows the results when the Numeric Rating Score (NRS) for pain is less than 4. **B**, Shows the results when the NRS for pain is greater than or equal to 4.

hours. Unfortunately, a method to continuously monitor pain and distress levels remains to be identified (21). An alternative to modelling COMFORT-B scores is the analysis of time to remedication events. For example, Elkomy et al (22) showed by analyzing the time to morphine remedication events after cardiac surgery in children that the sensitivity to morphine analgesia decreases with age and that higher doses are not incrementally effective.

Optimal Analgosedation After Cardiac Surgery

In this study, the children received morphine and midazolam according to an algorithm based on regular pain and distress assessments by the nursing staff. Donnelan et al (23) showed recently that the implementation of an algorithm reduced opioid and benzodiazepine dosing in children after cardiac surgery.

More than two thirds of the subjects in our study received midazolam at some point during their intensive care admission, and only half of them needed a midazolam infusion. This finding supports the practice of first addressing undersedation with a midazolam bolus, rather than proceeding immediately with continuous midazolam infusion. This is also supported by the findings of a randomized controlled trial by Penk et al (24) in children after cardiac surgery. It was found that pain was not better controlled with the addition of continuous infusions of morphine and midazolam when compared with intermittent dosing only. Still, the group with continuous infusions had received a significantly higher total dosage of these medications and had a longer length of stay.

After completion of our study, a "new" (and still off-label) player appeared in the field of analgosedation after pediatric cardiac surgery: dexmedetomidine. This sedative might be less suitable for children with Down syndrome, however, given the greater number of adverse cardiac events reported with dexmedetomidine in this population (25).

Future studies should be designed to answer the question of what is the optimal regimen of both maintenance and rescue doses of midazolam to establish an adequate level of comfort during intensive care admission. Data reflecting hemodynamic side-effects as well as the impact on sleep and delirium of such regimens must be captured (8).

Limitations

The children who required midazolam had a longer stay in the ICU and had been mechanically ventilated for a longer time. The observational nature of the study makes it difficult to draw conclusions on the requirements for midazolam after cardiac surgery.

Furthermore, since only children for elective cardiac surgery were included in this study, overall the duration of intensive care admission was relatively short, that is, a median of 4 days for the midazolam group and a median of 2 days for the children who did not require midazolam. This resulted in relatively low midazolam dosages and consequently low midazolam levels. Delirium assessments were not part of the study protocol, and therefore, we cannot report the incidence of postoperative delirium in the children with and without Down syndrome.

CONCLUSIONS

The pharmacokinetic and pharmacodynamic results from this study provide no evidence to support

altered dosing of midazolam in children with Down syndrome after cardiac surgery. This study confirms the observation that the majority of children with and without Down syndrome require sedation on top of morphine analgesia during intensive care admission after cardiac surgery. However, in both groups, the pharmacodynamic analysis revealed only a marginal effect of midazolam concentrations on the COMFORT-B scores.

ACKNOWLEDGMENTS

We would like to thank Claire Magner, PhD, Department of Anesthesia and Critical Care Medicine, Crumlin, Dublin 12, Ireland, for her support with the data collection.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

Supported, in part, by a grant (F/12/4) from the National Children's Research Centre, Dublin, Ireland.

Drs. Valkenburg's and Peeters's institutions received funding from National Children's Research Centre, Dublin, Ireland. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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