ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetics and Target Attainment of Allopurinol and Oxypurinol Before, During, and After Cardiac Surgery with Cardiopulmonary Bypass in Neonates with Critical Congenital Heart Disease

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Abstract

Background The CRUCIAL trial (NCT04217421) is investigating the effect of postnatal and perioperative administration of allopurinol on postoperative brain injury in neonates with critical congenital heart disease (CCHD) undergoing cardiac surgery with cardiopulmonary bypass (CPB) shortly after birth.

Objective This study aimed to characterize the pharmacokinetics (PK) of allopurinol and oxypurinol during the preoperative, intraoperative, and postoperative phases in this population, and to evaluate target attainment of the current dosing strategy.

Methods Nonlinear mixed-effects modeling was used to develop population PK models in 14 neonates from the CRUCIAL trial who received up to five intravenous allopurinol administrations throughout the postnatal and perioperative periods. Target attainment was defined as achieving an allopurinol concentration >2 mg/L in at least two-thirds of the patients during the first 24 h after birth and between the start and 36 h after cardiac surgery with CPB.

Results A two-compartment model for allopurinol was connected to a one-compartment model for oxypurinol with an auto-inhibition effect on the conversion, which best described the PK. In a typical neonate weighing 3.5 kg who underwent cardiac surgery at a postnatal age (PNA) of 5.6 days, the clearance (CL) of allopurinol and oxypurinol at birth was 0.95 L/h (95% confidence interval 0.75–1.2) and 0.21 L/h (0.17–0.27), respectively, which subsequently increased with PNA to 2.97 L/h and 0.41 L/h, respectively, before CPB. During CPB, allopurinol and oxypurinol CL decreased to 1.38 L/h (0.9–1.87) and 0.12 L/h (0.05–0.22), respectively. Post-CPB, allopurinol CL increased to 2.21 L/h (1.74–2.83), while oxypurinol CL dropped to 0.05 L/h (0.01–0.1). Target attainment was 100%, 53.8%, and 100% at 24 h postnatally, 24 h after the start of CPB, and 36 h after the end of cardiac surgery, respectively. The combined concentrations of allopurinol and oxypurinol maintained $\geq$ 90% inhibition of xanthine oxidase ($IC90_{XO}$) throughout the postnatal and perioperative period.

Conclusions The minimal target concentration of allopurinol was not achieved at every predefined time interval in the CRUCIAL trial; however, the dosing strategy used was deemed adequate, since it yielded concentrations well exceeding the $IC90_{XO}$. The decreased CL of both compounds during CPB suggests influence of the hypothermia, hemofiltration, and the potential sequestration of allopurinol in the circuit. The reduced CL of oxypurinol after CPB is likely attributable to impaired kidney function.

1 Introduction

Critical congenital heart disease (CCHD) affects 0.3% of newborns and necessitates cardiac surgery with cardiopulmonary bypass (CPB) within the first weeks of life for the majority of cases [1]. While up to 90% of neonates survive into adulthood, many experience long-term neurological deficits, such as motor, cognitive, and behavioral impairments

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Key Points

The dosing strategy used in the CRUCIAL trial achieved adequate xanthine oxidase inhibition in > 90% of neonates with critical congenital heart disease undergoing cardiac surgery with cardiopulmonary bypass (CPB) during the postnatal and perioperative periods.

Reduced clearance of allopurinol and oxypurinol found during the use of CPB is likely due to hypothermia, hemofiltration, and possible sequestration of allopurinol within the circuit.

The substantial decline in postoperative oxypurinol clearance suggests that impaired renal function, induced by CPB, may have influenced its elimination.

[2, 3]. During the critical periods surrounding birth and cardiac surgery with CPB, neonates with CCHD are at risk of hypoxic-ischemic brain injury due to hemodynamic instability [4, 5]. To address this concern, the CRUCIAL trial (NCT04217421) is currently investigating the neuroprotective potential of postnatal and perioperative allopurinol administration in minimizing perioperative brain injury in neonates with CCHD [6].

In prior clinical studies in neonates, allopurinol has shown promise as a neuroprotective agent in mitigating the effects of hypoxia and reperfusion [7]. Following a hypoxic-ischemic event, cytotoxic oxygen radicals are generated during the reperfusion and reoxygenation phases, leading to neuronal cell death. This destructive process is mediated by the enzyme xanthine oxidase (XO) [8, 9]. Allopurinol and its active metabolite oxypurinol act as XO inhibitors, thus preventing the formation of reactive oxygen species [10]. Previously, early postnatal allopurinol administration in asphyxiated neonates was found to provide a full XO inhibition for at least 24 h [11, 12]. Moreover, allopurinol has beneficial effects on the inflammatory response following ischemia-reperfusion events, and is known to improve postoperative outcomes in patients following CPB. This includes reduced inotropic scores, duration of mechanical ventilation, as well as length of stay in the intensive care unit and hospital [13, 14].

Neonates with CCHD require cardiac surgery with the support of CPB soon after birth, which is often accompanied by fluid resuscitation, therapeutic hypothermia, and hemofiltration [15]. The use of CPB is therefore often associated with hemodilution and hypothermia and is known to cause a profound change in blood flow, oxygen delivery, and enzyme activity [15, 16]. Moreover, during the first few hours or days following neonatal cardiac surgery with CPB, common complications such as cardiac stunning and inflammation can lead to low cardiac output syndrome and acute kidney injury (AKI) [17–19]. These potential physiological changes and CPB-induced complications can collectively affect metabolic enzymes and drug protein binding, and impair renal or hepatic function, which may alter the pharmacokinetics (PK) of allopurinol (metabolized by XO) and oxypurinol (cleared renally) during and after CPB [20, 21]. Moreover, the CPB circuit has been shown to sequester molecules in a highly unpredictable manner, especially for lipophilic or highly protein bound drugs [22, 23]. This effect is unclear for allopurinol and oxypurinol, which are hydrophilic compounds with low protein binding.

The PK of allopurinol and oxypurinol have been studied in asphyxiated neonates receiving 5–20 mg/kg of allopurinol postnatally [11, 12]. In neonates with moderate-to-severe hypoxic-ischemic encephalopathy (HIE), an auto-inhibition effect on allopurinol metabolism by oxypurinol was found, which was attributed to the involvement of XO in the metabolic pathway of allopurinol [12]. In critically ill neonates undergoing CPB, substantial alterations in PK parameters have been observed in more than 70% of studied drugs, including an increase in volume of distribution (Vd) and variable effects on clearance (CL) [24, 25]. Therefore, adjustments in dose level or dosing interval are often required in this population. The specific effects of CPB on the PK of allopurinol and oxypurinol during neonatal cardiac surgery remain unclear. The aim of this study was therefore to characterize the PK of allopurinol and oxypurinol during the postnatal and perioperative period, encompassing the early postnatal, preoperative, intraoperative, and postoperative phases, in neonates with CCHD undergoing cardiac surgery with CPB using a population PK modeling approach. The final population PK model was further used to evaluate the target attainment of the CRUCIAL trial under the current dosing strategy, and propose alternative dosing strategies when appropriate.

2 Methods

2.1 Patient Population, Blood Sampling, and Bioanalysis

The CRUCIAL trial is a phase III, randomized, quadruple-blinded, placebo-controlled, multicenter trial primarily investigating the effect of early postnatal and perioperative allopurinol administration on postoperative brain injury in neonates with CCHD. Evaluation of the PK profile of allopurinol and oxypurinol in this population was one of the secondary objectives of the trial. Specific details of the study protocol have been published [6] and the trial is registered at www.clinicaltrials.gov (NCT04217421). While the trial is being conducted in four academic centers in The Netherlands, the PK substudy was performed exclusively at Wilhelmina Children's Hospital, University

Medical Center Utrecht. In this center, neonates with a prenatal diagnosis of CCHD who were anticipated to require cardiac surgery with CPB within their first month of life were included in the PK substudy. Ethical approval was granted by the national and institutional Medical Research Ethics Committees and Central Committee on Research Involving Human Subjects (NL62772.041.18; EudraCT 2017-004596-31), and written informed consent for study participation was obtained from all parents or legal guardians. Randomization was performed by Ace Pharmaceuticals in blocking (by Randlist version 1.2 software). In its design and analysis, all measures were taken to ensure sustained blinding of the cases included in the PK substudy.

Schedules for dose administrations and blood samples for PK analysis are summarized in Fig. 1. In the intervention group, neonates diagnosed with CCHD before birth received five allopurinol administrations intravenously, with a dose of 20 mg/kg per administration: early postnatally within 45–60 min after birth (DOSE 1) and 12 h after the first dose (DOSE 2), preoperatively 12 h prior to cardiac surgery (DOSE 3), intraoperatively at the start of CPB (DOSE 4), and postoperatively 24 h after surgery (DOSE 5). To minimize the burden on the neonates, we applied a sparse blood sampling approach, limiting each sample to 0.5 mL. In addition, we combined blood sampling for this study as much as possible with clinically indicated blood draws. Samples were collected via arterial, venous, or capillary access. If there was no arterial or venous access, capillary blood sampling was exclusively performed when clinically warranted.

Plasma concentrations of allopurinol and oxypurinol were quantified by The Ardena Bioanalytical Laboratory in accordance with Good Clinical Practice guidelines. The applied assay was validated according to the European Medicines Agency guidelines (International Conference on Harmonisation 2012). Allopurinol and oxypurinol in human plasma samples were extracted by protein precipitation using ethanol. After precipitation and centrifugation, the supernatant was injected into the liquid chromatography-tandem mass spectrometry (LC–MS/MS) chromatographic system for the determination of allopurinol and oxypurinol. The chromatographic separation was performed on an Astec® CHIROBIOTIC®V HPLC column using isocratic elution. An API 4000 tandem mass spectrometer equipped with a turbo ion spray probe operating in the negative multiple reaction monitoring mode was used for quantification. The lower limit of quantification (LLOQ) was 0.05 mg/L for allopurinol and 0.0467 mg/L for oxypurinol. Accuracy and precision of all quality control samples met the predefined acceptance criteria.

2.2 Structural Model Development

Due to the expected pronounced impact of CPB on blood flow and fluid balance, a population PK model was developed in three sequential steps. The first step involved analyzing the PK of allopurinol and oxypurinol during the postnatal-preoperative period, followed by the intraoperative period, and finally the postoperative period. The three periods were divided by the start and end times of CPB. A table describing overall model development is provided in the electronic supplementary material (ESM).

As a starting point, our previously developed model describing allopurinol and oxypurinol in neonates with HIE was used as the base structural model (see the ESM) [11, 12]. This model consisted of two sequential one-compartment models with an auto-inhibition effect on allopurinol metabolism by oxypurinol. The CL and Vd of allopurinol and oxypurinol during the postnatal-preoperative period ($CL_{Postnatal}$ and $Vd_{Postnatal}$), as well as the effect of auto-inhibition, were estimated and were compared with the estimations in HIE neonates.

During the intraoperative period, an alteration in the CL and Vd of allopurinol and oxypurinol was anticipated. Besides several physiological changes during CPB, alterations in CL and Vd might also be attributed to the influence of the CPB circuit. To account for the impact of fluctuating blood flow and the potential for drug sequestration within the CPB circuits on the PK of allopurinol and oxypurinol, separate CL and Vd (CL_{CPB} and Vd_{CPB}) were estimated during this period using Eqs. (1) and (2).

$$CL_{CPB} = CL_{Postnatal} * E_{CL,\, CPB} \tag{1}$$

$$Vd_{CPB} = Vd_{Postnatal} * E_{Vd,\, CPB}, \tag{2}$$

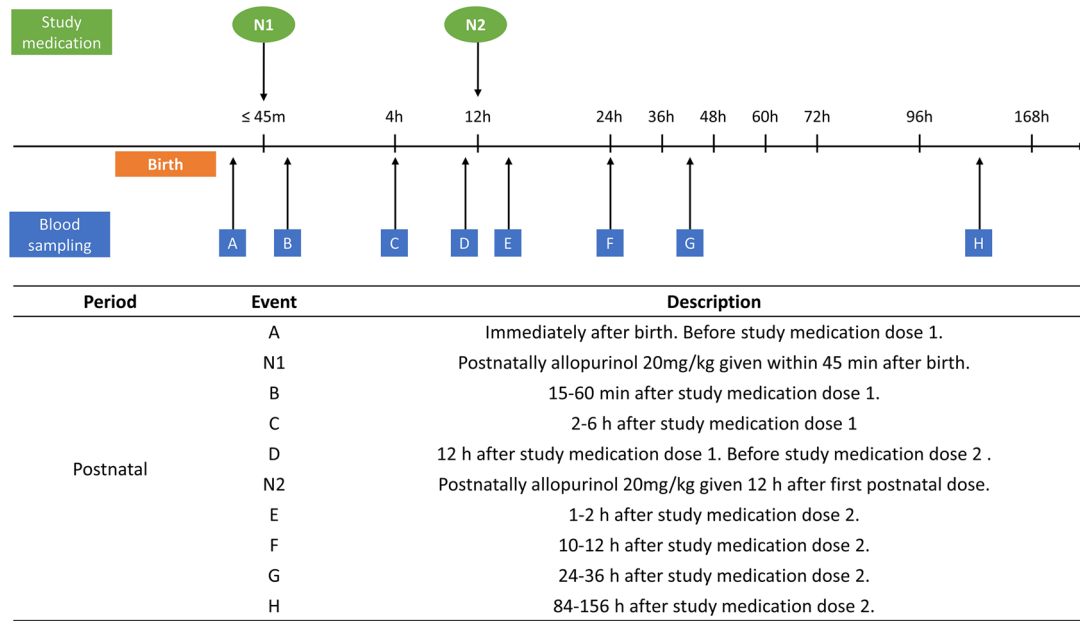where $E_{CL,CPB}$ and $E_{Vd,CPB}$ represent the fractional changes in CL and Vd compared with the values at the postnatal-preoperative period, respectively.

In the postoperative period, changes in PK were expected to be attributable to various factors related to the cessation of CPB, the change in hemodynamics, and the altered anatomical conditions (e.g., cardiac stunning), which could lead to potential impairment of renal or hepatic function. Therefore, to characterize the PK of allopurinol and oxypurinol during this period, an additional set of CL and Vd values were estimated using Eqs. (3) and (4).

$$CL_{Postop} = CL_{postnatal} * E_{CL,\, Postop} \tag{3}$$

$$Vd_{Postop} = Vd_{postnatal} * E_{Vd,\, Postop}, \tag{4}$$

(A) Postnatally

Period	Event	Description
Postnatal	A	Immediately after birth. Before study medication dose 1.
	N1	Postnatally allopurinol 20mg/kg given within 45 min after birth.
	B	15-60 min after study medication dose 1.
	C	2-6 h after study medication dose 1
	D	12 h after study medication dose 1. Before study medication dose 2 .
	N2	Postnatally allopurinol 20mg/kg given 12 h after first postnatal dose.
	E	1-2 h after study medication dose 2.
	F	10-12 h after study medication dose 2.
	G	24-36 h after study medication dose 2.
	H	84-156 h after study medication dose 2.

(B) Perioperatively

Period	Event	Description
Preoperative	I	0-3 h before study medication dose 3.
	N3	Preoperatively allopurinol 20mg/kg given 12 h before surgery.
	J	1-3 hours after study medication dose 3.
Intraoperative	K	0-1 h before study medication dose 4.
	N4	Intraoperatively allopurinol 20mg/kg given during surgery in the CPB.
	L	10 min after study medication dose 4.
	M	30 min after study medication dose 4.
	N	At the end of CPB.
Postoperative	O	4 h after surgery.
	P	0-3 h before study medication dose 5.
	N5	Postoperatively allopurinol 20mg/kg given 24 h after surgery.
	Q	1-3 h after study medication dose 5.
	R	48 h after study medication dose 5.

Fig. 1 Dosing and blood sampling schedule for pharmacokinetic analysis [6]. Sample A was intended for measuring biomarkers and was excluded from the analysis. *CPB* cardiopulmonary bypass

where the fractional changes in CL and Vd compared with the values at the postnatal-preoperative period were estimated, denoted as $E_{CL,Postop}$ and $E_{Vd,Postop}$, respectively.

2.3 Covariate Model Development

Parameters related to CL and Vd were modeled with body weight-based allometric scaling, using fixed power exponents of 0.75 and 1 for CL and Vd, respectively, and were normalized to a body weight of 3.5 kg to compare with previous models in neonates with HIE [11, 12]. In most critically ill

neonates, a gradual recovery of organ function and cardiac output after birth could be expected due to the stabilization under the setting of pediatric intensive care [26]. Therefore, during the postnatal-preoperative period, the effect of recovery on allopurinol and oxypurinol $CL_{postnatal}$ were evaluated using postnatal age (PNA) as an indicator, testing by a linear function (Eq. 5) and a sigmoidal Hill function (Eq. 6). In Eq. (6), TM_{50} is the PNA at which the recovery effect reaches 50% of the maximum value and the Hill coefficient describing the slope of the sigmoidal curve.

$$\text{Recovery} = 1 + \theta * \text{PNA} \qquad (5)$$

$$\text{Recovery} = 1 + E_{max} * \frac{\text{PNA}^{\text{Hill}}}{\text{TM}_{50}^{\text{Hill}} + \text{PNA}^{\text{Hill}}}. \qquad (6)$$

2.4 Pharmacokinetic Data Analysis

Population PK analysis was conducted using NONMEM (version 7.5; ICON Development Solutions, Ellicott City, MD, USA) [27], with support from Perl-speaks-NONMEM (PsN, version 5.0) [28] and Pirana (version 2.9.9) [29].

The first-order conditional estimation method with interaction (FOCE-I) option was employed to estimate PK parameters and their variability. Individual PK parameters were estimated using the maximum a posteriori Bayesian estimation method with the POSTHOC option in NONMEM.

Between-subject variability (BSV) was assessed using an exponential variance model assuming a log-normal distribution (Eq. 7). Residual unexplained variability was evaluated with a proportional error model, an additive error model, or a combined proportional and additive model (Eq. 8).

$$P_i = P_{pop} * e^{\eta_i} \qquad (7)$$

$$Y_{i,j} = C_{i,j} * \left(1 + \varepsilon_{1i,j}\right) + \varepsilon_{2i,j}, \qquad (8)$$

where P_{pop} is the population estimate for a parameter, P_i the individual value for that parameter, and η_i is the normally distributed between-subject variability of the ith individual with a mean of zero and a variance of ω^2. $Y_{i,j}$ is the observed concentration and $C_{i,j}$ is the predicted concentration for the jth observation of the ith individual. ε_1 and ε_2 are the proportional and additive residual errors, respectively, which are normally distributed with a mean of zero and a variance of σ^2.

2.5 Exposure and Target Attainment

The predefined objective of the CRUCIAL PK substudy was to attain a target concentration of allopurinol > 2 mg/L in at least two-thirds (> 66%) of the patients, postnatally within

Table 1 Patient demographics

Variable	Median [IQR]
Total number of patients	14
The total number of samples	
Postnatal-preoperative period	60
Intraoperative period	36
Postoperative period	44
Number of samples for each patient	10 [9, 12]
Birth weight (kg)	3.16 [2.75, 3.73]
Gestational age (weeks)	38.0 [38.0, 38.8]
Male sex [n (%)]	10 (71.4)
Apgar score at 1 min after birth[a]	8.00 [8.00, 9.00]
Apgar score at 5 min after birth[a]	9.00 [9.00, 10.0]
Cardiac pathology [n (%)]	
Single ventricle physiology	4 (28.6)
Aortic arch anomaly	2 (14.3)
Transposition of the great arteries	6 (42.9)
Other	2 (14.3)
Cardiac surgery with CPB [n (%)][b]	14 (100)
Postnatal age at the start of cardiac surgery (day)[b]	5.60 [4.78, 7.81]
Total duration of cardiac surgery with CPB (min)[b]	320 [280, 368]
Lowest rectal temperature during CPB (°C)	27.7 [23.7, 28]
Deep hypothermic cardiac arrest [n (%)][b]	1 (7.7)
Antegrade cerebral perfusion [n (%)][b]	4 (30.8)

IQR interquartile range, *CPB* cardiopulmonary bypass

[a]Apgar scores after birth were only recorded in 13 patients

[b]One patient had neonatal cardiac surgery performed in a non-participating center. PK samples for this patient were only collected during the postnatal period. Surgery-related variables were summarized based on 13 patients

approximately the first 24 h after birth, defined as the time period between DOSE 1 and 12 h after DOSE 2, and perioperatively between the start of cardiac surgery with CPB and 36 h after cardiac surgery with CPB, defined as the time period between DOSE 4 and 12 h after DOSE 5.

The predefined target concentration of allopurinol was chosen based on previous studies showing that allopurinol effectively inhibits XO at plasma concentrations exceeding 2 mg/L [30, 31]. We aimed to achieve this target concentration in more than 66% of the analyzed cases. This objective was outlined in the CRUCIAL study protocol [6], aligning with a recent report on neonates with HIE receiving allopurinol [11], and following guidance of the European Medicines Agency (scientific advice and protocol assistance).

To assess the effect of the current allopurinol dosing regimen used in the CRUCIAL trial, three PK targets were evaluated. First, as defined in the trial's protocol, allopurinol concentrations 12 h after each dose administration and 24 h after DOSE 2, DOSE 4 and DOSE 5 were derived from the final PK models. Target attainment of allopurinol concentration > 2 mg/L were calculated. Second, the concentrations

Fig. 2 Allopurinol and oxy-
purinol concentrations versus
numeral sampling time point.
A description of sampling time
points is provided in Fig. 1
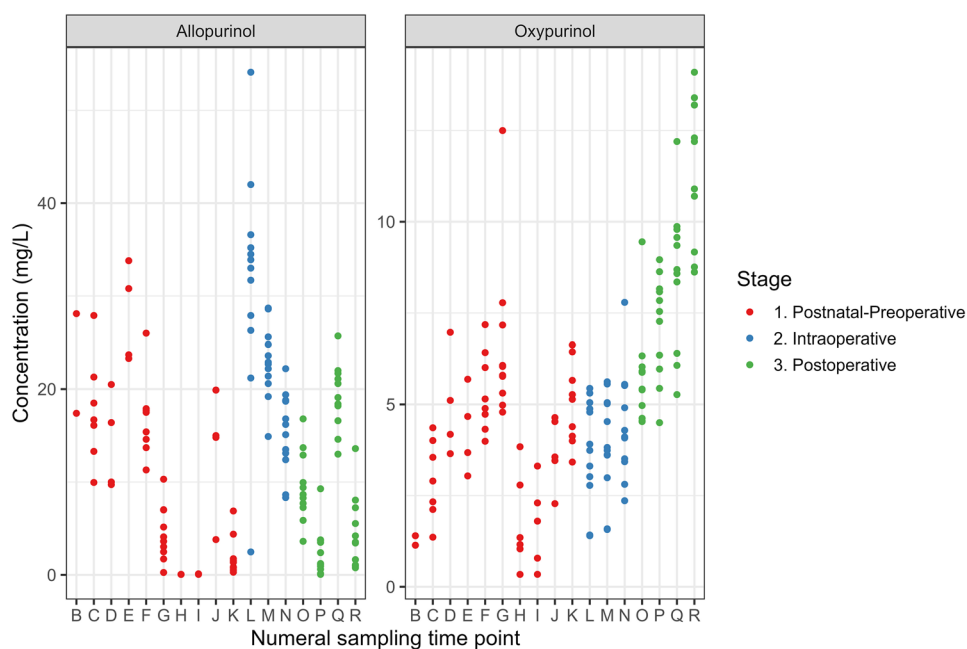
of allopurinol plus oxypurinol at the aforementioned time-
points were compared with a target concentration of 6.22
mg/L, which corresponds to 90% of maximal XO inhibition
($IC90_{XO}$), deriving from our previous study in neonates with
HIE [11]. Lastly, the area under the plasma concentration–
time curve (AUC) for 12 h after each dose was calculated
using the individual MAP Bayesian parameter estimates of
the final PK models, and were used to compare allopuri-
nol and oxypurinol exposures in neonates with CCHD and
those with moderate-to-severe HIE (ALBINO trial) [32].
In neonates with HIE receiving early postnatal allopurinol
administration, the median allopurinol and oxypurinol AUC
$_{12}$ were 129 mg/L*h (interquartile range 93.6–161) and 42.7
mg/L*h (29.4–59.3), respectively [12].

2.6 Model Evaluation

Model adequacy was guided by physiological plausibility,
statistical significance, and graphical evaluation. The change
in objective function value (OFV), which equals minus two
times the log-likelihood, was used to define statistical signif-
icance between hierarchical models following a Chi-square
distribution. A decrease in OFV of > 3.84 for 1 degree of
freedom, representing a p value of < 0.05, was considered
statistically significant. Akaike information criterion (AIC)
was used to compare the model fit between non-hierarchical
models, and goodness-of-fit plots were used to assist graphi-
cal evaluation using R (version 4.0) and Xpose (version 4).
A visual predictive check (VPC) [33] and sampling impor-
tance resampling (SIR) [34] were performed to assess the
predictive performance and parameter precision with 95%
confidence intervals (CIs) for the final model.

3 Results

3.1 Patient Characteristics

Allopurinol and oxypurinol data from 14 neonates with
CCHD were used for the PK analysis. In one neonate, the
cardiac surgery was performed in a non-participating center;
thus, the PK samples of this neonate were only available for
the postnatal stage. Thirteen neonates underwent neonatal
cardiac surgery at Wilhelmina Children's Hospital Utrecht
with the support of CPB starting at a median PNA of 5.6
days. The median total duration of the cardiac surgery was
320 min. Clinical characteristics of the included study popu-
lation are summarized in Table 1. The number of analyzed
allopurinol and oxypurinol observations during the postna-
tal-preoperative, intraoperative, and postoperative periods
was 60, 36, and 44, respectively. Only 5.8% of the measured
allopurinol concentrations were below the LLOQ, and were
therefore included as LLOQ/2, with an additive residual
error component of LLOQ/2 fixed to the error model. The
observed concentrations of allopurinol and oxypurinol are
plotted against the sampling time point in Fig. 2.

3.2 Model Development

The PK of allopurinol and oxypurinol were best described
by a two-compartment model and a subsequent one-com-
partment model with an auto-inhibition effect on allopurinol
metabolism by oxypurinol. The parameter estimates of the
final model are summarized in Table 2. A two-compartmen-
tal model was required to capture the maximal allopurinol
concentrations measured at 10 min after the onset of CPB,

Table 2 Pharmacokinetic parameter estimates of the final model

Parameter	Estimate	Precision (95% CI)[c]
Postnatal-preoperative period (samples B–J)		
Allopurinol clearance (All $CL_{Postnatal}$)[a]	0.95 L/h	0.75–1.2
Allopurinol volume of distribution (All $Vd_{Postnatal}$)[a]	2.22 L	2–2.49
Oxypurinol clearance (Oxy $CL_{Postnatal}$)[a,b]	0.21 L/h	0.17–0.27
Oxypurinol volume of distribution (Oxy $Vd_{Postnatal}$)[a,b]	12 L	9.87–15.33
Effect of recovery on $CL_{Postnatal}$		
Maximum fold of increase in All $CL_{Postnatal}$	3 (fixed)	–
Maximum fold of increase in Oxy $CL_{Postnatal}$	1.35 (fixed)	–
Hill coefficient	2.98 (fixed)	–
Postnatal age at 50% of maximum recovery effect	4.2 days (fixed)	–
Intraoperative period (samples K, L, M, N)		
Fraction of allopurinol clearance change compared with $CL_{Postnatal}$ (All $E_{CL,CPB}$)	1.46	0.96–2.13
Fraction of allopurinol volume of distribution change compared with $Vd_{Postnatal}$ (All $E_{Vd,CPB}$)	1.47	1.27–1.72
Fraction of oxypurinol clearance change compared with $CL_{Postnatal}$ (Oxy $E_{CL,CPB}$)	0.54	0.21–1.02
Fraction of oxypurinol volume of distribution change compared with $Vd_{Postnatal}$ (Oxy $E_{Vd,CPB}$)	1.3	1.2–1.43
Postoperative period (samples O, P, Q, R)		
Fraction of allopurinol clearance change compared with $CL_{Postnatal}$ (All $E_{CL,Postop}$)	2.33	1.95–2.84
Fraction of allopurinol volume of distribution change compared with $Vd_{Postnatal}$ (All $E_{Vd,Postop}$)	1.42	1.19–1.69
Fraction of oxypurinol clearance change compared with $CL_{Postnatal}$ (Oxy $E_{CL,Postop}$)	0.23	0.06–0.42
Fraction of oxypurinol volume of distribution change compared with $Vd_{Postnatal}$ (Oxy $E_{Vd,Postop}$)	1.48	1.34–1.63
Other structural parameters		
Allopurinol intercompartmental clearance (All Q1)	6.97 L/h (fix)	–
Allopurinol volume of central compartment (All V1)	0.1 L (fix)	–
Autoinhibition of allopurinol metabolism		
Maximum achievable autoinhibition effect	1 (fix)	–
Oxypurinol concentration at 50% of maximum autoinhibition effect ($IC_{50,auto-inhibition}$)	1.1 mg/L (fix)	–
Variability		
Between-subject variability on allopurinol CL (BSV All CL)	36% CV	24–50
Between-subject variability on oxypurinol Vd (BSV Oxy Vd)	42% CV	30–54
Between-occasion variability on allopurinol CL (BOV All CL)	18% CV	12V26
Between-occasion variability on oxypurinol CL (BOV Oxy CL)	43% CV	30–59
Residual proportional error for allopurinol	25% CV	21–29
Residual proportional error for oxypurinol	16% CV	14–18

CI confidence interval, *CV* coefficient of variation, approximated using $CV\% = \sqrt{\omega^2}*100$, *CL* clearance, *Vd* volume of distribution

[a]Clearances and volume of distributions are normalized to a body weight of 3.5 kg

[b]Oxypurinol clearances and volume of distributions are relative to formation fraction (assumed to be 1)

[c]Obtained by a sampling importance resampling procedure [34]

in which a very small central compartment (V1) of 0.1 L and a large inter-compartment CL (Q1) of 6.79 L/h were estimated. The AIC values were 839 for the one-compartment model and 736 for the two-compartment model, supporting the need for a two-compartment model. This additional fast distribution process was likely an artifact of the very short sampling interval in the intraoperative period. Therefore, V1 and Q1 were fixed during the model building process to provide an adequate model fit.

Following our previous model based on neonates with HIE, the metabolism of allopurinol was more accurately described by an auto-inhibition effect driven by oxypurinol. The effect size of the auto-inhibition was estimated based on the data collected during the early postnatal period (PNA ≤ 3 days), in which the half-maximum effect was reached with an oxypurinol concentration ($IC50_{auto-inhibition}$) of 1.1 mg/L. The $IC50_{auto-inhibition}$ value was fixed during the latter model development stages to improve model stability and to allow further covariate analysis.

Fig. 3 The clearance in a typical neonate (3.5 kg) over postnatal age, starting cardiac surgery with cardiopulmonary bypass at a postnatal age of 5.6 days. At birth, the clearance of allopurinol and oxypurinol was 0.95 L/h and 0.21 L/h, respectively, and increased to 2.97 L/h and 0.41 L/h before the start of CPB, respectively. During the period of cardiac surgery with CPB (shaded area), the clearance of allopurinol and oxypurinol decreased to 1.38 L/h and 0.12 L/h, respectively. After CPB, the clearance of allopurinol increased to 2.21 L/h, while clearance of oxypurinol dropped to 0.05 L/h. *CPB* cardiopulmonary bypass

*Normalized to body weight of 3.5kg
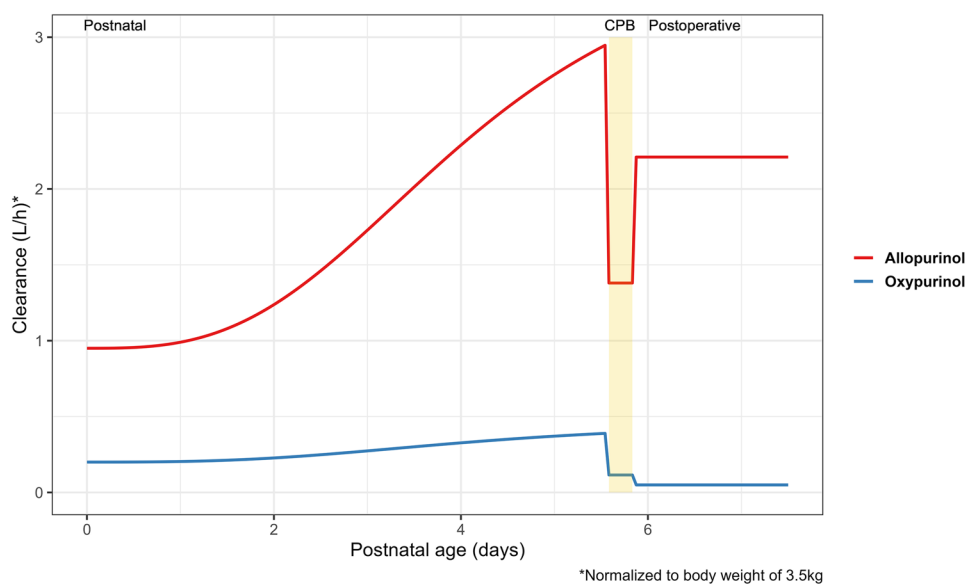
During the early postnatal period, the $CL_{Postnatal}$ of allopurinol and oxypurinol were comparable with neonates with HIE. Including PNA as a covariate on the $CL_{Postnatal}$ of allopurinol and oxypurinol significantly improved the model fit, with a dOFV of -80 with 2 degrees of freedom ($p < 0.01$), suggesting an impact of recovery on drug CL after birth. This recovery effect was empirically described by a sigmoidal Hill equation, with a TM_{50} of PNA 4.2 days and a Hill coefficient of 2.98. The maximal increase in allopurinol and oxypurinol $CL_{Postnatal}$ until the start of cardiac surgery (3- to 14-day interval) were 3-fold and 1.35-fold, respectively. The effect of recovery was fixed to the identified values for further model development. In Fig. 3, the CLs in a typical neonate (3.5 kg) who underwent cardiac surgery at a PNA of 5.6 days are illustrated. At birth, the $CL_{Postnatal}$ of allopurinol and oxypurinol were 0.95 L/h and 0.21 L/h, respectively; while before the onset of CPB, the $CL_{Postnatal}$ increased to 2.97 L/h and 0.41 L/h, respectively. During the period of cardiac surgery with CPB, the CL_{CPB} of allopurinol and oxypurinol decreased to 1.38 L/h and 0.12 L/h, respectively. Consequently, there was minimal fluctuation in oxypurinol concentrations during the onset of CPB (Fig. 2, samples L, M, and N). After the cessation of CPB, the CL_{Postop} of allopurinol increased to 2.21 L/h, while CL_{Postop} of oxypurinol dropped to 0.05 L/h, most likely due to AKI, which is a common complication of CPB [17–19].

The Vd of allopurinol and oxypurinol in neonates with CCHD was 2.22 L and 12 L at birth, respectively, similar to the values found in neonates with HIE. Throughout the perioperative period, including the intraoperative and postoperative stages, the Vd of allopurinol and oxypurinol gradually increased by 42% to 3.16 L and 48% to 18 L, respectively.

BSV in the CL of allopurinol and the Vd of oxypurinol across all periods were estimated at 36% and 42%, respectively. Between-occasion variability was estimated for the CL of allopurinol and oxypurinol between stages. The final model provided an adequate description of allopurinol and oxypurinol observations in neonates with CCHD during the postnatal-preoperative, intraoperative, and postoperative periods. Goodness-of-fit plots (Fig. 4) and the VPC (Fig. 5) based on the final model showed no major deviations. The precision of the parameter estimates in the final model were confirmed by SIR analysis.

### 3.3 Exposure and Target Attainment

The minimal target concentrations of allopurinol > 2 mg/L were reached in 100%, 53.8%, and 100% of patients at 24 h after birth, 24 h after the start of CPB, and 36 h after the end of cardiac surgery, respectively (Table 3). Although the predefined target of allopurinol concentration > 2 mg/L was not reached in $> 66\%$ of patients at 24 h after the start of CPB, dosing adjustments were considered not needed since allopurinol plus oxypurinol concentrations achieved $IC90_{XO}$ of 6.22 mg/L in $>90\%$ of patients at this time point, suggesting sufficient XO inhibition (Table 3 and Fig. 6) [11]. Allopurinol and oxypurinol AUC_{12} after each dose are shown in Fig. 7. The AUC_{12} of allopurinol and oxypurinol throughout the whole observation period was comparable with, or higher than, the exposures in neonates with HIE [12].
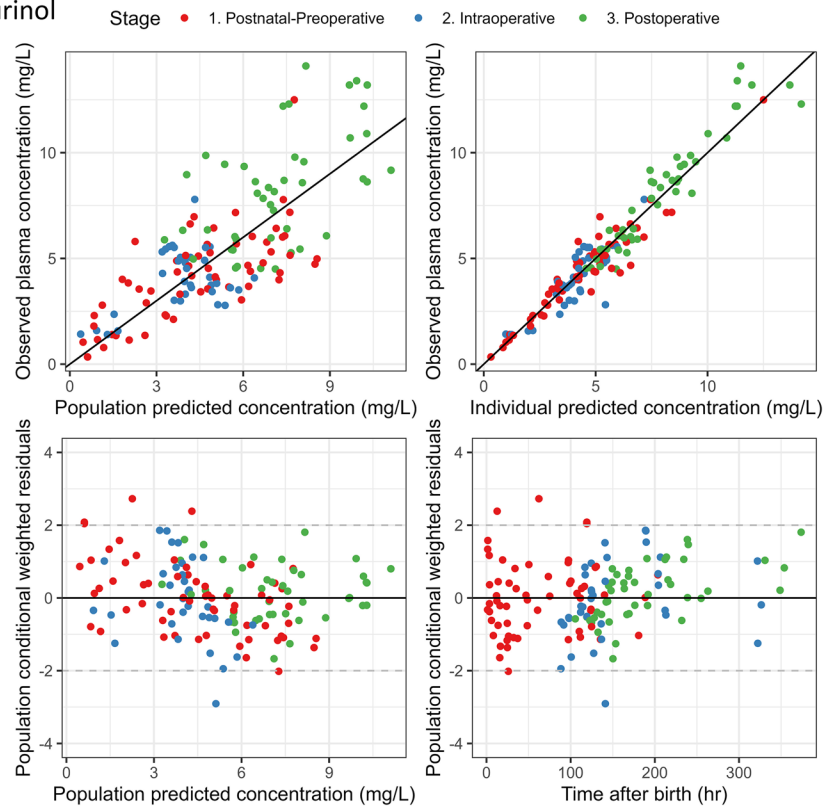
4 Discussion

This study aimed to evaluate the current dosing strategy of early postnatal and perioperative allopurinol administration in neonates undergoing cardiac surgery with CPB, as applied

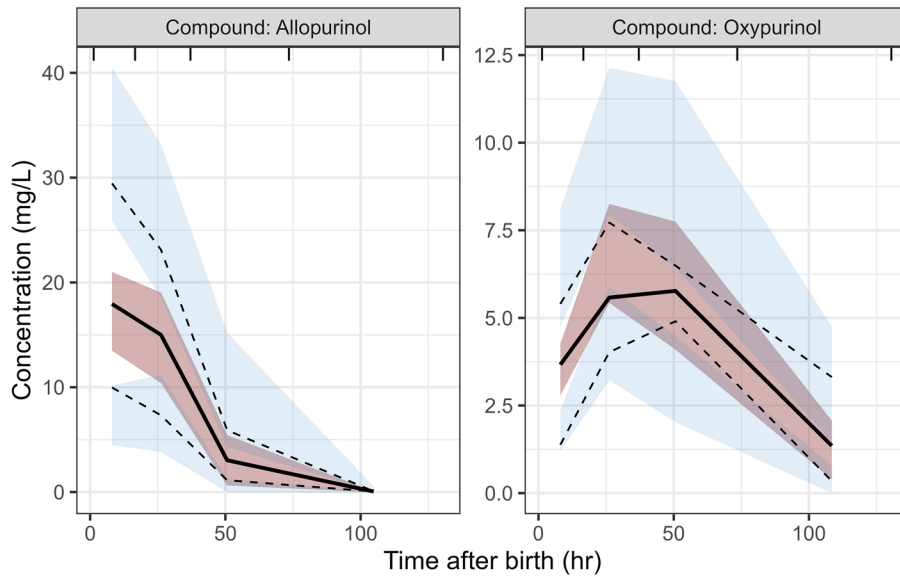**Fig. 4** Goodness-of-fit plots of the **a** allopurinol and **b** oxypurinol final models

(A) Postnatal period. X-axis represents time (in hours) after birth.
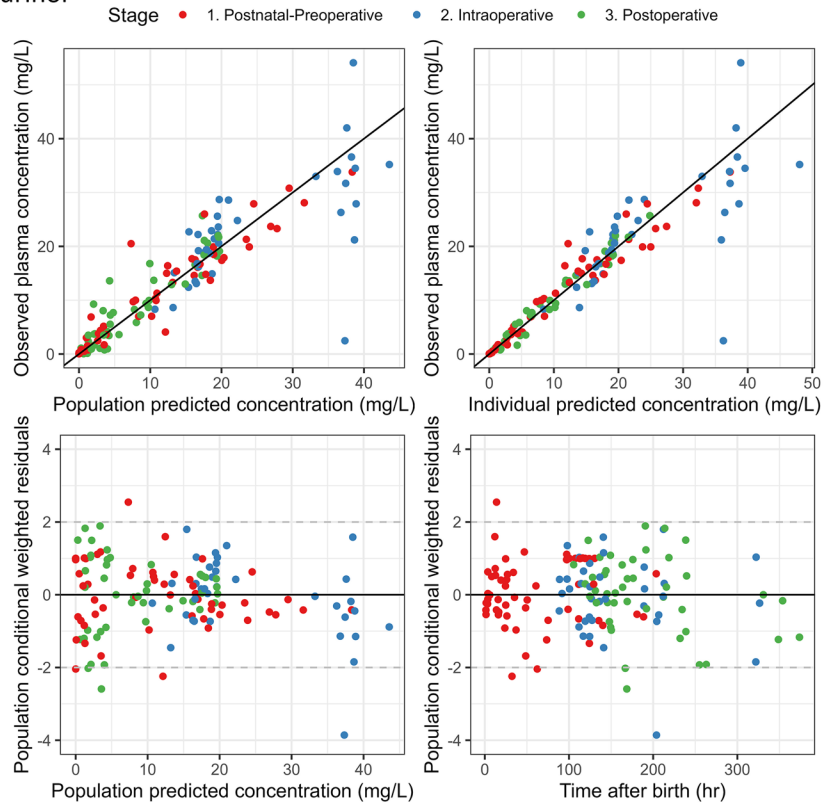
(B) Perioperative period including preoperative, intraoperative and postoperative phases. X-axis

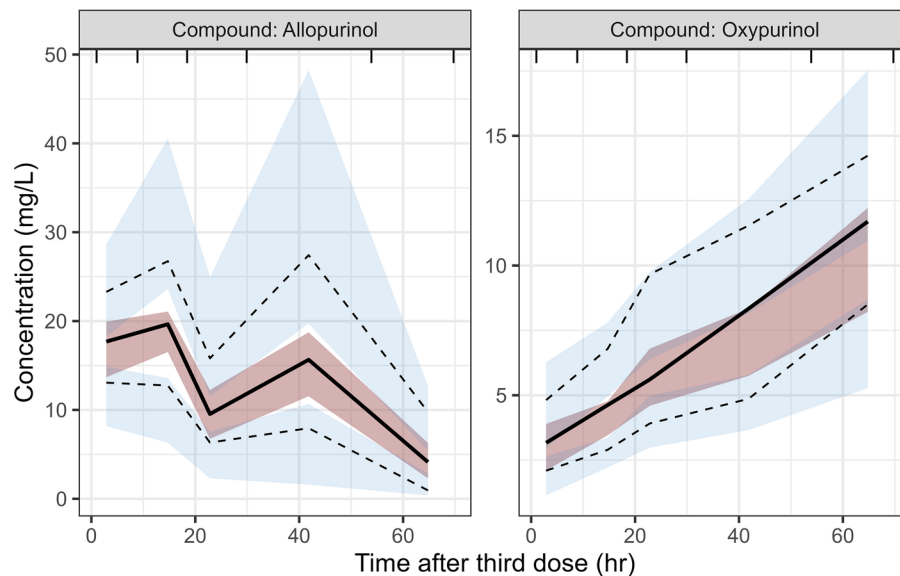represents time (in hours) after the third dose (sample J to R).

Fig. 5 Prediction-corrected visual predictive check of allopurinol and oxypurinol based on the final model. **a** Postnatal period; x-axis represents the time (in hours) after birth. **b** Perioperative period, including the preoperative, intraoperative and postoperative phases; x-axis represents the time (in hours) after the third dose (samples J–R). Black solid and dashed lines represent the median and 80% interval of the prediction-corrected observations; red shaded area represents the 95% CI of the median prediction; and blue shaded area represents the 95% CI of the 10th and 90th prediction intervals. Automatic binning was used, with the number of bins set to four for the postnatal period and five for the perioperative period. *CI* confidence interval

in the CRUCIAL trial, using a population PK model for allopurinol and oxypurinol. The predefined PK targets were to achieve allopurinol concentrations > 2 mg/L in more than 66% of patients during the first 24 h after birth and between the start of cardiac surgery and 36 h after cardiac surgery with CPB.

Our previous studies in neonates with moderate-to-severe HIE suggested that allopurinol and oxypurinol provided 90% XO inhibition with a combined concentration of 6.22 mg/L

Table 3 Target attainment and exposures.The predefined target in the CRUCIAL trail was concentration of allopurinol > 2 mg/L in > 66% of the patients in the first 24 h after birth and between the start of cardiac surgery and 36 h after cardiac surgery with CPB

Stage	Time	Allopurinol > 2 mg/L (%)	Allopurinol + oxypurinol > IC90$_{XO}$[b] (%)	Allopurinol AUC$_{12}$ (mg/L*h)	Oxypurinol AUC$_{12}$ (mg/L*h)
Postnatal	12 h after first dose	100	100	171 [160, 195]	38.6 [29.2, 44,2]
Postnatal[a]	12 h after second dose	100	100	291 [283, 302]	67.4 [53.7, 83.6]
Postnatal	24 h after second dose	91.7	100	–	–
Preoperative	12 h after third dose	36.4	73	95 [86, 131]	56.6 [50.9, 62.1]
Intraoperative[a]	12 h after fourth dose	92.3	100	154 [114, 163]	59.5 [53.7, 68.6]
Postoperative[a]	24 h after fourth dose	53.8	92	–	–
Postoperative[a]	12 h after fifth dose	100	100	175 [151, 196]	109 [87.5, 118]
Postoperative	24 h after fifth dose	78.6	100	–	–

AUC_{12} area under the plasma concentration-time curve from time zero to 12 h

[a]Time of interest defined in the CRUCIAL study protocol

[b]IC90$_{XO}$ represents allopurinol plus oxypurinol concentrations that provides 90% of maximal xanthin oxidase inhibition. The value of 6.22 mg/L is derived from previous study in neonates with hypoxic-ischemic encephalopathy [11]

[11]. In the current study, this IC90$_{XO}$ target was achieved in > 70% of analyzed neonates within 12–24 h after each dose. These results suggest that the current dosing strategy was sufficient in maintaining drug levels that provide adequate XO inhibition throughout the postnatal and perioperative time windows (Table 3 and Fig. 6). Therefore, although the predefined minimal allopurinol target concentration was not always achieved, the current dosing strategy employed in the CRUCIAL trial was considered sufficient. The effect of oxypurinol on XO inhibition was not taken into account for the definition of the target concentration in the clinical trial protocol [6]. It is known that oxypurinol inhibits XO as effectively as allopurinol and has a much longer half-life, which therefore is believed to be the primary active moiety responsible for its pharmacological effects [35].

Significant changes in the CL and Vd of allopurinol and oxypurinol among the postnatal, intraoperative, and post-operative phases were characterized in this population. Between birth and the start of cardiac surgery with CPB, the CL$_{Postnatal}$ of allopurinol and oxypurinol was found to increase with PNA. The maximal increase in CL$_{Postnatal}$ was threefold for allopurinol and 1.35-fold for oxypurinol up until 1.5 weeks of life, in which the half-maximum value was reached at 4.2 days of life. In critically ill neonates, several drugs predominantly cleared renally or hepatically have shown a strong increase in CL after birth [26, 36]. While this increase is likely partly due to maturation, it cannot be attributed solely to maturation effects [26, 37]. Previous studies suggested that the supportive and stabilizing environment of intensive care may play an important role in the observed increase in drug CL [26]. Such an effect is very likely also present in our study population, which may explain the increasing CL$_{Postnatal}$ of allopurinol and

oxypurinol. Nevertheless, as we lack data from critically ill and non-critically ill neonates administered the same drug, the effect of maturation and recovery from illness cannot be distinguished.

In addition to the effects of recovery, the substantial increase in allopurinol CL$_{Postnatal}$ found in neonates with CCHD may also be related to the development of hypoxic-ischemic events during the postnatal period [38]. Unlike neonates with HIE who experience severe fetal hypoxia, neonates with CCHD typically encounter milder hypoxic-ischemic events after birth. These events can be attributed to the cardiac defect itself, which alters blood flow and oxygen delivery, or may result from hemodynamic instability during the delivery process or therapeutic interventions (e.g., balloon atrial septostomy) [4]. A hypoxic-ischemic event is known to increase the level of highly activated XO as a consequence of primary energy failure [39]. In neonates with CCHD, the level of activated XO was likely lower at birth when compared with neonates with HIE, while elevated during the postnatal period, which explains the threefold increase in allopurinol CL in this period.

In this study, the median total duration of the cardiac surgery with CPB was 320 min. When compared with the PK parameters estimated before the start of CPB in a typical neonate with a PNA of 5.4 days, the CL$_{CPB}$ of allopurinol and oxypurinol decreased by 54% and 71%, respectively, and Vd$_{CPB}$ increased by 47% and 33%, respectively. In this study, neonates underwent therapeutic hypothermia during cardiac surgery, with the lowest rectal temperature during CPB measured at a median of 27.7 °C. The decreased CL$_{CPB}$ can be linked to the reduced enzyme activity resulting from the application of therapeutic hypothermia [16]. Additionally, the use of a CPB may reduce blood flow to vital metabolic

Fig. 6 Allopurinol plus oxypurinol concentrations over time after birth or time after the start of cardiac surgery compared with the IC90 value of 6.22 mg/L for xanthine oxidase inhibition [11]. The dotted line corresponds to 72 h after birth. *IC90* 90% inhibitory concentration
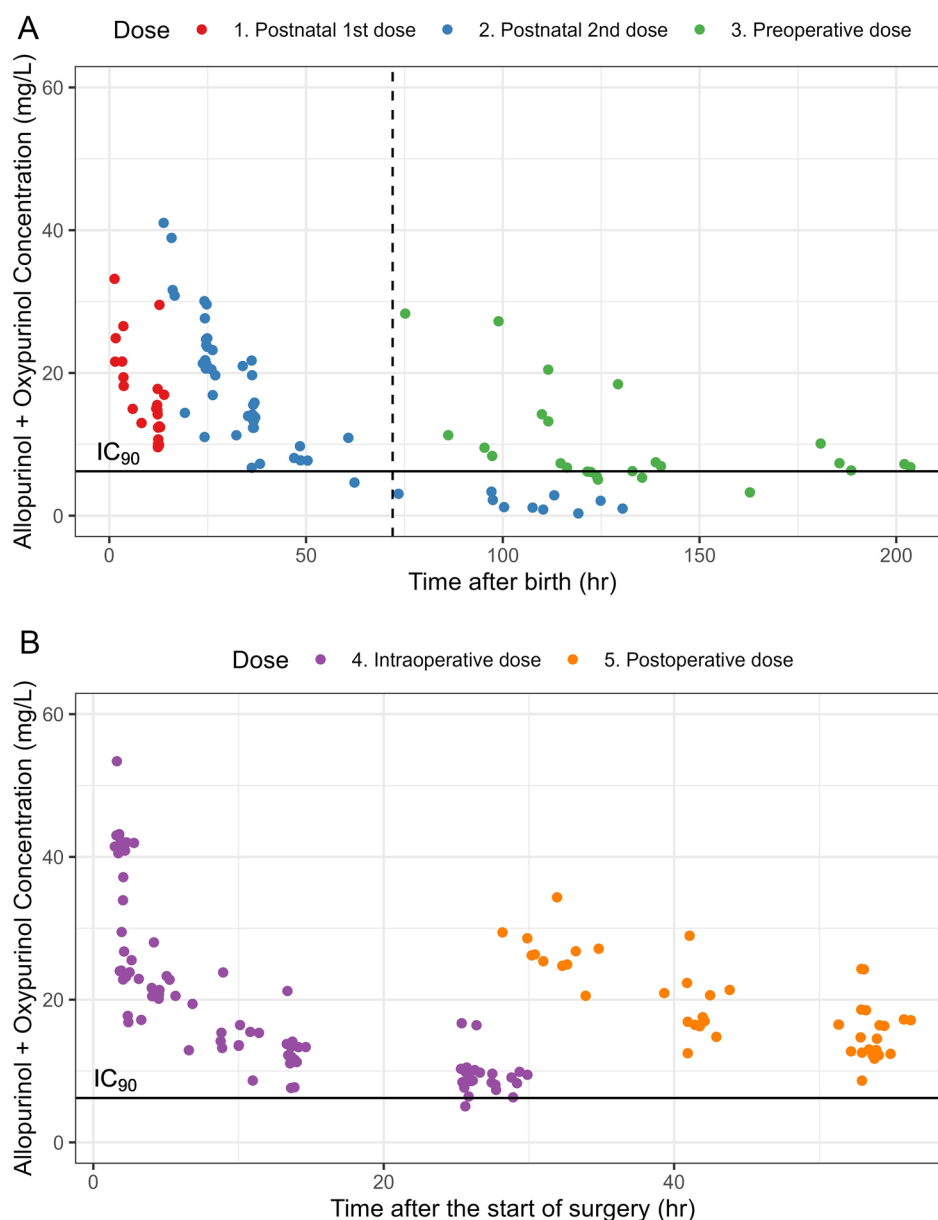
organs such as liver and kidneys, subsequently causing a decrease in drug CL [15]. The increased Vd_{CPB} could be a consequence of hemodilution resulting from fluid support required to maintain circulation throughout the surgery with CPB [20, 21]. Moreover, since both allopurinol and oxypurinol are hydrophilic drugs, factors such as the additional volume required for the CPB device and those related to the CPB procedure (e.g., capillary leakage) could also contribute to the increased Vd.

Of note, during the CPB period, a decrease in allopurinol concentrations was observed, while the oxypurinol concentrations remained stable at lower values (Fig. 2, samples L, M, and N) when compared with the last observation before the surgery (Fig. 2, sample K). This

result suggested that allopurinol was likely not fully converted to oxypurinol during the CPB period, which may be attributed to the use of conventional ultrafiltration during CPB or CPB sequestration. Nevertheless, a full conversion of allopurinol to oxypurinol was assumed in this analysis due to limited data. Conventional ultrafiltration is frequently utilized during CPB to mitigate the consequences of hemodilution and anemia by removing intravascular plasma water [40]. Consequently, conventional ultrafiltration might have a significant role in drug CL during CPB, which warrants additional investigation. Although the CPB circuit is more likely to retain drugs that are highly lipophilic and protein-bound, which is not the case for allopurinol and oxypurinol, the potential

Fig. 7 Allopurinol and oxy-
purinol exposures compared
with neonates with moderate-
to-severe hypoxic-ischemic
encephalopathy (ALBINO trial)
[32]. Shaded areas represent the
IQR of allopurinol and oxypuri-
nol AUC_{12} in neonates from the
ALBINO study, in which the
median (IQR) was 129 mg/L*h
(93.6–161) and 42.7 mg/L*h
(29.4–59.3), respectively [12].
IQR interquartile range, AUC_{12}
area under the plasma concen-
tration-time curve from time
zero to 12 h
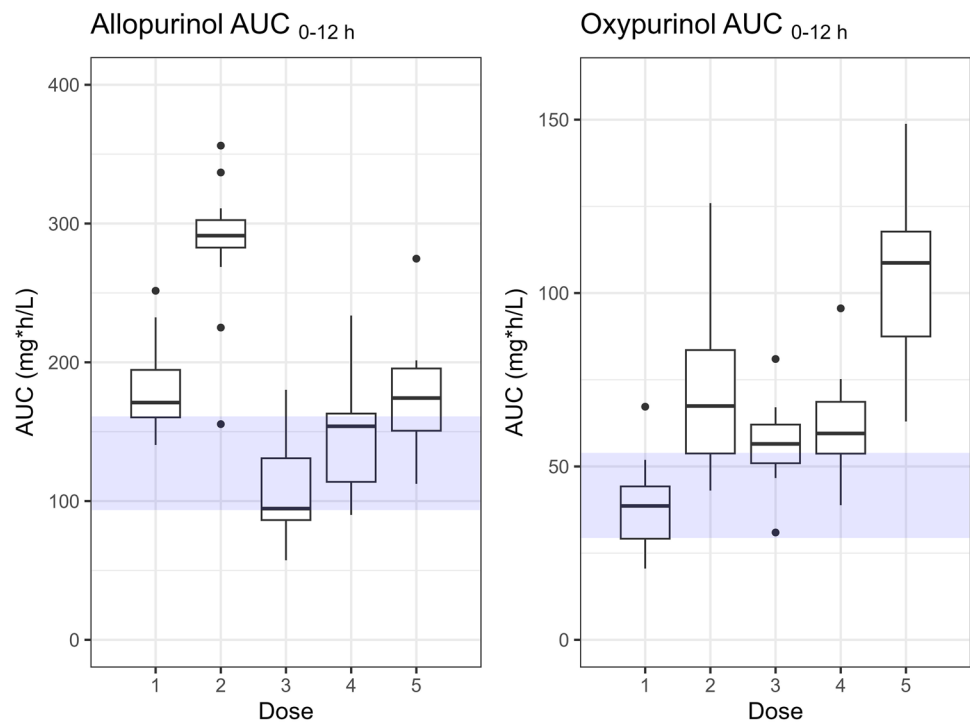
allopurinol loss in the circuit cannot be ruled out [22, 23].
In a previous study, hypoxanthine, which is a structural
analog of allopurinol, was found to accumulate in isolated
extracorporeal membrane oxygenation circuits over time
during bypass [41].

A significant reduction in postoperative oxypurinol CL
was found, dropping to 0.05 L/h, which was even lower
than the 0.21 L/h observed shortly after birth (Table 2).
This decreased CL led to a rapid increase in oxypurinol
exposure (Fig. 7), potentially providing additional cer-
ebral protection to neonates with CCHD following sur-
gery with CPB. The decline in oxypurinol CL is likely
attributed to impaired renal function caused by AKI,
which is a common complication that can arise after sur-
gery with CPB. Ischemia-reperfusion injury is one of its
major causes, which occurs when the kidneys experience
reduced blood flow during CPB, followed by reperfusion,
resulting in kidney damage [17, 18]. Furthermore, an
immediate recovery of allopurinol CL was observed after
CPB. This increase in allopurinol CL might be related to
the cessation of CPB, which is known to induce hypoxia
and subsequently elevate XO activity [5].

To capture the maximal allopurinol concentrations
measured 10 min after the onset of CPB, a very small
central compartment and a large intercompartment CL
were assumed. This approach was necessary due to the
intensive sampling schedule during the CPB period (10
and 30 min post-dose) compared with other periods
(1–3 h post-dose). Therefore, these parameter settings
were included to improve model fit and stability, despite
lacking pharmacological and physiological interpretation.

5 Conclusion

This study represents the first characterization of the PK of
allopurinol and oxypurinol in neonates with CCHD under-
going cardiac surgery with the support of CPB throughout
the postnatal and perioperative periods. The CL of both
compounds increased significantly after birth, which may
be attributed to organ recovery during stabilization in the
intensive care unit or the progression of hypoxemia resulting
from multiple mild hypoxic-ischemic insults due to hemody-
namic instability associated with the cardiac defect. Changes
in drug CL and Vd with the use of CPB were quantified and
a potential loss of allopurinol was revealed, underlying a mix
effect associated with hypothermia, hemodilution, hemofil-
tration, and sequestration by the CPB circuit. Furthermore,
a decrease in oxypurinol CL was observed, likely indicating
impaired kidney function following CPB. This reduced CL
led to higher oxypurinol exposure, which could potentially
enhance cerebral protection. Most importantly, plasma con-
centrations of allopurinol and oxypurinol were maintained
at sufficient concentrations to inhibit XO, thereby rendering
dose adjustment unnecessary.

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Declarations

Conflict of interest Wan-Yu Chu, Maaike Nijman, Raymond Stegeman, Johannes M. P. J. Breur, Nicolaas J.G. Jansen, Joppe Nijman, Kim van Loon, Erik Koomen, Karel Allegaert, Manon J.N.L. Benders, Thomas P.C. Dorlo, and Alwin D.R. Huitema have no conflicts of interest to declare that may be relevant to the contents of this article.

Availability of data and material The raw data are available upon reasonable request by an e-mail to the corresponding author, while blinding for group allocation should be respected until the primary and secondary outcome analyses have been finalized.

Code availability The codes are available upon reasonable request.

Authors' contributions RS, MN, MB, JB, NJ, JN, KvL, EK, and the CRUCIAL study group were responsible for protocol development, study conduct, study registration, study recruitment, and data collection. Population PK modeling was performed by WC, KA, TD, and AH. The draft of this manuscript was written and reviewed by WC, MN, KA, TD, and AH. All authors and contributors have read and commented on the manuscript and have approved the submitted version.

Ethics approval The CRUCIAL trial (EudraCT 2017-004596-31; ClinicalTrials.gov NCT04217421) was conducted according to the principles of the Helsinki Declaration (2013). The trial was approved by the Medical Research Ethical Committee of UMC Utrecht (reference number NL62772.041.18) and the Dutch national competent authority Central Committee on Research Involving Human Subjects (reference number NL62772.041.18).

Consent for publication Not applicable.

Consent to participate Written informed consent was collected from all parents or legal guardians before study participation. Parents were informed about the study by the obstetrician or fetal cardiologist between 24 and 36 weeks of gestation and were asked for written consent before the start of delivery.

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