Larger dose reductions of vancomycin required in neonates with patent ductus arteriosus receiving indomethacin vs. ibuprofen

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Running title: Vancomycin dosing for neonates co-treated with NSAIDs

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Abstract

Ibuprofen and indomethacin are commonly used to induce ductus arteriosus closure in preterm neonates. Our group previously reported that ibuprofen decreased vancomycin clearance by 16%. In this study, we quantified the impact of indomethacin co-administration on vancomycin clearance by extending our vancomycin population pharmacokinetic model with a dataset containing vancomycin concentrations measured in preterm neonates co-medicated with indomethacin.

The modeling dataset includes concentration-time data of vancomycin administrated alone or in combination with either ibuprofen or indomethacin collected in the neonatal intensive care units of UZ Leuven (Leuven, Belgium) and São Francisco Xavier Hospital (Lisbon, Portugal). The derived vancomycin pharmacokinetic model was subsequently used to propose dose adjustments that yield effective vancomycin exposure (i.e., $AUC_{0\text{-}24h}$ between 300-550 mg·h/L, with a probability below 0.1 of sub-therapeutic exposure) in preterm neonates with patent ductus arteriosus.

We found indomethacin co-administration to reduce vancomycin clearance by 55%. Model simulations showed that the most recent vancomycin dosing regimen which was based on an externally validated model, requires a 20% and 60% decrease of the loading and maintenance dose of vancomycin, respectively, when aiming for optimized exposure in the neonatal population.

By analyzing vancomycin data from preterm neonates co-medicated with indomethacin we found a substantial decrease in vancomycin clearance of 55% versus a previously reported 16% for ibuprofen. This decrease in clearance impacts vancomycin dosing and we anticipate that

41 other drugs eliminated by glomerular filtration are likely to be affected to a similar extent as

42 vancomycin.

Introduction

Vancomycin is frequently used in neonates as therapy for late onset infections with coagulase-negative *Staphylococcus* or as an alternative therapy for methicillin-resistant *Staphylococcus aureus*(1). Recently, Janssen *et al*[2] proposed a vancomycin dosing regimen for both preterm and term neonates, based on an externally validated population pharmacokinetic (PK) model yielding effective and safe vancomycin exposure (i.e., an area under the curve (AUC) around 400 mg·h/L) from the start of treatment(2).

Co-medication given to preterm neonates with a patent (symptomatic) ductus arteriosus (PDA) include ibuprofen and indomethacin, which have been proven to effectively induce PDA constriction and closure(3). Both nonsteroidal anti-inflammatory drugs (NSAIDs) are known to have renal side effects, as they suppress the vasodilatory effects of prostaglandins leading to vasoconstrictive renal hypoperfusion, even though exact quantification is incomplete(3),(4). Vancomycin clearance (CL) was shown to decrease by 16% when co-administrated with ibuprofen(5), upon which it was proposed to decrease the vancomycin dosage for neonates with PDA co-medicated with ibuprofen(2). Less is known about the impact of indomethacin on vancomycin CL. Upon quantifying the influence of indomethacin on vancomycin CL we could improve vancomycin dosing in this special population. And, since vancomycin CL is mainly eliminated by glomerular filtration, a reduction in CL of vancomycin as a result of co-administration with ibuprofen or indomethacin may also imply a reduction in CL for other drugs such as aminoglycosides(5, 6) cleared by the same pathway.

In the current analysis, our goal is to quantify the impact of indomethacin co-administration on vancomycin CL in neonates with PDA, in addition to the previously quantified impact of

ibuprofen on vancomycin CL in this population. For this, vancomycin PK data collected during routine therapeutic drug monitoring (TDM) in preterm patients pharmacologically treated for PDA with indomethacin(7) were analyzed within the context of a previously published population pharmacokinetic model for vancomycin and vancomycin co-administrated with ibuprofen(5). This model has been externally validated and used to propose dosing guidelines for vancomycin in neonates(2). Model-based simulations were subsequently used to evaluate available dosing regimen(2, 8–10) for vancomycin in preterm neonates with PDA co-medicated with ibuprofen or indomethacin and to propose dose adjustments.

Methods

Data exploration

For this analysis we used vancomycin PK data collected during routine TDM at two neonatal intensive care units: University Hospitals Leuven (Leuven, Belgium; hereafter referred to as UZ Leuven) and São Francisco Xavier Hospital (Lisbon, Portugal; hereafter referred to as HSFX). All preterm neonates diagnosed with PDA received either ibuprofen (UZ Leuven) or indomethacin (HSFX) together with vancomycin. Data on vancomycin without co-medication from neonates without PDA were all collected in UZ Leuven. Findings from both sets of data have been published separately before by De Cock *et al.* 2014(5) (UZ Leuven) and Silva *et al*. 1998(7) (HSFX). The combined dataset was used for model development in the current analysis. A summary of the demographics of the patients included in this analysis is provided in Table 1,

85 which shows a large degree of similarity regarding age and weight related demographics in
86 these preterm neonates.

87 ## Model development

88 The previously published population PK model, developed with the data collected at UZ Leuven
89 to characterize vancomycin disposition and quantify the impact of ibuprofen on vancomycin
90 CL(5), was used as a basis for the current analysis. Briefly, this model concerns a two-
91 compartment model that includes birth body weight (BW), postnatal age (PNA) and ibuprofen
92 co-administration as covariates on CL and current body weight (CW) as a covariate on the
93 central and peripheral distribution volumes (V_1, V_2)(5). This model was externally validated in a
94 previous study(2). In the current analysis, all population parameters describing vancomycin
95 disposition and the influence of ibuprofen on CL were fixed to the estimates reported by De
96 Cock *et al.*(5). The combined dataset including the data from both UZ Leuven and HSFX (7) was
97 used to quantify the influence of indomethacin co-administration as a covariate (F_{indo}) on CL and
98 V_1.

99 Model selection was based on numerical and graphical criteria (e.g., decrease in objective
100 function value > 3.84 with one more degree of freedom ($p < 0.05$), relative standard errors
101 below 30%, and unbiased goodness-of-fit plots).

102 ## Model Validation

103 The robustness of the parameter estimates of the final model was assessed by a non-parametric
104 bootstrap. For this, the extended dataset was resampled with replacement 1000 times and
105 stratified on vancomycin co-medication (i.e., vancomycin without co-medication, vancomycin

with ibuprofen or vancomycin with indomethacin). The resampled datasets were subsequently fitted with the final model, after which median and 95% confidence intervals of the parameters were obtained.

The predictive properties of the model were assessed by a normalized prediction distribution error (NPDE)(11) analysis using the NPDE package in R v3.3.2. Each observed concentration was compared to 1000 simulated values for that observation to calculate the prediction error(11). The results of the NPDE were also stratified by co-medication.

Vancomycin dosing optimization

The final vancomycin PK model was used for Monte Carlo simulations and stochastic simulations to guide dose adjustments upon co-administration with either ibuprofen or indomethacin. For this purpose, we defined a safe and effective vancomycin target exposure, i.e. an AUC in the first 24 hours ($AUC_{0\text{-}24h}$) ranging between 300 - 550 mg·h/L, which should lead to a median AUC/MIC of 400 mg·h/L for a minimum inhibitory concentration (MIC) of 1 mg/mL. For the recommended dose adjustments, we aimed for a probability of reaching sub-therapeutic exposures ($AUC_{0\text{-}24h}$ < 300 mg·h/L) below 0.1.

As basis for our proposed vancomycin dosing adjustments, we used a recently published dosing regimen for vancomycin(2) (Table 2) that reaches and maintains the vancomycin target $AUC_{0\text{-}24h}$ in children, including preterm neonates. This dosing regimen was based on an externally validated population PK model and proposed a fixed dose reduction of 2 mg/kg/dose for both the loading and the maintenance dose, upon co-administration with ibuprofen, to account for the reduced vancomycin CL. This regimen was evaluated together with other dosing guidelines for vancomycin that are currently in clinical use, but that have not been optimized for scenarios

with co-administration of NSAIDs (Table S1 – Dutch Children's Formulary(10), British National Formulary(9), and Neofax(8)).

Monte Carlo simulations in virtual preterm neonates pharmacologically treated for PDA

For the Monte Carlo simulations, a virtual patient population was created by resampling with replacement 1000 patients from our original sample of patients with PDA. The final model was used to simulate individual vancomycin concentration-time profiles following dosing with the different guidelines and to calculate $AUC_{0\text{-}24h}$ values for each of the virtual patients. The results are presented as probabilities of exposure attainment within, above or below the predefined $AUC_{0\text{-}24h}$ target range.

Stochastic simulations in hypothetical preterm neonates pharmacologically treated for PDA

For the stochastic simulations, three individuals with birth body weights representing the 1st quartile (BW = 770 g), median (BW = 1050 g), or 3rd quartile (BW = 1250 g) and postnatal ages (PNA) of 6, 9 and 12 days, respectively, were derived from the sample of patients with PDA.

For each of these individuals, 1000 stochastic simulations were performed with the final model taking inter-individual variability of the model parameters into account. Simulated individual concentration-time profiles obtained after dosing vancomycin following different guidelines were used to calculate $AUC_{0\text{-}24h}$ for each hypothetical individual.

Results

Population pharmacokinetic model

Our analysis showed that indomethacin reduced vancomycin clearance by 55% (Table S1 - fraction of 0.447 (RSE of 14%)), while the reduction for ibuprofen was 16%(5). Adding indomethacin co-administration as a covariate on V_1 did not lead to statistically significant improvement of the model.

Figure 1 illustrates these findings showing the relationship between individual vancomycin CL values and body weight of patients in the overall dataset, in the presence or absence of either ibuprofen or indomethacin. Besides the systematic difference in vancomycin CL values between the three groups, a relatively high overall inter-individual variability of 33.6% in vancomycin clearance was estimated (Table S1, Figure 1).

The model described the data with good accuracy, as confirmed by the goodness-of-fit plots, for all three patient groups (no NSAID, ibuprofen and indomethacin) (Figure S1), while the NPDE analysis confirmed accurate predictions (Figures S2 and S3). Estimated PK parameters had acceptable precision, as indicated by the relative standard errors (RSE%) of the estimates being well below 20%. The bootstrap analysis confirms the robustness of the model (Table S1).

Vancomycin dosing optimization

Simulations showed that, to maintain an effective vancomycin exposure (i.e., $AUC_{0\text{-}24h}$ within 300-550 mg·h/L) when NSAIDs are co-administered in preterm neonates with PDA, different dose adjustments should be made for ibuprofen and indomethacin to compensate for the differences in decreases in vancomycin CL. Table 2 displays how the vancomycin dosing regimen

167 proposed by Janssen *et al.*(2) for neonates without co-administration of NSAIDS (grey columns)
168 should be adapted when NSAIDs are co-administrated, i.e. a decrease of the maintenance dose
169 by 20 % for ibuprofen and a decrease in both the loading and the maintenance dose by 20% and
170 60%, respectively, for indomethacin (Table 2).

171 *Monte Carlo simulations in virtual preterm neonates pharmacologically treated for PDA*

172 Figure 2 shows the probabilities of attaining vancomycin exposure within, above or below the
173 predefined target range of 300-550 mg·h/L following the dosing guidelines of Janssen *et al.*(2)
174 (with and without dose reduction of 2 mg/kg/dose for ibuprofen co-administration) and our
175 proposed dose adjustments for co-administration with ibuprofen or indomethacin (see Table 2),
176 in virtual patients resampled from the available PDA patient group.

177 The proposed dose reduction when ibuprofen is co-administrated decreases the probability of
178 under dosing, especially in the smallest children (Figures 2 and 3 – left panel). Using vancomycin
179 dosing regimens with no adjustments or with the same adjustment for both NSAIDs would lead
180 to major differences in vancomycin target attainment (Figure 3) and particularly increase the
181 probability for over-exposure and, thereby, the risk of experiencing side effects.

182 *Stochastic simulations in hypothetical preterm neonates pharmacologically treated for PDA*

183 Figure 3 shows results of stochastic simulations in representative, hypothetical patients with
184 pharmacologically treated PDA illustrating how variability in vancomycin CL is reflected into
185 $AUC_{0\text{-}24h}$ values following vancomycin administration with our proposed dosing (Table 2) and
186 published dosing guidelines (Table S2), with adjustments for co-medication when available[3-6].
187 Remaining variability in these plots results from random inter-individual variability in
188 vancomycin CL, for which TDM remains necessary.

189 Figure 3 illustrates that large variability in exposure may be expected depending on both the
190 selected dosing regimen, the birth body weight of the neonate and the NSAID involved (Figure
191 3).

192

193 ## Discussion

194 In preterm neonates treated concomitantly with ibuprofen for PDA and with vancomycin for
195 suspected or confirmed late onset sepsis, a 16% decrease in vancomycin clearance has been
196 reported previously(5). In the current study, we found a 55% decrease in vancomycin clearance
197 when PDA is treated with indomethacin. Based on these findings we propose dose adjustments
198 to ensure a safe and effective vancomycin treatment for this special population, i.e. a decrease
199 of the vancomycin maintenance dose by 20% when ibuprofen is co-administrated and a
200 decrease of the loading and the maintenance dose of vancomycin by 20% and 60%, respectively,
201 when indomethacin is co-administrated.

202 In the model-based simulations, $AUC_{0\text{-}24h}$ values (between 300-550 mg·h/L) were defined as
203 targets, as proposed in recent publications(2, 12). However, vancomycin trough concentrations
204 taken at the end of the first day of treatment are still commonly used as surrogate markers for
205 vancomycin exposure. In adults, trough concentrations above 15 mg/L are associated with an
206 effective vancomycin exposure of around 400 mg·h/L. However, Neely *et al.* showed, using
207 Bayesian modeling, that 60% of adult patients with a vancomycin AUC of at least 400 mg·h/L,
208 had a trough concentration below 15 mg/L(13). For neonates, Frymoyer *et al.* showed that
209 trough levels ranging between 7 and 10 mg/L were highly predictive of an $AUC_{0\text{-}24h}$ above 400
210 mg·h/L(12). Both these studies suggest that guiding dose individualization based on a trough

211 concentration of 15 mg/L could lead to over-exposure and increased risk of adverse events. In
212 addition, when correlating trough concentrations with $AUC_{0\text{-}24h}$, vancomycin dosing frequency
213 should be accounted for(14).

214 To ensure an efficacious vancomycin treatment, a target $AUC_{0\text{-}24h}$ around 400 mg·h/L for a
215 pathogen MIC of 1 mg/L should be attained from the start of therapy, as this was correlated
216 with a better treatment outcome and a shorter time to reach steady-state(15). Therefore, we
217 decided to aim for a therapeutic window of 300-550 mg·h/L. US guidelines recommend an
218 $AUC_{0\text{-}24h}$ around 700 mg·h/L for efficiency, when MIC is above 1.5 mg/L. A higher pathogen MIC
219 indicates development of bacterial resistance and would justify the use of a higher therapeutic
220 target(16) or an alternative drug. When aiming for an (median) AUC of 700 mg·h/L the dosing
221 advice in Table 2 should be adjusted by 700/400.

222 Previously, Janssen *et al.* proposed to decrease the vancomycin dose by 2 mg/kg/dose when co-
223 administrated with ibuprofen(2). This recommendation was shown to have a relatively larger
224 impact in small neonates (see Figure 3), who receive lower doses on average, tending towards
225 under-exposure. This limitation has been considered in the current proposal by decreasing the
226 dose proportionally to the decrease in CL (Table 2).

227 Even though both ibuprofen and indomethacin belong to the same drug class (NSAIDs) and are
228 used for the same therapeutic indication, the extent to which they influence vancomycin
229 clearance is more than 3-fold different. While it is unknown whether this results from the drug
230 itself or a non-equivalent dose compared to this side effect, it seems that a specific dose
231 adjustment for each NSAID should be applied for the best vancomycin treatment outcome.
232 Ibuprofen is associated with a decreased risk of necrotizing enterocolitis and transient renal

insufficiency as compared to indomethacin(17). There are no reviews comparing how different dosing regimens or modes of administration of the different NSAIDs used to treat PDA affect the treatment outcome or the risk for side effects(18). From these results it also seems that dose adjustments might be required for other drugs with similar physico-chemical properties to vancomycin that are co-administrated with NSAIDs and are eliminated by glomerular filtration(5). The proposed dosing regimen should be prospectively validated before applying them in clinical practice.

Supplemental figure S4-A shows the probability of target attainment for $AUC_{0\text{-}24h}$ between 300 - 500 mg·h/L derived from Monte Carlo following various currently advised vancomycin dosing regimen without dose adjustments in patients with NSAID co-administration. Dosing according to the Dutch Children's Formulary, British National Formulary and NeoFax (meningitis) guidelines results in considerable under-exposure in neonates with neither PDA nor co-therapy with NSAIDs, therefore, it is important that these dosing guidelines are not further reduced using our proposal.

The results of our stochastic simulations show how the relatively high inter-individual variability in vancomycin CL is carried over to the yielded exposure, as this variability in CL cannot be accounted for *a priori* (Figure 3). The high inter-individual variability in vancomycin CL in all neonates makes dosing challenging. Therefore, even though the proposed adjustments improve the vancomycin target attainment in the population as a whole, TDM is still required to individualize dosing in clinical practice.

Conclusions

In preterm neonates with suspected or confirmed late onset sepsis and pharmacologically treated for PDA, vancomycin CL is reduced by 16% and 55% when co-administered with ibuprofen or indomethacin, respectively. To reach the same exposures as in patients without PDA and co-administration with NSAIDs, we propose dosing adjustments of 20% in maintenance dose when ibuprofen is co-administrated and reductions of 20% and 60% in loading dose and maintenance dose, respectively, when indomethacin is co-administrated, as compared to previously reported neonatal dosing guidelines(2). Therapeutic drug monitoring is still required due to the remaining random variability on vancomycin CL that can yield high exposures which increase the risk of adverse events. PK of drugs with similar properties to vancomycin that are also eliminated by glomerular filtration may be affected to a similar extent by NSAIDs co-administration.

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317 acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm
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319

320 Tables

321 *Table 1. Summary of demographic characteristics of the patients included in this analysis - mean (range)*
322 *for the studied population (N = 319) treated with vancomycin only (n=263) or vancomycin co-*
323 *administrated with either ibuprofen (n=23) or indomethacin (n=33).*

324

325 *Table 2 - Vancomycin dosing regimen according to Janssen et al.*(2) *(grey) and proposed vancomycin*
326 *doses for ibuprofen and indomethacin co-administration (no background) resulting from model-based*
327 *simulations with the final model, aiming for a target of* $AUC_{0\text{-}24h}$ *between 300 - 550 mg·h/L.*

328

329 Figures

330 *Figure 1 – Vancomycin individual clearance values versus body weight in the overall studied neonatal*
331 *population (semi-log scale). Light grey circles – vancomycin clearance in neonates without NSAIDs co-*
332 *administration; Blue circles – vancomycin clearance in preterm neonates with PDA with indomethacin co-*
333 *administration; Orange circles – vancomycin clearance in preterm neonates with ibuprofen co-*
334 *administration.*

335

336 *Figure 2 –Probability of target attainment for* $\boldsymbol{AUC_{0\text{-}24h}}$ (first day of treatment) *between 300 - 550 mg·h/L*
337 *for vancomycin for different dosing regimens, derived from Monte Carlo simulations in virtual preterm*
338 *neonates with PDA. The left panel shows the results in preterm neonates with PDA after vancomycin co-*
339 *administrated with ibuprofen and the right panel for preterm neonates with PDA after vancomycin co-*
340 *administrated with indomethacin. Each bar represents the results obtained with one dosing regimen (see*
341 *Table 2 for detailed descriptions the dosing regimens).*

342

343 *Figure 3 –Vancomycin* $\boldsymbol{AUC_{0\text{-}24h}}$ *values on the first day of treatment obtained following stochastic*
344 *simulations for each dosing regimen in hypothetical individuals with birth body weights of 770 g, 1050 g*
345 *and 1250 g and postnatal ages of 6, 9 and 12 days, respectively. Each color represents one dosing*
346 *regimen (see Table 2 and Table S2 for details of each dosing regimen) and the colors intensify with*
347 *increasing birth body weight. The left panel shows the results in preterm neonates with PDA after*
348 *vancomycin co-administrated with ibuprofen and the right panel for neonates with PDA after vancomycin*
349 *co-administrated with indomethacin. The dashed lines represent the target* $AUC_{0\text{-}24h}$ *of 300 – 550 mg·h/L*
350 *(red) and 400 mg·h/L (black)*

Table 1.

	Vancomycin treatment only(5) (N = 263)	Vancomycin treatment with ibuprofen(5) (N = 23)	Vancomycin treatment with indomethacin(7) (N = 33)
Postmenstrual age (weeks)	31 (24-38)	28 (24-33)	29 (26-35)
Gestational age (weeks)	29 (23-34)	27 (24-33)	28 (25-34)
Postnatal age (days)	14 (1-28)	7 (2-12)	11 (4-30)
Birth body weight (g)	1150 (385-2550)	832 (415-1930)	1000 (570-1960)
Current body weight* (g)	1256 (485-2630)	810 (415-1930)	981 (628-1850)

* the patient's body weight at the start of the treatment

Table 2

Clinical characteristics		*Vancomycin Dosing*(2)*		*Vancomycin with ibuprofen co-administration*		*Vancomycin with indomethacin co-administration*	
PNA (days)	*BW (g)*	*Loading Dose*	*Maintenance Dose*	*Loading Dose*	*Maintenance Dose (20% reduction)*	*Loading Dose (20% reduction)*	*Maintenance Dose (40% reduction)*
0-7	*≤700*	*16 mg/kg*	*15 mg/kg/day in 3 doses*	*16 mg/kg*	*12 mg/kg/day in 3 doses*	*13 mg/kg*	*9 mg/kg/day in3 doses*
	700-1000		*21 mg/kg/day in 3 doses*		*17 mg/kg/day in 3 doses*		*13 mg/kg/day in 3 doses*
	1000-1500		*27 mg/kg/day in 3 doses*		*22 mg/kg/day in 3 doses*		*16 mg/kg/day in 3 doses*
	1500-2500		*30 mg/kg/day in 4 doses*		*24 mg/kg/day in 4 doses*		*18 mg/kg/day in 4 doses*
8-14	*≤700*	*20 mg/kg*	*21 mg/kg/day in 3 doses*	*20 mg/kg*	*17 mg/kg/day in 3 doses*	*16 mg/kg*	*13 mg/kg/day in 3 doses*
	700-1000		*27 mg/kg/day in 3 doses*		*22 mg/kg/day in 3 doses*		*16 mg/kg/day in 3 doses*
	1000-1500		*36 mg/kg/day in 3 doses*		*29 mg/kg/day in 3 doses*		*22 mg/kg/day in 3 doses*
	1500-2500		*40 mg/kg/day in 4 doses*		*32 mg/kg/day in 4 doses*		*24 mg/kg/day in 4 doses*
14-28	*≤700*	*23 mg/kg*	*24 mg/kg/day in 3 doses*	*23 mg/kg*	*19 mg/kg/day in 3 doses*	*18 mg/kg*	*19 mg/kg/day in 3 doses*
	700-1000		*42 mg/kg/day in 3 doses*		*34 mg/kg/day in 3 doses*		*25 mg/kg/day in 3 doses*
	1000-1500		*45 mg/kg/day in 3 doses*		*36 mg/kg/day in 3 doses*		*27 mg/kg/day in 3 doses*
	1500-2500		*52 mg/kg/day in 4 doses*		*42 mg/kg/day in 4 doses*		*31 mg/kg/day in 4 doses*
21-28	*≤700*	*26 mg/kg*	*24 mg/kg/day in 3 doses*	*26 mg/kg*	*19 mg/kg/day in 3 doses*	*21 mg/kg*	*19 mg/kg/day in 3 doses*
	700-1000		*42 mg/kg/day in 3 doses*		*34 mg/kg/day in 3 doses*		*25 mg/kg/day in 3 doses*
	1000-1500		*45 mg/kg/day in 3 doses*		*36 mg/kg/day in 3 doses*		*27 mg/kg/day in 3 doses*
	1500-2500		*52 mg/kg/day in 4 doses*		*42 mg/kg/day in 4 doses*		*31 mg/kg/day in 4 doses*

**Janssen et al.* (2)*proposes a decrease of 2 mg/kg/dose of both the maintenance and loading dose when ibuprofen co-administration*