1314. Neonatal Serum Gentamicin Concentrations following Maternal Once-daily Gentamicin Dosing

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Background. Gentamicin is commonly used for peripartum infections. Given literature supporting efficacy of once-daily dosing (ODD) of 5 mg/kg for chorioamnionitis, University of Chicago Medicine made the change from three times daily dosing (TIDD) to ODD. As gentamicin readily cross the placenta, it would be expected that maternal ODD would result in higher gentamicin neonatal serum concentrations following birth.

Methods. This was a single-center, retrospective chart review of all neonates born to mothers receiving peripartum ODD gentamicin within 12 hours of delivery between October 2019 and March 2020. A STAT random gentamicin serum concentration was obtained upon admission in neonates when initiation of antibiotics was desired. Specific dosing recommendations (Table 1) were developed utilizing neonatal population-based pharmacokinetics. The primary outcome was initial neonatal gentamicin serum concentration at birth. Other outcomes were also evaluated. Results were evaluated in two groups based on neonatal serum concentrations of less than 2 mcg/mL (Group 1) versus 2 mcg/mL or greater (Group 2).

Table 1: Neonatal gentamicin dosing algorithm

Gentamicin serum concentration (mcg/mL)	Birth weight < 2kg	Birth weight ≥ 2kg
≥ 6	36 hours after level, start gent 4 mg/kg q36h	24 hours after level, start gent 4 mg/kg q24h
4 to < 6	24 hours after level, start gent 4 mg/kg q36h	12 hours after level, start gent 4 mg/kg q24h
2 to < 4	12 hours after level, start gent 4 mg/kg q36h	6 hours after level, start gent 4 mg/kg q24h
< 2	NOW, start gent 4 mg/kg q36h	NOW, start gent 4 mg/kg q24h

Results: Thirty-two mother-newborn dyads were included in this study. Baseline demographics are shown in Table 2. Newborns had a median gestational age of 39.4 weeks and median birth weight of 3.39 kilograms. The mean initial gentamicin concentration was supratherapeutic at 3.06 + 1.92 mcg/mL among all newborns (Table 3). The mean maternal dose in Group 1 (n=11) was 3.52 mg/kg (3.34, 4.77) based on actual body weight and 4.78 mg/kg (4.34, 5.18) in Group 2 (n=21) (p=0.025). The median time between maternal gentamicin administration and time of delivery varied between the groups at 0.5 hours versus 2.63 hours, respectively (p=0.005). All newborn gentamicin concentrations were less than 2 mcg/mL for maternal doses given less than 1 hour prior to delivery (n=8) (Figure 1). Overall protocol compliance rate was 81.3%. There were no significant differences in nephrotoxicity or ototoxicity between groups.

Table 2. Baseline Demographics

Characteristics	All subjects (n=32)	Group 1 Gent < 2 (n=11)	Group 2 Gent > 2 (n=21)	*p*-value (Gent < 2 vs Gent ≥ 2)
Maternal				
Age (years)	29.19 ± 5.64	30.73 ± 5.44	28.38 ± 5.71	0.271
Actual Body Weight (kg)	79.0 (69.5, 90.0)	82.6 (67.1, 136.3)	78.0 (70.7, 84.8)	0.592
Gentamicin Dose (mg/kg) – Actual Body Weight	4.56 (4.03, 5.12)	3.52 (3.34, 4.77)	4.78 (4.34, 5.18)	0.025
Time between gentamicin administration and delivery (hours)	1.83 (0.78, 3.33)	0.50 (0.32, 1.37)	2.63 (1.72, 3.35)	0.005
Neonatal				
Gestational Age (weeks)	39.4 (37.4, 40.2)	39.1 (35.0, 40.3)	39.4 (38.6, 40.1)	0.842
Weight (kg)	3.39 (3.00, 3.73)	3.67 (2.98, 3.87)	3.37 (3.01, 3.70)	0.525
Sex (Male)	20 (62.5)	7 (63.6)	13 (61.9)	1.000
Time between delivery and serum gentamicin concentration (min)	43 (37, 64.5)	43 (36, 80)	43 (37, 64)	0.781
Other ototoxic medications during admission	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Other nephrotoxic medications during admission	1 (3.1)	1 (9.1)	0 (0)	0.344

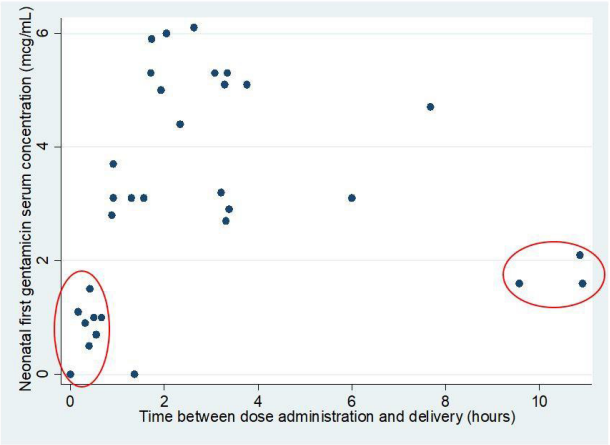
All data presented as n(%), median (IQR), or mean±SD

Table 3. Outcomes

Outcomes	All subjects (n=32)	Group 1 Gent < 2 (n=11)	Group 2 Gent > 2 (n=21)	*p*-value (Gent <2 vs Gent ≥ 2)
Initial serum gentamicin concentration (mcg/mL)	3.06 ± 1.92	0.90 ± 0.57	4.19 ± 1.27	< 0.0001
Compliance to Protocol	26 (81.3)	9 (81.8)	17 (81.0)	1.000
Failed initial hearing screen	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Failed repeat hearing screen	1 (3.1)	0 (0)	1 (4.8)	1.000
Serum creatinine increase by 0.3 mg/dL or ≥ 1.5x baseline in the first 7 days of life	2 (6.3)	1 (9.1)	1 (4.8)	1.000
Positive blood culture within the first 72 hours of life • Organism • Days to clearance of culture	1 (3.1)	0 (0) N/A N/A	1 (4.8) E. coli (S to gent) 1 day	1.000
14-Day Mortality	0 (0)	0 (0)	0 (0)	1.000

All data presented as n(%) or mean±SD

Figure 1. Comparison of maternal gentamicin time from administration to delivery and neonatal serum gentamicin concentrations



Conclusion: This study suggests peripartum ODD of gentamicin may lead to clinically significant serum concentrations in neonates if administered between 1 to 12 hours of birth. Further studies are warranted to evaluate the effects of maternal ODD of gentamicin on newborns.

Disclosures. **All Authors**: No reported disclosures

1315. No Dose Adjustment of Metformin with Fostemsavir Coadministration Based on Mechanistic Static and Physiologically Based Pharmacokinetic Models

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Background. Fostemsavir (FTR) is an oral prodrug of the first-in-class attachment inhibitor temsavir (TMR) which is being evaluated in patients with multidrug resistant HIV-1 infection. In vitro studies indicated that TMR and its 2 major metabolites are inhibitors of organic cation transporters (OCT)1, OCT2, and multidrug and toxin extrusion transporters (MATEs). To assess the clinical relevance, of OCT and MATE inhibition, mechanistic static DDI prediction with calculated $I_{max,u}/IC_{50}$ ratios was below the cut-off limits for a DDI flag based on FDA guidelines and above the cut-off limits for MATEs based on EMA guidelines.

Methods. Metformin is a commonly used probe substrate for OCT1, OCT2 and MATEs. To predict the potential for a drug interaction between TMR and metformin, a physiologically based pharmacokinetic (PBPK) model for TMR was developed based on its physicochemical properties, in vitro and in vivo data. The model was verified and validated through comparison with clinical data. The TMR PBPK model accurately described AUC and C_{max} within 30% of the observed data for single and repeat dose studies with or without food. The SimCYP models for metformin and ritonavir were qualified using literature data before applications of DDI prediction for TMR

Results. TMR was simulated at steady state concentrations after repeated oral doses of FTR 600 mg twice daily which allowed assessment of the potential OCT1, OCT2, and MATEs inhibition by TMR and metabolites. No significant increase in metformin systemic exposure (AUC or C_{max}) was predicted with FTR co-administration. In addition, a sensitivity analysis was conducted for either hepatic OCT1 Ki, or renal OCT2 and MATEs Ki values. The model output indicated that, a 10-fold more potent Ki value for TMR would be required to have a ~15% increase in metformin exposure

Conclusion. Based on mechanistic static models and PBPK modeling and simulation, the OCT1/2 and MATEs inhibition potential of TMR and its metabolites on metformin pharmacokinetics is not clinically significant. No dose adjustment of metformin is necessary when co-administered with FTR

Disclosures. Xiusheng Miao, PhD, GlaxoSmithKline (Employee) Mindy Magee, Doctor of Pharmacy, GlaxoSmithKline (Employee, Shareholder) Peter D. Gorycki, BEChe, MSc, PhD, GSK (Employee, Shareholder) Katy P. Moore, PharmD, RPh, ViiV Healthcare (Employee)

1316. Pharmacokinetic/Pharmacodynamic Analyses of Cefiderocol in Critically Ill Patients

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