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Population pharmacokinetics define dosing recommendations of oseltamivir in neonates and infants with influenza

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Introduction

- Influenza morbidity and mortality in children are highest in those aged <1 year.[1]
- Scarcity of data on which to base oseltamivir dosing in this high-risk population has led to conflicting recommendations in the USA and Europe.[2,3]
- As part of the effort to address these issues, two studies focusing on the pharmacokinetics (PK), pharmacodynamics (PD) and safety of oseltamivir in this age group have recently been carried out.
- The National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) study 114 (NCT00391768) took place in the USA from 2006 to 2010 in 72 children aged <2 years.[4] The European WP22849 trial (NCT01286142) was carried out during 2011–2012 in 65 children aged <1 year.[5]
- Data from children aged <1 year in these studies were pooled to build a population PK (PPK) model. This was then used to optimise the dosing of oseltamivir in this age group.

Methods

Patients and dosing

- Patients had influenza symptoms for ≤96 hours and a positive PCR or rapid diagnostic test for influenza.
- Age-stratified weight-based doses of oseltamivir oral suspension twice daily for 5 days were used in both studies (**Table 1**).

Table 1. Study design: dosing in CASG114 and WP22849.

Age group (months)	Age (days)	Twice-daily dose (mg/kg) CASG114	Twice-daily dose (mg/kg) WP22849	Number of patients (%)
0–1	≤30		2.0	13 (9.8)
1–3	31–90		2.5	33 (24.8)
3–6	91–180	3.0		23 (17.3)
6–9	181–270		3.0	35 (26.3)
9–12	≥271	3.0 or 3.5		29 (21.8)

Population pharmacokinetic analysis and covariate model development

- Non-linear mixed effects modeling (NONMEM) was used, with parent oseltamivir described by a linear two-compartment model with first-order absorption and the oseltamivir carboxylate (OC) metabolite described using a one-compartment model. Complete oseltamivir to OC conversion was assumed, and the OC central compartment volume was estimated.
- Weight was used to account for body size differences across age groups; clearance and volume parameters were allometrically scaled using fixed exponents of 0.75 and 1, respectively. Covariates including study, age, post-conceptual age, gestational age, bodyweight, gender and ethnicity were investigated using the full model approach.
- The final model was evaluated using visual and posterior predictive checks and a non-parametric bootstrap. Putative targets were selected either (i) via integrated PK/PD analysis or (ii) by a bridging analysis. In the latter, infant exposures were compared to exposures based on historical data for older children and adults receiving approved and clinically tested doses.

Integrated pharmacokinetic/pharmacodynamic analysis

- Endpoints in the integrated PK/PD analysis included: temperature reduction versus time, time to resolution of fever, rate of decline of viral DNA, time to cessation of viral shedding, treatment emergent genotypic/phenotypic resistance, and relationships between drug exposure and safety/tolerability.

Pharmacokinetic bridging analysis

- Predetermined OC exposure targets in the bridging analysis were based on the area under the curve (AUC) distribution in a previous small study in young children (age 1–2 years)[6] in which oseltamivir 30mg twice daily for 5 days showed the lowest probability of generating resistance
  - targets were steady-state AUC_τ >2,618hr•ng/mL in ≥95% of infants (minimum), >1,807hr•ng/mL in ≥84% (proportion above average minus 1 standard deviation), and >3,905hr•ng/mL in ≥50% (average).
  - the lowest OC exposures were required to be similar to those with approved dosages in other populations, with adequate safety margins for AUC and maximum concentration (C_{max}).
- Comparative data for bridging included single-dose exposure data from children aged 1–2 or 3–5 years[6] and steady-state data from adults receiving 75mg to 450mg oseltamivir twice daily.[7–9]
- Model-based simulations were carried out to identify dosing regimens based on AUC, minimum concentration (C_{min}) and C_{max} values optimised for bridging purposes.

Results

Patients

- The analysis dataset contained 604 oseltamivir and 648 OC plasma samples from 133 patients. Thirteen infants (9.8%) were aged 13 days to <1 month, 33 (24.8%) 1 to <3 months, 23 (17.3%) 3 to <6 months, 35 (26.3%) 6 to <9 months and 29 (21.8%) 9 to <12 months (**Table 2**).

Population pharmacokinetic model

- The concentration-time courses of oseltamivir and OC in infants aged <1 year were accurately described by the three-compartment PK model with first-order absorption. In this model, two compartments described oseltamivir PK while the third compartment described OC.
- For a typical infant weighing 8kg and aged 24 weeks:
  - oseltamivir PK parameters were estimated as: oral clearance = 80.4L/hr (95% confidence interval [CI]: 74.3–85.6), central volume = 166L (95% CI: 139–206), inter-compartment clearance = 19.6L/hr (95% CI: 16.0–23.8) and peripheral volume = 348L (95% CI: 221–574)
  - OC PK parameters were estimated as: oral clearance = 4.75L/hr (95% CI: 4.41–5.11) and central volume = 40.2L (95% CI: 36.4–44.6).

Table 2. Baseline characteristics and categorical covariates.

Parameter/study or category	
Patients, n (%)	
CASG114	68 (51.1)
WP22849	65 (48.9)
Gender, n (%)	
Female	59 (44.4)
Male	74 (55.6)
Mean bodyweight, kg (SD) [range]	
CASG114	6.4 (2.2) [3.3–11.3]
WP22849	6.5 (2.1) [2.9–12.4]
All	6.5 (2.1) [2.9–12.4]
Mean age, weeks (SD) [range]	
CASG114	24.6 (14.8) [1.9–48.6]
WP22849	22.4 (15.1) [2.6–49.9]
All	23.5 (14.9) [1.9–49.9]
Mean gestational age, weeks (SD) [range]	
CASG114	36.7 (4.8) [24–41]
WP22849	39.5 (3.5) [27.0–43.0]
All	38.1 (4.5) [24.0–43.0]
Mean post-conceptual age, weeks (SD) [range]	
CASG114	61.2 (15.5) [38.4–88.6]
WP22849	62.0 (15.2) [40.9–90.0]
All	61.6 (15.3) [38.4–90.0]
Ethnicity, n (%)	
Hispanic	34 (25.6)
Non-Hispanic/Latino	93 (69.9)
Other	12 (9.0)
Unknown	6 (4.5)
Race, n (%)	
White	105 (78.9)
Black	14 (10.5)
Other	12 (9.0)
Unknown	2 (1.5)

- All oseltamivir oral clearance and volume parameters depended on bodyweight via allometric scaling with fixed powers of 0.75 and 1, respectively. OC oral clearance and distribution volume also increased linearly with age. Model parameters were independent of gender, and there was no evidence of any clinically relevant effect of ethnicity or race (n.b. most patients were White).
- Interindividual PK variability was highest in neonates, potentially reflecting differences in hepatic conversion to OC and renal maturation.
- Parameter estimates for the final model are shown in **Table 3**. All parameters were estimated with adequate precision (relative standard error: 4.40–28.7%).

Table 3. PK parameter estimates for the final model.

PK parameter	Parameter estimate (95% CI)	Interindividual variability (% CV)
Absorption rate constant (1/hr)	0.905 (0.691–1.12)	–
Oseltamivir oral clearance (L/hr)	80.4 (72.6–88.2)	39.3
Oseltamivir central volume (L)	166 (124–209)	81.4
Oseltamivir peripheral volume (L)	348 (152–544)	–
OC oral clearance (L/hr)	4.75 (4.34–5.16)	35.7
OC central volume (L)	40.2 (36.6–43.8)	–

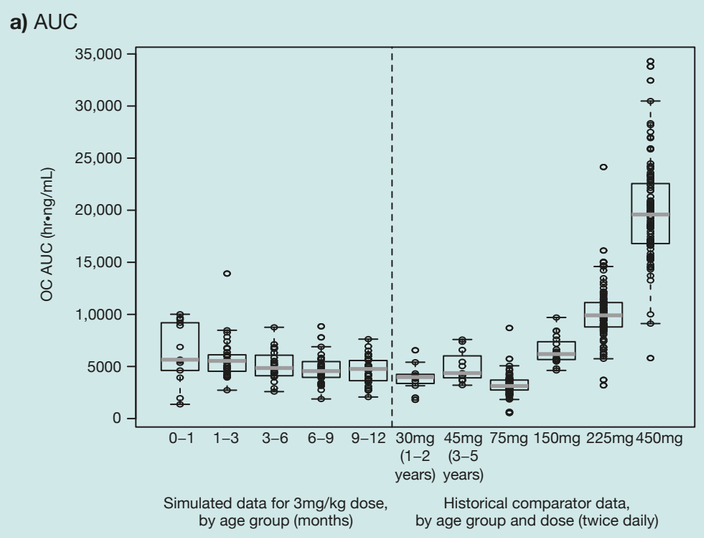
CV = coefficient of variation

- Model diagnostics showed the ability to predict central tendency and spread of concentrations in the target population (**Figure 1**).

Integrated and bridging analyses and dose simulation

- Possibly because of the narrow exposure ranges studied, the PK/PD analysis showed no association between drug exposure parameters and defined PD endpoints (temperature, fever, viral load/shedding, resistance and adverse events).
- Because of this, bridging of infant exposure to that seen in children aged 1–3 years and in adults was used for dose selection. Simulations showed that OC exposures (AUC, C_{min} and C_{max}) in infants for all age groups receiving 3mg/kg oseltamivir twice daily would achieve the predetermined systemic target concentrations associated with efficacy and be unlikely to produce antiviral resistance.
- Simulation of doses of 3mg/kg twice daily showed a tendency for predicted OC exposures in children aged <1 year to exceed those observed in adults receiving 75mg twice daily and children aged 1–5 years receiving approved dosages (**Figure 2**). Simulation of 2.5 and 2mg/kg doses showed a tendency towards lower exposures compared with benchmark comparators.
- OC exposures with 3mg/kg twice daily dosing across different infant age cohorts are therefore expected to be similar to those associated with 150mg twice daily in adults, a dosage shown to be safe and well tolerated in Phase 3 studies.[8,9]

Figure 2. Model simulations and PK bridging. Comparisons of predicted distributions of steady-state exposure to OC listed by age group with similar distributions in adult and pediatric patients. (a) AUC, (b) C_{min}, (c) C_{max}.



Boxes indicate interquartile ranges (IQRs); whiskers = 1.5 x IQR; circles = outliers; note median values (black lines in centres of boxes)

Conclusions

- The disposition of oseltamivir and OC in children aged <1 year is described by a PPK model incorporating allometric scaling and a linear increase of OC clearance with age.
- Across all age groups, 3mg/kg twice daily oseltamivir will yield OC exposures known to be safe and well tolerated, with the potential to minimise the risk of underexposure, subsequent resistance and/or treatment failure.
- These analyses were pivotal in gaining FDA approval of oseltamivir for the treatment of influenza in infants and neonates.

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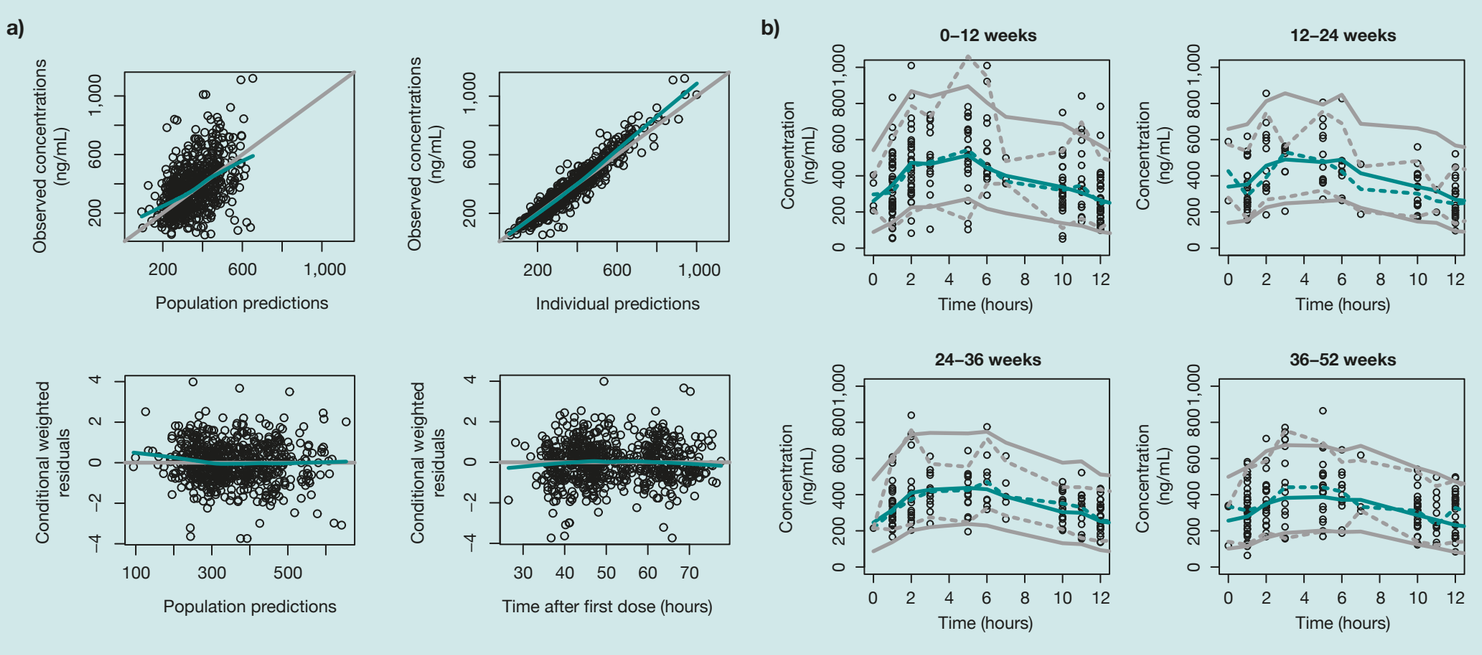
Figure 1. Model diagnostics. (a) Goodness of fit for final model: OC. (b) Visual predictive check: concentration versus time after dose by age group for OC.



Circles = observed concentrations; lines = median (blue), 5th and 95th percentiles (grey); solid lines = simulated data; dotted lines = actual data