very steep plasma concentration declines in patients aged over 7 days (Figure 1).

These clearance and terminal half-life values therefore make it difficult to reconcile the presented PTA curves and model parameter estimates, in particular for the older (7–14 and 14–28 day) age groups. For example, Darlow and Hope[1] report an approximate PTA of 70%–90% for 40% time above 1 mg/L, which does not appear to accord with a typical pharmacokinetic profile plot from their reported model parameters (Figure 1). Caution should therefore be taken in using this model to infer dosing and this example highlights a limitation of ignoring biological priors in the parameter structure of neonatal pharmacokinetic covariate models.

Transparency declarations
None to declare.

References

1 Darlow CA, Hope W. Flomoxef for neonates: extending options for treatment of neonatal sepsis caused by ESBL-producing Enterobacterales. *J Antimicrob Chemother* 2022; **77**: 711–8.

2 Calvier EAM, Krekels EHJ, Välitalo PAJ *et al.* Allometric scaling of clearance in paediatric patients: when does the magic of 0.75 fade? *Clin Pharmacokinet* 2017; **56**: 273–85.

3 Germovsek E, Lutsar I, Kipper K *et al.* Plasma and CSF pharmacokinetics of meropenem in neonates and young infants: results from the NeoMero studies. *J Antimicrob Chemother* 2018; **73**: 1908–16.

4 Germovsek E, Osborne L, Gunaratnam F *et al.* Development and external evaluation of a population pharmacokinetic model for continuous and intermittent administration of vancomycin in neonates and infants using prospectively collected data. *J Antimicrob Chemother* 2019; **74**: 1003–11.

5 Kane Z, Gastine S, Obiero C *et al.* IV and oral fosfomycin pharmacokinetics in neonates with suspected clinical sepsis. *J Antimicrob Chemother* 2021; **76**: 1855–64.

6 Germovsek E, Kent A, Metsvaht T *et al.* Development and evaluation of a gentamicin pharmacokinetic model that facilitates opportunistic gentamicin therapeutic drug monitoring in neonates and infants. *Antimicrob Agents Chemother* 2016; **60**: 4869–77.

7 Ikawa K, Morikawa N, Ikeda K *et al.* Development of breakpoints of cephems for intraabdominal infections based on pharmacokinetics and pharmacodynamics in the peritoneal fluid of patients. *J Infect Chemother* 2008; **14**: 141–6.

Flomoxef for neonates: extending options for treatment of neonatal sepsis caused by ESBL-producing Enterobacterales—authors' response

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We thank Joseph F. Standing for his comments[1] regarding our recently published population pharmacokinetic model for flomoxef in neonatal populations aged <4 weeks.[2]

To briefly summarize our approach: we fitted a population model to the flomoxef pharmacokinetic data (available in the public domain) for infants predominantly aged <28 days. The fitting of a base model to the data (i.e. without the inclusion of covariates such as age and weight) somewhat surprisingly showed an exponential rise in clearance in the first 28 days of life. This observation is accounted for by a combination of changes in size (allometry) and development (ontogeny). We could have estimated the scaling exponent that relates size (weight) to clearance, but we would have constrained the potential value(s) to <1 to avoid violating well-characterized allometric relationships that are operational in a wide range of biological contexts. Ultimately, we chose to fix this value at 0.75. We attributed the additional changes in clearance with increasing age and weight to time- and gestation-dependent maturation in renal function, with the subsequent scalars of these parameters estimated from the data. We note that significant (but, as yet, uncharacterized) drug transporters, with their own idiosyncratic ontogeny functions,[3] rather than passive glomerular filtration alone, likely account for a large proportion of the total flomoxef clearance.[4] This insight highlights the danger of mechanistically linking clearance to glomerular filtration rate.

While we agree the overall shape of the clearance versus weight and age curves are ultimately sigmoidal with the upper limit approximating adult values, we had no data to estimate the transition of clearance from neonates to children and adults. We could have constrained the solution and/or used a different structural model, but, in the absence of data, we did not feel this was appropriate. A consequence of that decision is that the model only describes the pharmacokinetics of flomoxef in neonates aged <28 days.

Our population pharmacokinetic model enabled us to describe the prolonged gamma phase of flomoxef even in heavier and older infants. The Monte Carlo simulations were well-centred and recapitulated the original population, including older heavier infants. We note the series of figures that accompany the letter by Standing,[1] but we do not believe they are reflective of the time–concentration profiles predicted by our model (Figure 1). Our own approach is to apply considerable caution in making predictions from pharmacokinetic models to populations other than those for which they are developed, and this is no exception to that rule. We confirm that (for neonates aged <28 days) the candidate regimens and PTA analyses we report are robust, with findings that are congruent with those described in the flomoxef Summary of Product Characteristics,[5] and we continue to
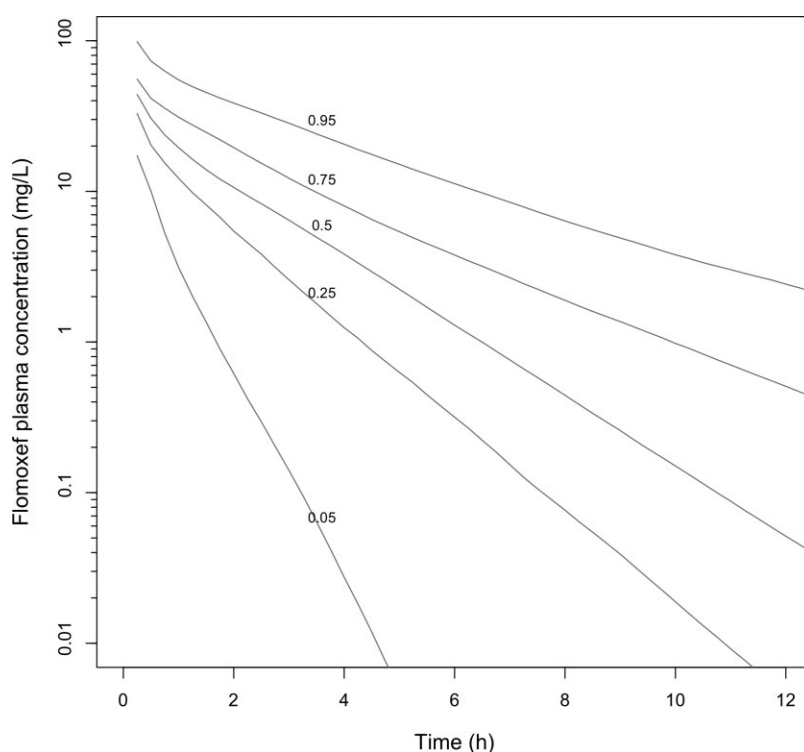
Figure 1. Monte Carlo simulation of flomoxef drug exposures following a single 20 mg/kg IV dose of flomoxef in 10 000 neonates aged 21–28 days, weighing 2–4 kg, with time–concentration profiles for the 5th, 25th, 50th, 75th and 95th centiles of the simulated population.

suggest that flomoxef is potentially an extremely valuable agent for the treatment of neonatal sepsis.

Transparency declarations

References

1 Standing JF. Comment on: Flomoxef for neonates: extending options for treatment of neonatal sepsis caused by ESBL-producing Enterobacterales. *J Antimicrob Chemother* 2022; **77**: 2046–7.

2 Darlow CA, Hope W. Flomoxef for neonates: extending options for treatment of neonatal sepsis caused by ESBL-producing Enterobacterales. *J Antimicrob Chemother* 2022; **77**: 711–8.

3 Cheung KWK, van Groen BD, Spaans E *et al.* A comprehensive analysis of ontogeny of renal drug transporters: mRNA analyses, quantitative proteomics, and localization. *Clin Pharmacol Ther* 2019; **106**: 1083–92.

4 Darlow CA, da Costa RMA, Ellis S *et al.* Potential antibiotics for the treatment of neonatal sepsis caused by multidrug-resistant bacteria. *Paediatr Drugs* 2021; **23**: 465–84.

5 Shionogi. *Flumarin for Intravenous Injection SPC*. 2009.