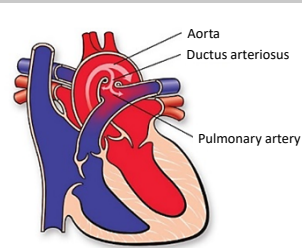


Paracetamol concentrations and time-course of ductus arteriosus diameter in extremely preterm neonates: a population pharmacokinetic-pharmacodynamic analysis

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Background



Patent ductus arteriosus (PDA) is a common complication of extreme prematurity. This cardiac shunt is associated with life-threatening morbidity, including respiratory and cardiac failure [1]. Although prophylactic treatment with indomethacin or ibuprofen reduces the risk of developing a PDA, it does not reduce mortality and morbidity, possibly due of the numerous adverse effects [2].

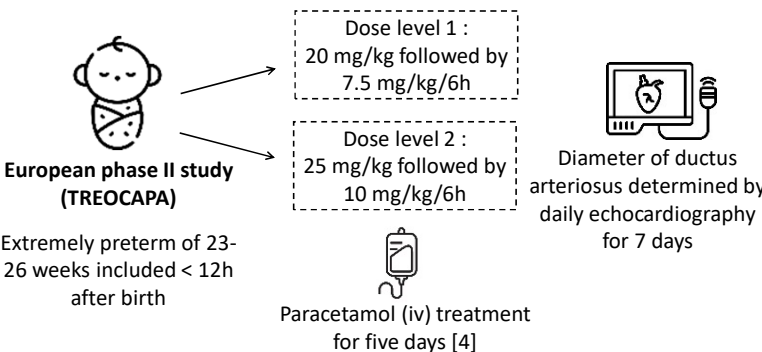
Early prophylactic treatment by paracetamol could be a safe and effective alternative [3]. However, current studies include very few extremely preterm neonates and no concentration-effect relationship is available.

Objectives

- To describe the effect of paracetamol on the longitudinal evolution of the ductus arteriosus diameter in extremely preterm neonates of 23 to 26 weeks of gestational age
- To assess the minimum effective dose

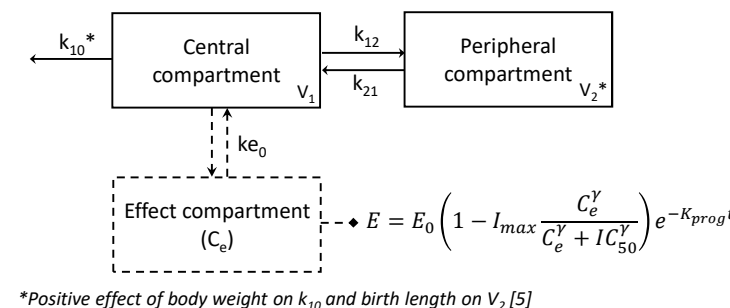
Materials and methods

Study participants and sampling :



Pharmacokinetic-pharmacodynamics (PKPD) modelling :

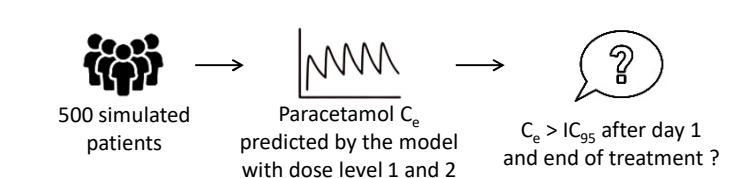
Figure 1 : Schematic representation of the structural pharmacokinetic-pharmacodynamic model



*Positive effect of body weight on k_{10} and birth length on V_2 [5]

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Simulations :



C_e : concentration in the effect compartment

IC_{95} : concentration needed to achieve 95% of the maximal inhibition

Results

- 29 preterm neonates**, with 119 plasma concentrations and 174 measurements of ductus arteriosus diameters available.

Table 1 : Characteristics of the study population at inclusion

Characteristics	Total	
Dose level 1 / Dose level 2	20 (69%) / 9 (31%)	
Gestational age (weeks) :		
23	2	2 (6.9%)
24	8	8 (27.6%)
25	7	7 (24.1%)
26	12	12 (41.4%)
Birth weight (g)	800 [670 ; 860] (470 ; 920)	
Birth length (cm)	33 [31.5 ; 34.8] (28 ; 36.5)	
Maximum FiO ₂ used during transfer to NICU	30 [21 ; 40] (21 ; 100)	
Intubation and mechanical ventilation at inclusion	14 (48.3%)	

key : Categorical data are expressed as numbers (percentages, %) and continuous data are expressed as median [interquartile range, IQR] and (range). FiO₂ : fraction of inspired oxygen; NICU, neonatal intensive care unit.

Covariate effects on ke_0 :

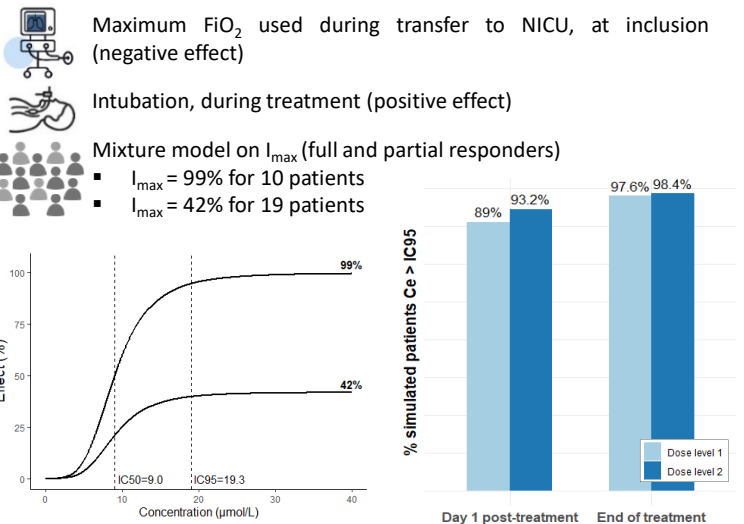


Figure 2 : Concentration-effect curve

Conclusion

- Maximum FiO₂ used during transfer to NICU, indicating a severe respiratory distress and impaired oxygenation, was associated with a slower transfer rate of the drug into the effect compartment, suggesting a delay in the drug effect on ductus arteriosus inhibition.
- Intubated patients exhibited a higher transfer rate, suggesting an acceleration of the drug transfer into the effect compartment. This could indicate that mechanical ventilation improves drug distribution mediated by an increase in cardiac output or enhanced systemic circulation.
- Maximal drug effect on diameter of ductus arteriosus was 99% in full responders and 42% in partial responders.
- Intravenous paracetamol treatment with a loading dose of 25 mg/kg within 12 hours after birth followed by 10 mg/kg every 6 hours appears to be effective to accelerate time to ductus closure with limited benefit of a further dose increase.

References

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