Electronic Supplementary Material

Clinical Pharmacokinetics

Population pharmacokinetics of intravenous salbutamol in children with refractory status asthmaticus

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Figure 1. The measured concentrations presented over time after start.

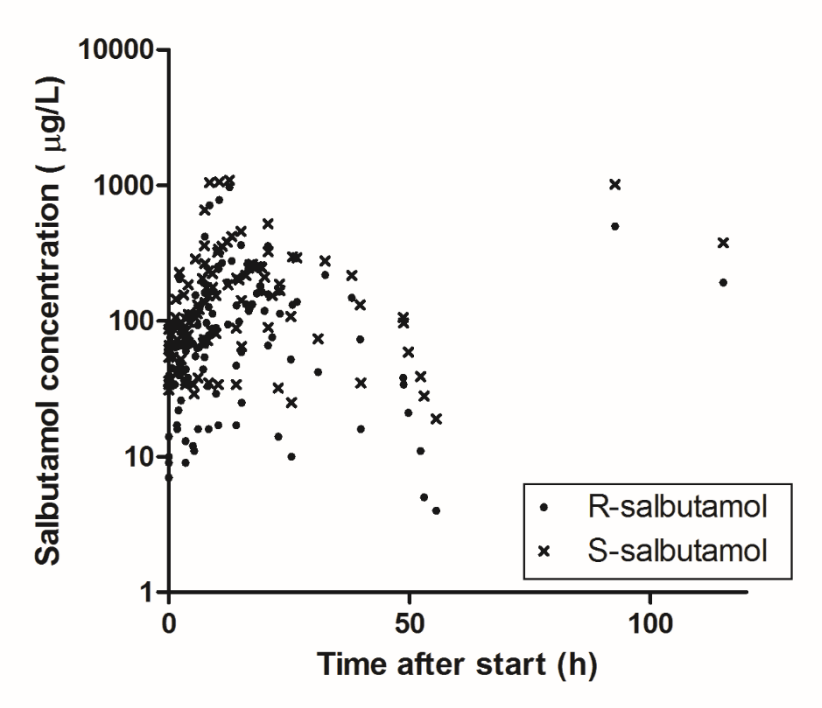
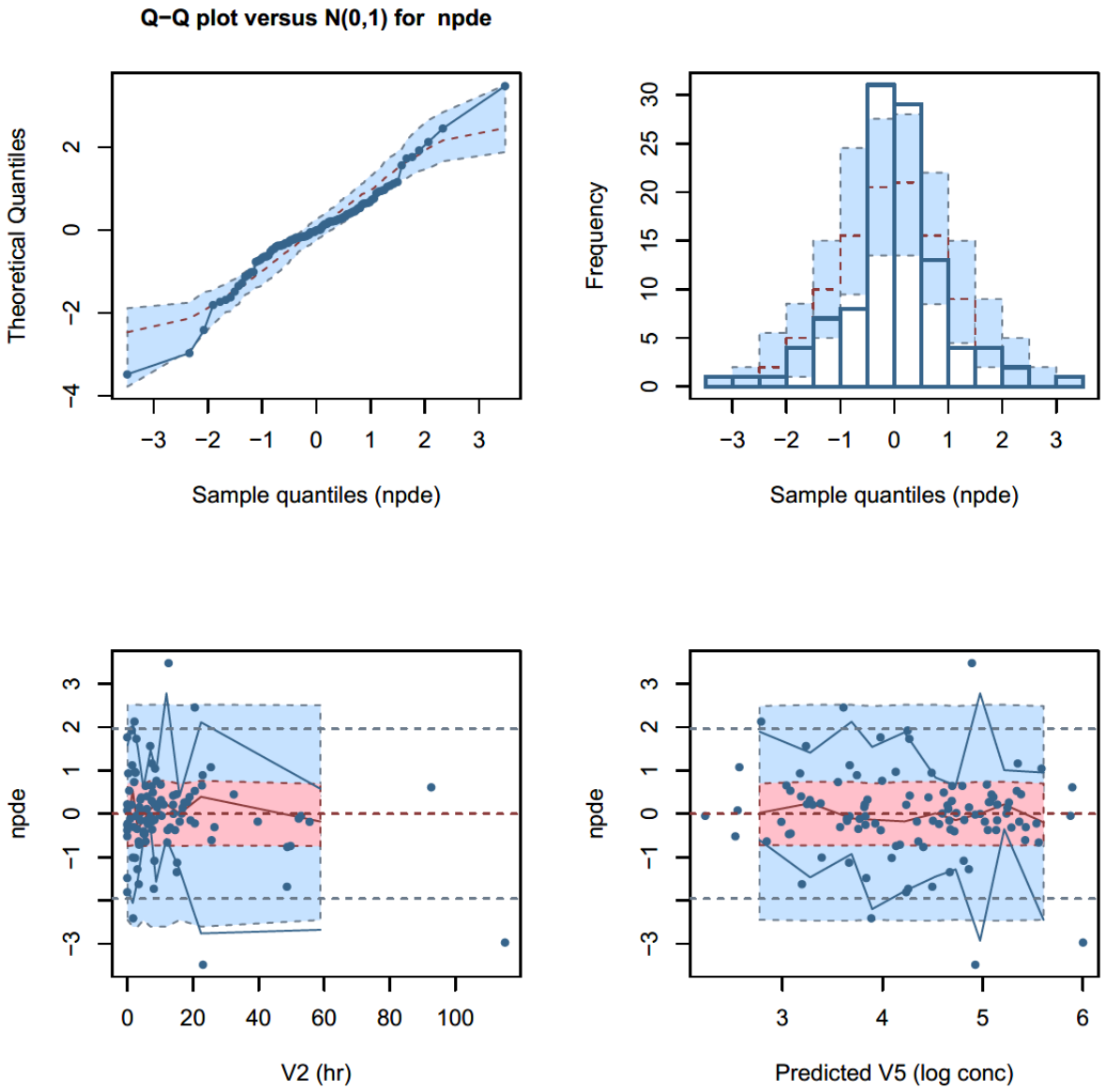
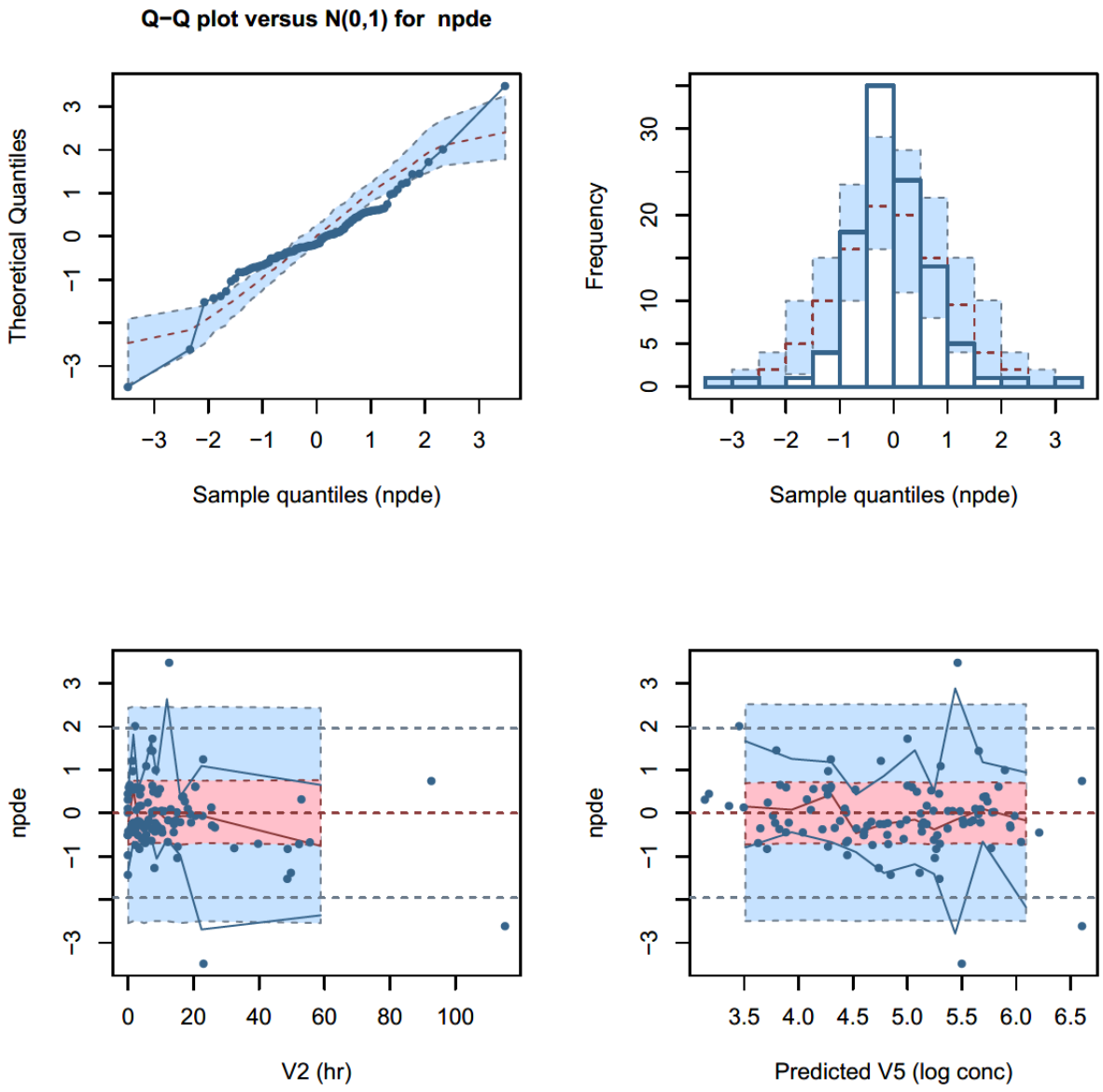


Figure 2. Normalized prediction distribution error (NPDE) of the final model with body weight included as covariate for (**a**) R-salbutamol (**b**) S-salbutamol. The Q-Q plot, histogram of the distribution and the distribution of the NPDE over time (V2) and concentration (V5) are presented for both isomers.

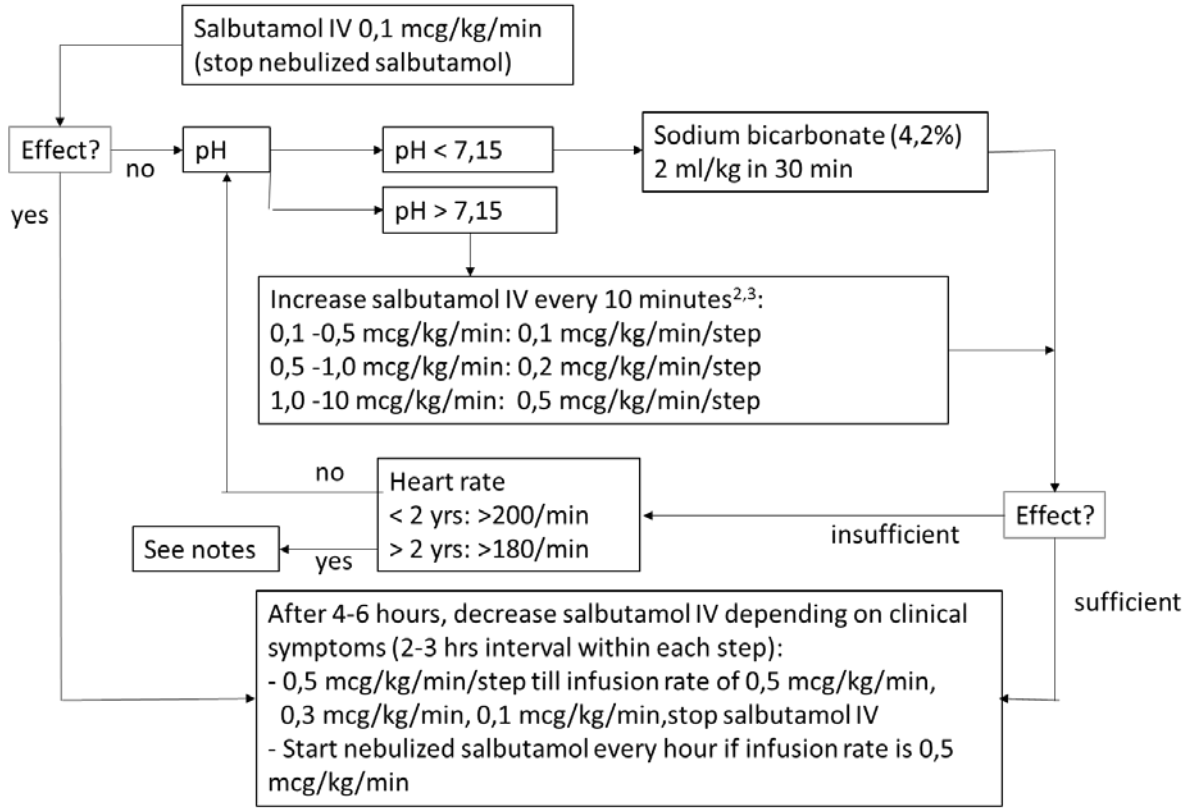
(a)



(b)


Q−Q plot versus N(0,1) for npde
Theoretical Quantiles
Sample quantiles (npde)
Frequency
Sample quantiles (npde)
npde
V2 (hr)
npde
Predicted V5 (log conc)

Appendix I. Clinical protocol for status asthmaticus



Notes:

1. Assess Airway, Breathing, Circulation and Disability at each step. Consider intubation.
2. If the infusion rate of salbutamol IV is 2 mcg/kg/min and further increasement has no clinical effect, stop increasing salbutamol IV (inflammation and mucus plugging is the problem)
3. Consult pediatric pulmonologist and intensivist. Consider ketamine, DNAse, inhalation anesthetics and inhalation corticosteroids

Appendix II. Salbutamol assay / analysis

Blood samples were analysed for R-salbutamol and S-salbutamol separately using a validated liquid chromatorgraphy-tandem mass spectrometry (LC-MS/MS) method. A Dionex Ultimate UPLC System (Thermo Scientific) with a quaternary pump and flow through needle injection coupled to a Thermo TSQ Vantage triple quadrupole mass spectrometer with (H)ESI-probe was used for analysis. As internal standard salbutamol-d3 100 ng/230 µL in acetone (Dr. Ehrenstorfer) was used. Chromatographic separation of R- and S-salbutamol was achieved by using an ASTEC Chirobiotic Teicoplanin column, 4.6 x 250mm, particle size 5µm (Sigma Aldrich). Mobile Phase: 1 L methanol with 5 mL acetic acid and 1 mL ammoniumhydroxide (all LC-MS grade). Isocratic elution was applied with a flow of 0,8 mL/min and a total runtime of 15 min. Column oven was kept at 30°C and the autosampler temperature was set at 15°C. For detection positive electrospray mode was used. The SRM (Selected Reaction Monitoring)-transition for both R- and S-salbutamol was 240 > 148 m/z. The SRM transition for salbutamol-d3 was 246>148. Spray voltage was set at 5000V, capillary temperature and vaporizer temperature were set at 200 and 300°C, respectively. For sample preparation 50µL aliquot of human plasma 200µL of methanol (containing 2,5µg/L internal standard) was added for protein precipitation. After vortexing and 5 minutes centrifugation at 16100 RCF, 20µl of the clear supernatant was injected on the UPLC system. Calculation with a linear curve of the relative response (area peak/area internal standard), with a weighing factor of 1/x, origin excluded, was linear over the range of 10-500 µg/L for both enantiomers. The deviation was <9% and the imprecision <4% for R- and S-salbutamol.