**Supplementary Material**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Supplementary Table 1. Pharmacokinetic Model for Risperidone and 9-hydroxy-risperidone (n=108)** | | | | |
| Parameters | Base Model | | Final Model | |
| Fixed Effects | Parameter estimates | RSE (%) | Parameter estimates | RSE (%) |
| Ka (/hr) (fixed) | 2 | - | 2 | - |
| VRISP (L) | 281 | 16 | 272 | 16.4 |
| CLRISP (L/hr) | 11.1 | 26.3 | 8.87 | 24.8 |
| *β Latent category (2) CLp* | 1.3 \*\*\* | 20.2 | 1.4 \*\*\* | 15.8 |
| *β tAge CLp* | - | - | -3.1 \*\*\* | 30.2 |
| V9-OH-RISP (L) | 1703 | 60.1 | 2030 | 49.2 |
| CL9-OH-RISP (L/hr) | 53.2 | 13.6 | 52 | 13.5 |
| Interindividual variability, |  |  |  |  |
| ω\_ VRISP % | 42.5 | 32.7 | 45.2 | 39.2 |
| ω\_ CLRISP % | 53.8 | 23.5 | 46.8 | 20.9 |
| ω\_ V9-OH-RISP % | 133 | 40.2 | 97.0 | 47.5 |
| ω\_ CL9-OH-RISP % | 55.4 | 16.4 | 55.6 | 17.6 |
| Residual unexplained variability |  |  |  |  |
| σ Risperidone mcg /L (%) | 0.1 (56.2) | 36.6 (15.3) | 0.1(55.6) | 21.1 (11.6) |
| σ 9-OH-risperidone mcg/L (%) | 0.7 (28.2) | 35.4 (16.3) | 0.7 (28.7) | 39.0 (15.0) |
| Probability of being in latent category, % | 31.6 | 35.4 | 21.7 | 40.2 |
| -2 x Log likelihood/ Bayesian Information Criteria | 1700/1766 | | 1688/1759 | |

Abbreviation*s: Ka -*first-order absorption rate constant (fixed at 2); VRISP *-* Volume of distribution for risperidone;  *CLRISP -* clearance of risperidone; *V9-OH-RISP -* Volume of distribution for 9-OH-risperidone; *CL9-OH-RISP* clearance of 9-OH-risperidone; *β-*beta coefficient*; ω -* coefficient of variation of inter-individual variability (expressed as a percentage); *σ* - coefficient of variation of residual unexplained variability (expressed as a percentage); *tAge* – age log transformed and centred around the mean; *RSE* relative standard error; *ne* not estimated

\*\*\* p<0.0001

**Supplementary Fig 1. Visual predictive checks**

Visual predictive checks (VPC): 95% prediction intervals around the 10th (lower blue shaded area), 50th (pink shaded area) and 90th (upper blue shaded area) percentiles are shown for the final model overlaid to observed data for risperidone in A) Functionally poor metabolisers and B) Functionally normal metabolisers. Each blue circle represents a single plasma sample. Blue lines represent the empirical predictions for each percentile and outliers are circled in red.

A close up of a map

Description automatically generated

|  |  |  |  |
| --- | --- | --- | --- |
| **Supplementary Table 2: Pharmacokinetic Biomarkers and Functional Metaboliser Status** | | | |
| **Biomarker** | **Functionally Poor, PM(n=18)** | **Functionally Normal, NM (n=82)** | **Mann Whitney U, p value** |
| **Mean (SD) Peak plasma concentrations, ng/mL** | | |  |
| Risperidone | 5.4 (3.2) | 3.6 (2.4) | 0.005 |
| 9-OH-Risperidone | 12.7 (7.6) | 9.5 (8.2) | 0.03 |
| Active Moiety | 17.6 (9.1) | 12.4 (9.9) | 0.007 |
| **Mean (SD) Trough plasma concentrations, ng/mL** | | |  |
| Risperidone | 3.9 (2.3) | 1.5 (1.4) | <0.0001 |
| 9-OH-Risperidone | 12.5 (7.5) | 9.2 (8.1) | 0.02 |
| Active Moiety | 16.3 (8.7) | 10.7 (9.3) | 0.003 |
| **Mean (SD) Average plasma concentrations, ng/mL** | | |  |
| Risperidone | 2.6 (1.6) | 0.5 (0.8) | <0.0001 |
| 9-OH-Risperidone | 12.1 (7.4) | 8.6 (7.8) | 0.01 |
| Active Moiety | 14.6 (8.0) | 9.0 (8.4) | 0.002 |
| **Mean (SD) trough active moiety concentration: dose (C/D) ratio, ng/mL per mg/day** | 20.2 (7.2) | 7.6 (4.9) | <0.0001 |