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SHORT COMMUNICATION

Guiding safer risperidone prescribing in Alzheimer's disease with therapeutic drug monitoring

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Previous analysis of pharmacokinetic data on risperidone-treated patients with dementia predicted that 20% had concentration-to-dose (C/D) ratios of the active moiety (risperidone and 9-hydroxy(OH)-risperidone) above 14 ng/mL per mg/day, which were in turn associated with a greater risk of extrapyramidal side effects. This study aimed to further explore risperidone pharmacokinetics in a second dataset. Nonlinear mixed effects modelling, using a Bayesian approach, was applied to data from a randomized controlled trial of risperidone in people with dementia. Covariates included age and glomerular filtration rate (GFR). Age had a significant effect on risperidone clearance ($\beta = -1.5$) and GFR on 9-OH-risperidone clearance ($\beta = 0.2$). The model predicted that 26.2% (95% confidence interval 18.6-32.6%) had C/D ratios above 14 ng/mL per mg/day. These findings confirm the importance of age-related risperidone dose adjustments and argue strongly for therapeutic drug monitoring in the initial stages of treatment to identify those at greatest risk of toxicity.

KEYWORDS
Alzheimer's disease, Bayesian, pharmacokinetics, poor metabolizer, risperidone

1 | INTRODUCTION

Antipsychotic drug use is associated with substantial harm (falls, worsening cognition, parkinsonism, stroke) and increased mortality[1] in older people with dementia and is restricted to those with severe symptoms unresponsive to psychosocial interventions. Risperidone is the only antipsychotic drug licensed in the European Union for the treatment of aggression and psychosis in people with dementia. The drug is typically prescribed across a dose range of 0.25-2 mg daily, based on meta-analyses of placebo-controlled trials of risperidone that suggest that for the average person 1 mg/day may optimally balance efficacy and side effects.[2] There is, however, wide interindividual variation in plasma concentrations of risperidone and its active metabolite 9-hydroxy-(OH)-risperidone for a given dose. This is partly explained by genetic or other causes of variation in the activity of metabolizing enzymes cytochrome **P450 (CYP) 2D6** and CYP3A4, and factors that affect renal excretion of 9-OH-risperidone.[3,4] The therapeutic reference range for the active moiety (summed concentrations of risperidone and 9-OH-risperidone) for adults with schizophrenia is 20-60 ng/mL,[5] but there is no established reference range for older adults with dementia and psychosis or aggression, who typically require lower doses and hence lower plasma concentrations.

Reeves et al[6] previously developed a pharmacokinetic model for risperidone and 9-OH-risperidone in older patients with Alzheimer's disease (AD), using data from the Clinical Trials of Intervention Effectiveness in Alzheimer's disease (CATIE-AD) study[7] and used model-based outputs to explore the relationship between pharmacokinetic biomarkers and side effects. There was an age-related

reduction in risperidone clearance and slower clearance of the active moiety in 20% of patients, such that trough concentration-to-dose (C/D) ratios of the active moiety were >14 ng/mL per mg/day.[8] Elevated trough concentrations of the active moiety and greater dementia severity were independent predictors of treatment-emergent parkinsonism.[6]

These preliminary findings argue strongly for dose reductions based on age and dementia severity, and suggest that 20% of patients may be at greater risk of toxicity as plasma concentrations of the active moiety were threefold higher for a given dose compared to other trial participants. This analysis aimed to further explore pharmacokinetic variability in a second clinical trial dataset that included data on renal function, with the following aims:

1.1) Investigate the effects of age and glomerular filtration rate (GFR) on clearance of risperidone and 9-OH-risperidone, respectively.
2.2) Use model-based outputs to estimate the proportion of patients with high (>14 ng/mL per mg/day) trough C/D ratios.

What is already known about this subject

- Risperidone is the only licensed antipsychotic drug in the European Union for the treatment of aggression and psychosis in people with dementia.
- Interindividual plasma concentrations of risperidone and its active metabolite (9-hydroxy(OH)-risperidone) vary widely and side effects can be significant in older adults with dementia.
- Previous pharmacokinetic analysis predicted that 20% of people with dementia had high concentration-to-dose ratios of the active moiety, which were associated with a greater risk of emergent extrapyramidal side effects.

What this study adds

- Age and renal function impacted on clearance of risperidone and 9-OH-risperidone, respectively.
- Model-based estimates suggest that 26% of patients had high concentration-to-dose ratios of the active moiety.
- Therapeutic drug monitoring could be used at the start of risperidone treatment to identify those at greatest risk of side effects during dose titration.

2 | METHODS

2.1 | Data source

De-identified patient-level data from the trial Risperidone in the Treatment of Behavioral Disturbances in Demented Patients: an International, Multicenter, Placebo-controlled, Double-blind, Parallel-group Trial Using Haloperidol as Internal Reference (NCT00249145)[9] was accessed via the Yale University Open Data Access (YODA) Project. Data were available from 115 institutionalized patients, prescribed 0.25 mg risperidone twice daily, increased if necessary up to 2 mg twice daily, over 12 weeks. At weeks 4 and 12, venous blood samples were collected in heparinized or EDTA-containing tubes, and the plasma concentration of risperidone and risperidone plus 9-OH-risperidone (active moiety) was determined by radioimmunoassay procedures. Quantification limits were 0.10 ng/mL for risperidone and 0.20 ng/mL for the active moiety.

2.2 | Data extraction

Data included age, sex, height, weight, ethnicity and serum creatinine. Pharmacokinetic data extracted included dose, treatment duration (weeks), time since last dose (hours) and plasma concentrations of risperidone and 9-OH-risperidone. Nine participants aged over 89 years were coded as '90+' in the dataset, and age was thus imputed as 93 years. Missing serum creatinine measurements in four participants were imputed using the sample median for the participant's age and sex. Estimated GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[10] Participants with no recorded dose, plasma concentrations, sample time or day were excluded.

2.3 | Statistical analysis

All analyses were undertaken within the secure YODA Project platform on R version 4.1.3 and the R Interface to Stan (rstan) version 2.21.1. The concentration-time profiles of risperidone and 9-OH-risperidone were investigated using a pharmacokinetic model that accounted for repeated sampling and included an absorption rate constant (*ka*) and the following apparent parameters: (i) risperidone clearance ($CL_{risperidone}$), (ii) risperidone volume of distribution ($V_{risperidone}$), (iii) 9-OH-risperidone volume of distribution ($V_{9\text{-}OH\text{-}risperidone}$) and (iv) 9-OH-risperidone clearance ($CL_{9\text{-}OH\text{-}risperidone}$). The latter parameters were estimated up to the transfer rate from the parent to the metabolite compartment. Interindividual and residual unexplained variability were described. Age at baseline and GFR on each occasion were included as covariates and centred around the median values in the sample.

A Bayesian approach was used, in which parameter estimates from the CATIE-AD analysis were used as informative priors for *V* and CL of risperidone and 9-OH-risperidone; previous estimates of the effect of age on $CL_{risperidone}$[6] and renal function on $CL_{9\text{-}OH\text{-}risperidone}$[11,12] were used as informative priors for the magnitude of covariate effects and *ka* was fixed at 2 h^{-1}.[6] The model was updated using information from the trial dataset to produce a posterior distribution

of the parameters. The Hamiltonian Monte Carlo algorithm ran with four chains of 1400 iterations including 400 burn-in. Convergence and efficiency were considered using Rhat (<1.05) and Neff (>500) statistics, respectively, and model fit was evaluated using visual predictive checks (VPCs).

The last 1000 samples for each individual parameter estimates, from the final model, were used to simulate 1000 datasets and predict the distribution of trough concentrations of risperidone, 9-OH-risperidone and the active moiety in these virtual populations. C/D ratio was calculated by dividing active moiety trough concentration by the risperidone dose. A C/D threshold of 14 ng/mL per mg/day was used to identify patients with slow clearance of the active moiety.[8]

3 | RESULTS

3.1 | Sample characteristics

There were 142 samples from 86 risperidone-treated participants (median 1.6, range 1-2 per person). The median age of participants was 81 (range 68-93), 48 (56%) were female and 85 (98.8%) were Caucasian. The median GFR was 61 (range 36-100) mL/min/1.73 m^2. Patients were prescribed a median dose of 1.0 (range 0.3-3.5) mg daily and the median sampling time was 10.6 (range 0.2-16.0) hours post dose. Median (range) plasma concentrations of risperidone and 9-0H-risperidone were 1.9 (0-30.2) and 7.3 (0-56.9) ng/mL, respectively.

3.2 | Model development

Parameter estimates from the model are described in Table 1. There was a significant effect of age on $CL_{risperidone}$ clearance. For a 60-year-old person, clearance of risperidone was estimated as 22.0 *vs* 10.8 L/h for a 95-year-old. A modest effect of GFR on $CL_{9\text{-}OH\text{-}risperidone}$ was found, such that predicted clearance was 52.9 *vs* 75.9 L/h for someone with a GFR of 20 and 90 mL/min/1.73 m^2, respectively. A relatively high degree of residual unexplained variability was noted for both risperidone and 9-0H-risperidone. VPCs demonstrated adequate model fit (Figure 1).

3.3 | Model-based outputs

Median (interquartile range [IQR]) (range) trough concentration of the active moiety in the 1000 simulated datasets was 7.5 (4.2-13.3) (0.0-291.0) ng/mL. Median (IQR) (range) C/D ratio of the active moiety in the simulated datasets was 8.8 (5.6-14.4) (0.0-145.5) ng/mL/mg/day. The proportion of participants with a C/D ratio >14 ng/mL/mg/day was 26.2% (95% confidence interval [CI] 18.6-32.6%). Figure 2 demonstrates the distribution of the C/D ratio in the simulated datasets.

4 | DISCUSSION

This analysis aimed to establish whether the preliminary findings in the CATIE-AD dataset could be replicated in a separate dataset. There was a significant age-related reduction in $CL_{risperidone}$ and a more

TABLE 1 Prior and posterior distributions of parameter estimates.

	Prior		
Parameter (units)	**Distribution**	**Mean (95% credibility intervals)**	**Posterior mean (95% credibility intervals)**
$CL_{risperidone}$ (L/h)	Lognormal	10.4 (6.2-16.3)	13.9 (11.9-16.1)
$V_{risperidone}$ (L)	Lognormal	303.8 (115.7-607.5)	216.8 (158.2-291.4)
$CL_{9\text{-}OH\text{-}risperidone}$ (L/h)	Lognormal	51.6 (30.4-80.3)	69.1 (54.0-88.7)
$V_{9\text{-}OH\text{-}risperidone}$ (L)	Lognormal	1844.7 (717.7-3728.9)	2014.4 (750.6-4536.3)
β Age_$CL_{risperidone}$	Normal	−3.1 (−4.8 to −1.5)	-1.5 (−2.8 to −0.3)
β GFR_$CL_{9\text{-}OH\text{-}risperidone}$	Normal	0.3 (0.1-0.5)	0.2 (0.1-0.4)
Interindividual variability			
ω $CL_{risperidone}$	Normal	0.16 (0.02-0.35)	0.54 (0.45-0.64)
ω $V_{risperidone}$	Normal	0.31 (0.08-0.53)	0.23 (0.04-0.40)
ω $CL_{9\text{-}OH\text{-}risperidone}$	Normal	0.64 (0.07-1.37)	0.13 (0.007-0.34)
ω $V_{9\text{-}OH\text{-}risperidone}$	Normal	0.64 (0.07-1.37)	0.59 (0.04-1.41)
Residual unexplained variability			
σ risperidone	Normal	0.16 (0.02-0.37)	0.55 (0.47-0.64)
σ 9-OH-risperidone	Normal	0.78 (0.13-1.52)	0.46 (0.39-0.55)

Notes: Volumes and clearances are apparent parameters, that is, known up to the bioavailability which cannot be estimated following oral administration. Here and in the core of the manuscript, we provide 95% credibility intervals of the a priori and/or posteriori distributions and not confidence intervals. Abbreviations: $CL_{9\text{-}OH\text{-}risperidone}$, clearance of 9-OH-risperidone; $CL_{risperidone}$, clearance of risperidone; GFR, estimated glomerular filtration rate; $V_{9\text{-}OH\text{-}risperidone}$, volume of distribution for 9-OH-risperidone; $V_{risperidone}$, volume of distribution for risperidone; β, beta coefficient; σ, coefficient of variation of residual unexplained variability; ω, coefficient of variation of interindividual variability.

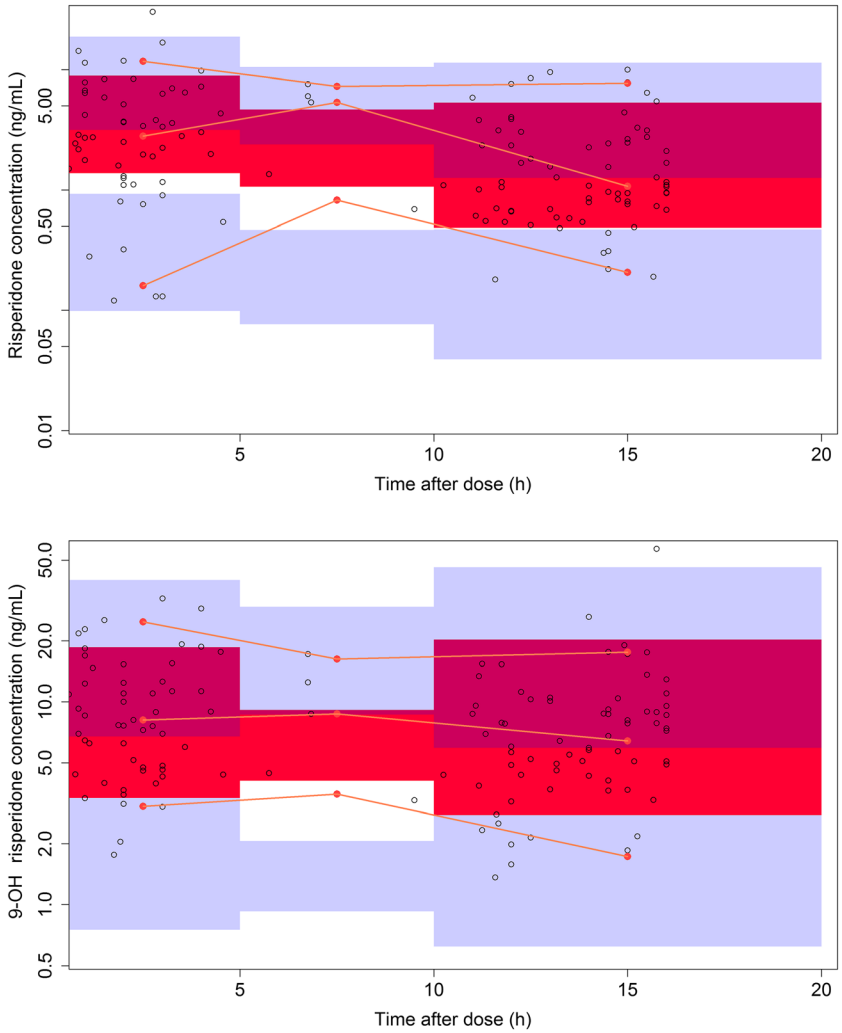

FIGURE 1 Visual predictive check for parent (top) and metabolite (bottom) obtained from 4000 samples of the model parameter a posteriori distribution. 95% prediction intervals around the 5th (lower blue shaded area), 50th (red shaded area) and 95th (upper blue shaded area) percentiles for the model, overlaid to observed data for risperidone (small black circles). Coral-coloured lines represent the empirical predictions for each percentile.

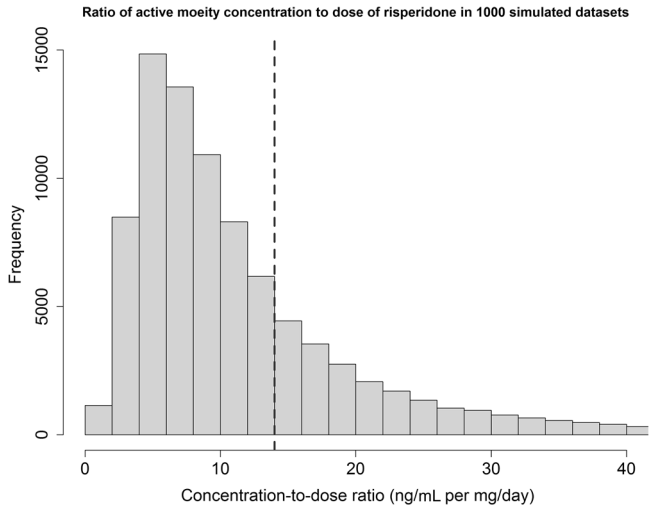

FIGURE 2 Ratio of concentration of active moiety to risperidone dose in the 1000 simulated datasets. Black dotted line indicates concentration-to-dose ratio of >14 ng/mL per mg/day.

modest effect of GFR on $CL_{9\text{-OH-risperidone}}$ Model-based predictions suggested that 26% of patients had C/D ratios >14 ng/mL/mg/day, indicative of slower clearance of the active moiety.

This is a higher proportion than was identified in the CATIE-AD analysis, but our 95% credibility interval includes their estimate (20%). The effect of age on risperidone clearance was smaller than was previously reported, but the upper limit of the credibility interval overlapped with previous findings.[6]

Estimated concentrations of the active moiety were lower than the therapeutic reference range for schizophrenia (20-60 ng/mL)[5] but were consistent with data on CATIE-AD participants,[6] in whom parkinsonism emerged from trough active moiety concentrations of 3.4 ng/mL in those with severe dementia and concentrations exceeded 10 ng/mL in eight of 14 patients who developed parkinsonism.

Renal function had a small effect on 9-OH-risperidone clearance, and the data were not very informative as the posterior distribution was closely aligned to the prior. This may be explained by the lack of patients with severe renal impairment in the sample. Early studies of 9-OH-risperidone pharmacokinetics suggested that renal clearance was the main route of elimination, with 59% of the dose excreted unchanged in urine.[13] This study, however, only included five healthy male participants. A population pharmacokinetic study of oral risperidone did not find an association between renal function and clearance, although this included only healthy adults and used a different

analytic approach.[14] Studies of intramuscular 9-OH-risperidone (paliperidone) have reported a significant effect of renal creatinine clearance on the elimination of 9-OH-risperidone, 0.38[12] and 0.32[11] in younger adults with predominantly normal renal function. Gründer et al,[15] in their retrospective evaluation of a therapeutic drug monitoring database, did include participants with GFRs as low as 30 mL/min/1.73 m^2. They demonstrated dose-corrected 9-OH-risperidone levels were significantly higher in patients with lower GFRs and a weak but statistically significant negative association between eGFR and dose-corrected 9-OH-risperidone concentration, which is in keeping with our findings. Comparative studies in older adults with dementia are, however, lacking.

5 | LIMITATIONS

Limitations include sparse sampling and incomplete data and/or data entering errors, which meant that only 142 of 178 plasma samples were included. We were unable to account for the impact of concomitant medications or medical comorbidities on pharmacokinetic variability. These factors and the absence of information on body mass index may have contributed to the unexplained variability in plasma concentrations.

Medication compliance can be an issue when treating patients with dementia, but compliance data from the trial were not available to us. All patients were institutionalized, however, which may have aided compliance. Furthermore, the 12-h dosage interval and the fact that risperidone and 9-OH-risperidone have relatively long half-lives suggest that an occasional missed medication dose would not have a large impact on steady-state concentration levels.

CYP2D6 and CYP3A4 are both involved in the metabolism of risperidone, and knowledge of genotype, which was not available in the trial dataset, could have helped to identify patients at risk of side effects. Multiple factors influence the pharmacokinetics of risperidone and 9-OH-risperidone in older adults, however, and the C/D ratio demonstrates functional metabolizer status, which in clinical practice may be more useful.

The parameter estimates for $V_{9\text{-OH-risperidone}}$ demonstrated a large degree of uncertainty (relative standard deviation about 50%) and contributed to a right skew of the simulated pharmacokinetic biomarkers. This could have resulted in higher simulated trough 9-OH-risperidone concentrations and might possibly explain the greater proportion of participants with a C/D ratio >14 ng/mL/mg/day compared to CATIE-AD.

6 | IMPLICATIONS

Our findings confirm the importance of age-related dose adjustments and suggest that at least 20% of older patients with AD are at risk of excessive drug exposure due to slower drug clearance. A single predose blood sample, taken at steady state, could be used to avoid dose escalation in patients with C/D ratios over 14 ng/mL per mg/day. Future research is required to evaluate the feasibility, acceptability and clinical utility of this in healthcare settings.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[16]

CONTRIBUTORS

Research idea, study design and data acquisition: Matthew Roughley, Robert Howard, Suzanne Reeves and Julie Bertrand. Developing statistical models, data analysis and figure production: Matthew Roughley, Carlos Mena, Suzanne Reeves and Julie Bertrand. All authors participated in drafting, revising and granting final approval of the article.

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COMPETING INTERESTS

The authors report no conflict of interests.

DATA AVAILABILITY STATEMENT

Data used in the preparation of this study were from the trial Risperidone in the Treatment of Behavioral Disturbances in Demented Patients: an International, Multicenter, Placebo-controlled, Double-blind, Parallel-group Trial Using Haloperidol as Internal Reference (NCT00249145). Data were accessed through the Yale University Open Data Access Project.

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