ORIGINAL RESEARCH ARTICLE

Pipamperone Population Pharmacokinetics Related to Effectiveness and Side Effects in Children and Adolescents

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Abstract

Background Pipamperone is a frequently prescribed antipsychotic in children and adolescents in the Netherlands, Belgium, and Germany. However, pediatric pharmacokinetics and the relationship with side effects and efficacy are unknown. Currently, divergent pediatric dosing recommendations exist.

Objectives The objective of this study was to describe the population pharmacokinetics of pipamperone in children and adolescents; to correlate measured and predicted pipamperone trough concentrations and predicted 24-h area under the curves with effectiveness, extrapyramidal symptoms, and sedation; and to propose dose recommendations based on simulations.

Methods Pipamperone concentrations were collected from Dutch pediatric patients in a prospective naturalistic trial ($n = 8$), and German pediatric patients in a therapeutic drug monitoring service ($n = 22$). A total of 70 pipamperone concentrations were used to develop a population pharmacokinetic model with non-linear mixed-effects modeling (NONMEM®). Additionally, an additional random sample of 21 German patients with 33 pipamperone concentrations from the same therapeutic drug monitoring service was used for external validation. Pharmacokinetic parameters were related to clinical improvement, sedation, and extrapyramidal symptoms. Simulations were performed to determine optimal dosages.

Results In a one-compartment model, the apparent volume of distribution was 416 L/70 kg and the apparent clearance was 22.1 L/h/70 kg. Allometric scaling was used to correct for differences in bodyweight. The model was successfully externally validated. The median [25th–75th percentile] measured pipamperone trough concentrations were numerically higher in responders (98.0 μg/L [56.0–180.5 μg/L]) than in non-responders (58.0 μg/L [14.9–105.5 μg/L]), although non-significant ($p = 0.14$). A twice-daily 0.6-mg/kg dosage was better than a fixed dosage to attain the concentration range observed in responders.

Conclusions Our findings suggest that pipamperone therapeutic reference ranges may be lower for children with behavioral problems than recommended for adults with psychotic symptoms (100–400 μg/L). When dosing pipamperone in children and adolescents, bodyweight should be taken into account.

1 Introduction

Pipamperone is one of the most frequently prescribed antipsychotics for children and adolescents in the Netherlands, Germany, and Belgium [1–3]. Between 2005 and 2015, 18% of all antipsychotics prescribed to children and adolescents

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in the Netherlands concerned pipamperone, with similar but slightly lower prescription rates in Germany and Belgium [1–3]. These prescription rates have been fairly constant for the past decades.

Pipamperone, being introduced in 1961 as Dipiperon® by Janssen Pharmaceutica, is considered a low-potency antipsychotic owing to the relatively low affinity for the D_2 receptor. The antagonism of the serotonin 5-HT$_2$ and adrenergic alpha$_1$ receptor is more pronounced [4], which explains its sedative effect, which is partly the result of relative hypoperfusion in the brain [5, 6]. For this reason, pipamperone has not only been explored for its antipsychotic properties [7], but also as a hypnotic in patients with sleep disorders, showing good efficacy [8].

Key Points

Pipamperone pharmacokinetic parameters in children and adolescents are comparable to adult values from the literature.

Children and adolescents with responses during pipamperone treatment have higher pipamperone trough concentrations and 24-h area under the curves than non-responders.

Bodyweight-adjusted pipamperone dosages are better than fixed dosages to attain the concentrations observed in responders. A twice-daily dosing scheme is recommended based on a relatively long elimination half-life (13 h).

However, in children and adolescents, pipamperone is particularly prescribed for behavioral problems, like other antipsychotics in this population [2, 9, 10]. Severe behavioral problems in youths represent the main symptoms of conduct disorder, or may occur within other psychiatric disorders such as autism spectrum disorder, attention-deficit/hyperactivity disorder, or mental retardation. Pipamperone may be a preferred antipsychotic for these indications, mainly because of the calming effects and the availability of an oral liquid formulation, enabling flexible dosing [11, 12]. However, despite the extensive practical experience in children and adolescents, the evidence for the efficacy of pipamperone is very limited. Although two small open-label studies from the 1970s showed positive results for the treatment of behavioral problems in children and adolescents, randomized controlled trials are lacking [13, 14]. For this reason, prescribing pipamperone to youths is currently considered off-label or restricted to use with particular consideration of the benefit-risk ratio, depending on the country [15, 16]. Indications for use as mentioned in the summary of product characteristics within the Netherlands, Germany, and Belgium include psychomotor agitation and behavioral problems, with depression of the central nervous system being a major clinical contra-indication [4, 15, 17].

Side effects of pipamperone mainly concern sedation and extrapyramidal symptoms (EPS) [4, 18]. Prolactin elevation has also been reported, and is associated with galactorrhea and amenorrhea [4]. Although weight gain and metabolic changes have become the major concern for atypical antipsychotic use in children and adolescents [19], these side effects have not been described in the literature for pipamperone. However, as antipsychotic-induced weight gain is believed to be partly attributed to the serotonin system [20], the 5-HT_2 antagonism of pipamperone is likely to induce weight gain as well.

While data on the efficacy and side effects are scarce, publicly available pharmacokinetic data of pipamperone in children and adolescents are completely missing. In adults, some pharmacokinetic studies have been performed, showing a maximum plasma concentration after 1–2 h and an elimination half-life of 12–30 h [4, 21, 22]. However, in children and adolescents, both pharmacokinetics and pharmacodynamics are expected to be considerably different, as some consensus based-dosing guidelines advise lowering the starting dose in this population by 95% compared to recommended doses in adults, resulting in 2 mg instead of 40 mg [16].

The aim of this study was to describe the population pharmacokinetics of pipamperone in children and adolescents. Furthermore, the relationships of the pharmacokinetic parameters of pipamperone with both clinical improvement and side effects, including sedation and EPS in children and adolescents, were explored. These data will provide a more solid basis for pipamperone dose recommendations in this vulnerable patient population.

2 Methods

2.1 Study Population

The study population consisted of two samples. The first sample included children and adolescents who were prospectively enrolled in a Dutch multicenter observational trial (SPACe, NTR6050). Inclusion criteria were: age 6–18 years, documented clinical diagnosis of autism spectrum disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [23] or Fifth Edition [24] and comorbid behavioral problems, and treatment with pipamperone. Exclusion criteria were: type 1 or 2 diabetes mellitus, congenital or acquired syndrome associated with changes in appetite, body weight or lipid profile (e.g., Prader Willi), treatment with another antipsychotic within the last 6 months, or known Long QT syndrome. Eligible patients were treated in an inpatient or outpatient setting in one of the seven participating centers in the south-west region of the Netherlands (two academic tertiary care centers and five psychiatric secondary care centers). Subjects were prescribed flexible pipamperone dosages once or twice daily, as part of routine clinical care by the treating physician. Pipamperone was prescribed as a tablet formulation or oral solution. Patients were recruited between August 2016 and May 2018. All patients and/or their legal representatives gave written informed consent before entering the study. The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, the Netherlands (number MEC 2016-124).

The second sample consisted of children and adolescents of whom pipamperone concentrations had been measured as

part of the routine therapeutic drug monitoring (TDM) service of the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy at the University Hospital of Wuerzburg, Germany. Subjects were treated at this clinic or at associated clinics for child and adolescent psychiatry within the competence network of TDM in child and adolescent psychiatry, which is described elsewhere [25]. Patients were prescribed flexible dosages of pipamperone as a tablet or oral solution, being administered once up to five times daily. The pipamperone samples were collected between June 2008 and February 2015 in patients with various psychiatric diagnoses. The Medical Ethics Committee of the University of Wuerzburg approved the study (study number 27/04) and waived informed consent, as drug concentrations were measured as part of routine care. Both studies were conducted in accordance with the Declaration of Helsinki.

2.2 Pipamperone Concentrations

In the Dutch trial, a total of six pipamperone drug concentrations per subject were collected at random time points on two separate days during a 6-month follow-up with 3–6 months in between sampling. The time between two samples was at least 1 h. Samples were collected with venipuncture and the dried blood spot (DBS) method. The time of sampling, time of last pipamperone intake, the pipamperone dosages, and comedication during follow-up were recorded. Both samples in steady state and non-steady state were collected. The Dutch samples were analyzed using previously validated, ultra-high performance liquid chromatography-mass spectrometry methods for plasma and DBS [26–28]. The lower limit of quantification (LLOQ) was 1.5 µg/L. The accuracy of the quality-control samples was well below a limit of relative standard deviation of 15% and the intra- and inter-assay imprecision was less than 15% during the study period.

Within the German TDM service, samples were collected with venipuncture in the morning before the first pipamperone dosage of that day (trough concentrations) [21]. The pipamperone dosage and administration time (morning, midday, evening) were reported on the request form. Only concentrations measured in steady state were included for analyses, as for non-steady state samples previous dosages were not known. The German samples were analyzed with a validated serum high-performance liquid chromatography-ultraviolet (HPLC–UV) method for plasma. The LLOQ was 8 µg/L. The method was linear in a range of 2–1050 µg/L ($r^2 = 0.99952$). Concentrations below the LLOQ were excluded, as for these no quantification of the plasma concentration was provided.

2.3 *Assessment of* Clinical *Outcomes*

In the Dutch trial, measures of clinical effectiveness and side effects were collected at baseline and prospectively during the 6-month follow-up (at 6 months and for a subset of patients at 1 and 3 months). Clinical effectiveness was measured by the Clinical Global Impression (CGI) Scale [29]. This scale describes the severity of psychopathology (CGI-S) and its improvement (CGI-I) by seven categories, rated by the treating physician. The CGI-S describes the severity of illness relative to the physicians' experience with patients with the same diagnosis: 0 = not assessable; 1 = normal; 2 = borderline; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = extremely ill. The CGI-I rates the improvement in comparison to the original medication-naive state of symptoms: 0 = not assessable, 1 = very much better, 2 = much better, 3 = moderately better, 4 = unchanged, 5 = minimally worse, 6 = much worse. Extrapyramidal symptoms were measured with the Abnormal Involuntary Movement Scale (AIMS) (completed by the treating physician or researcher) [29] and sleepiness with the Epworth Sleepiness Scale (completed by parents) [30]. Biochemical laboratory check-ups were performed at baseline, after 6 months, and for a subset of children at 3 months, and included renal function, liver function, fasting glucose, glycosylated hemoglobin, prolactin, cholesterol, fatty acids, and albumin. During follow-up, medication adherence was measured with questionnaires (Medication Adherence Rating Scale, MARS-5 [31], completed by parents, and a visual analog scale, completed by parents and treating physician) and during the last month of follow-up with an electronic monitoring system (MEMS©) [32]. Weight and height were measured at baseline, at the time of blood sampling and, for a subset of children, after 1 month of follow-up.

At the German TDM service, the following information was recorded on the request form at the time of sampling: renal dysfunction, hepatic dysfunction, smoking status, current infection, comedication, CGI-S, CGI-I, and side effects with the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale [33]. The Udvalg for Kliniske Undersøgelser Side Effect Rating Scale rates the severity of side effects with the following categories: 0 = no side effects; 1 = mild, 2 = moderate, and 3 = severe. The nature of the side effects was also recorded and classified as follows: sedation, dermatological, tension, salivation (more/less), accommodation disorder, polydipsia, delirium, EPS, cardiovascular, gastrointestinal, urogenital, other.

2.4 Population Pharmacokinetic Modeling

Pharmacokinetic analysis was performed by non-linear mixed-effects modeling using NONMEM® Version 7.4.2 (FOCE + I; ICON Development Solutions, Ellicott City,

MD, USA) and PsN® Version 4.7.0. Pirana® software version 2.9.7 was used as an interface between NONMEM® and R (version 3.4.4).

2.4.1 Base Model Development

One- and two-compartment models were considered with first-order absorption with and without lag time. Typical values for volume of distribution and clearance were estimated as ratios, as bioavailability could not be quantified (apparent volume of distribution and apparent clearance). As the absorption rate constant could not be estimated, it was fixed at 2/h, based on the previous literature [21]. For each pharmacokinetic parameter, inter-patient variability (IPV) was evaluated and shrinkage was calculated for all parameters for which IPV was established. A shrinkage value below 25% was considered acceptable [34]. Allometric scaling was used to account for the influence of bodyweight on pharmacokinetic parameters, which was explored with a fixed exponent of 0.75 for apparent clearance and 1 for apparent volume of distribution, and with exponents estimated by the model. Residual variability was modeled as a separated additive and proportional error for the analytical method (liquid chromatography-mass spectrometry vs HPLC–UV) and sampling method (DBS vs venepuncture). Model selection was based on minimum objective function values, parameter precision, error estimates, shrinkage values, and visual inspection of the goodness-of-fit plots.

2.4.2 Covariate Model Development

The following covariates were considered as potential model covariates: sex, age, body mass index, weight, comedication, psychiatric disorder, somatic comorbidities, smoking, renal function, liver function, pipamperone dose, and dose/kg. For the Dutch patients, albumin, hematocrit, and medication adherence were also known and evaluated as covariates. The correlation between the covariates and IPV was first evaluated graphically. Subsequently, covariates with a visual relationship with IPV were individually added to the model. Continual covariates were described using an exponential function and categorical covariates using a proportional function. The forward inclusion-backward elimination method was used [35]. Covariates that significantly improved the model with the univariate analysis ($p < 0.05$) were selected for the multivariate analysis. During the backward elimination process, covariates that improved the model at a level of $p < 0.001$ were selected.

2.4.3 Internal Model Evaluation

Two methods were used for the internal validation of the model. First, a bootstrap analysis was performed [36]. One thousand bootstrap datasets were randomly resampled from the original dataset with replacement. The validity of the model was evaluated by comparing the bootstrap estimates and their 95% confidence intervals with the values generated by the original dataset. Second, the model was evaluated with the visual predictive check, using a set of 1000 simulated datasets to compare the observed concentrations with the distribution of the simulated concentrations [37].

2.4.4 External Model Evaluation

An additional dataset of another group of German patients from the same TDM service was used for external validation of the final model. Goodness-of-fit plots and a normalized prediction distribution error analysis ($n = 1000$) were used to evaluate the external validity [38].

2.5 Pharmacodynamic Analyses

The medians with 25th–75th percentiles of measured trough concentrations were correlated with CGI-I, EPS, and sedation. As trough pipamperone concentrations were not available for all Dutch patients, individual trough concentrations were also predicted for all patients, next to 24-h area under the concentration–time curves (AUC_{24h}). These pharmacokinetic parameters were also correlated to CGI-I, EPS, and sedation. A subject was considered a responder when the CGI-I was rated "very much better", "much better", or "moderately better", and a non-responder when another score was given (except from "not assessable"). Extrapyramidal symptoms were scored positive when at least two times "mild" or one time "moderate" in the first seven items had been filled in on the AIMS (Dutch patients), or when "EPS" was filled in as a side effect on the application form (German patients). Sedation was considered as a score ≥ 1 on the Epworth Sleepiness Scale (Dutch patients) or as "sedation" being filled in as side effect on the application form (German patients). The pipamperone trough concentration, predicted trough concentration, and predicted AUC_{24h} at the time of the first response or side effect (EPS and sedation) was used for the analyses. In this analysis, efficacy was accepted as an endpoint regardless of the time interval since the initiation of treatment (but within the study period). If no response or side effect was observed, the highest concentration during the follow-up was used. Laboratory findings were compared with age- (and if applicable sex-) specific reference values as used in the Erasmus MC, University Medical Center Rotterdam in July 2019 [39]. The Mann–Whitney U test was used to compare trough concentrations and AUC_{24h} between groups. The Fisher's Exact test was used to compare proportions. A p value < 0.05 was considered significant. Graphpad Prism 5 (GraphPad Software, La Jolla, CA, USA) was used for the analyses.

2.6 Predictions

Pipamperone concentrations using a twice-daily 30-mg dosing regimen were predicted for a patient of 25, 50, and 75 kg during a 12-h time interval. After graphical inspection, a mg/kg dosage was chosen for optimal attainment of the concentration range associated with response based on pharmacodynamic analyses. This mg/kg dosage was evaluated with additional predictions for a patient of 25, 50, and 75 kg. The population predictions were used as means with a 95% confidence interval based on 1000 simulations of individual predictions.

3 Results

Thirty patients with 70 measured pipamperone concentrations were included in the model building group (Dutch patients $n = 8$ and German patients $n = 22$). Two German samples were below the LLOQ and were not included. The pipamperone concentrations were collected in the entire absorption and elimination phase, as can be seen in Fig. 1. Subsequently, 21 extra patients with 33 measured pipamperone concentrations were included in the external validation group (German patients). The baseline characteristics of the included patients are presented in Table 1. Most patients were diagnosed with autism spectrum disorder, attention deficit/hyperactivity disorder, or mental retardation. The median (range) measured pipamperone concentration was 66.5 μg/L (0.21–1068 μg/L) in the model building group and 88 μg/L (16–337 μg/L) in the model validation group.

In the model building group, the $n = 1$ sample was below the LLOQ (Dutch sample). In the model validation group, no samples below the LLOQ were included.

Indications for a pipamperone concentration measurement in the German TDM service were known for $n = 60$ samples (90.9% of total $n = 66$ German samples). Most pipamperone concentrations were measured because of non-effectiveness ($n = 16$, 26.7%) or dosage change ($n = 16$, 26.7%). Other indications included drug–drug interaction ($n = 13$, 21.7%), start of therapy ($n = 10$, 16.7%) adherence ($n = 8$, 13.3%), or side effects ($n = 5$, 8.3%); more than one reason could apply.

3.1 Pharmacokinetic Analyses

3.1.1 Base Model

The data were best described using a one-compartment model. This model was further improved by including an IPV on clearance. The residual error was described by a combined error model with an extra additional error for HPLC–UV concentrations. As the conversion of DBS
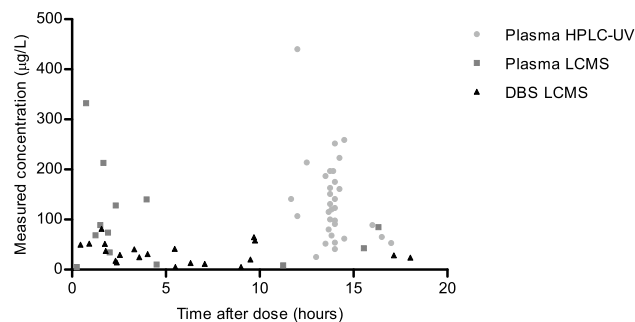

Fig. 1 Measured pipamperone concentrations used for model development vs time after dose. Pipamperone concentrations were collected during the absorption and elimination phase. The presented dried blood spot (DBS) concentrations are measured concentrations before conversion to estimated plasma concentrations. Four samples are not shown for readability of the figure ($x = 182$, $y = 0.21$; $x = 118.63$, $y = 2.69$; $x = 121.4$, $y = 4.82$; $x = 12.25$, $y = 1068$). *HPLC–UV* high-performance liquid chromatography-ultraviolet, *LCMS* liquid chromatography-mass spectrometry

concentrations to plasma concentrations based on the previously conducted clinical validation study [28] showed a trend towards under-estimation of the predicted concentrations by the model, a model-based conversion was calculated that showed better predictions. The goodness-of-fit plots of the final model are presented in Fig. 2, and the parameter estimates of the final model are presented in Table 2.

3.1.2 Covariate Analysis

After graphical analysis, the univariate analysis resulted in three significant covariates for the IIV on clearance (bodyweight, creatinine, body mass index). These covariates were added to the base model for multivariate analysis. No covariates remained significant after backward elimination except for bodyweight, which was best described using fixed exponents with allometric scaling.

3.1.3 Evaluation of the Final Model

The model-based parameter estimates were similar to the values computed from the bootstrap analysis, indicating the stability of the model (see Table 2). The extra additional error for HPLC–UV concentrations was 26.6 (μg/L). The visual predictive check showed a good predictive performance (figure not shown).

The model was successfully externally validated, as is shown by the goodness-of-fit plots and normalized prediction distribution error analysis. The goodness-of-fit-plots show that the model adequately describes the observed concentrations (Fig. S1 of the Electronic Supplementary Material [ESM]), and the normalized prediction distribution error analysis shows a normal distribution of the normalized

Table 1 Patient characteristics

	Model building group ($n=30$)	Model validation group ($n=21$)
Male (n)	21 (70%)	13 (61.9%)
Age (years)	13.0 (5.6–17.7)	14.9 (7.2–20.6)
Body weight (kg)	50.4 (24.8–100.4)	47.4 (24.0–118.0)
Height (cm)	152 (123–180)	155 (122–186)
Body mass index (kg/m^2)	20.41 (14.3–37.2)	19.0 (12.2–43.3)
Body mass index Z score	0.98 (−2.57 to 3.49)	0.38 (−4.49 to 4.25)
Daily dosage (mg)	45 (12–400)	60 (10–180)
Psychiatric comedication		
Antipsychotic drugs	18 (60%)	8 (38.1%)
ADHD drugs[a]	6 (20%)	8 (38.1%)
Tricyclic antidepressant drugs	1 (3.3%)	2 (9.5%)
Selective serotonin re-uptake inhibitors	0 (0%)	3 (14.3%)
Benzodiazepine agonists	1 (3.3%)	2 (9.5%)
Lithium	1 (3.3%)	0 (0%)
Other comedication		
Antiepileptic drugs	4 (13.3%)	5 (23.8%)
Diagnosis		
Autism spectrum disorder	22 (73.3%)	4 (19.0%)
ADHD	12 (40%)	5 (23.8%)
Schizophrenia spectrum and other psychotic disorders	2 (6.7%)	0 (0%)
Conduct disorder	1 (3.3%)	0 (0%)
Mental retardation	9 (30%)	4 (19%)
Setting[b]		
Clinical	22 (73.3%)	19 (90.5%)
Outpatient	7 (23.3%)	2 (9.5%)
No. of pipamperone samples per patient		
Pipamperone concentration (μg/L)[c]	1.5 (1–6)	1 (1–6)
Clinical Global Impression Scale score	5 (4–7)	5 (4–7)

Patient characteristics at the time of the first pipamperone concentration measurement. Presented as median and range for continuous variables

The model building group consisted of patients from a Dutch multicenter observational trial and patients from a German TDM service. The model validation group consisted of patients from the same German TDM service. Clinical Global Impression Scale was missing for $n=2$ in the model building group and $n=2$ in the model validation group [1 = normal; 2 = borderline; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = extremely ill]

ADHD attention deficit/hyperactivity disorder, *DBS* dried blood spot, *TDM* therapeutic drug monitoring

[a]Includes methylphenidate, amphetamine, and atomoxetine

[b]Unknown for $n=1$ patient in the model building group

[c]Includes DBS concentrations before conversion to estimated plasma concentrations

errors and some overestimation of variability (Fig. S2 of the ESM).

3.2 Pharmacodynamic Analyses

3.2.1 Effectiveness

For a total of 35 patients, CGI improvement scores were reported; 28 (80%) of them were rated as responders, and seven as non-responders (20%). Psychotropic comedication was common in both responders (68%) and non-responders (57%), but non-significantly different ($p=0.67$).

For 29 of these patients, both CGI improvement scores and measured pipamperone trough concentrations were available. The median [25th–75th percentile] pipamperone trough concentration was higher in responders (98.0 μg/L [56.0–180.5], $n=24$) than in non-responders (58.0 μg/L
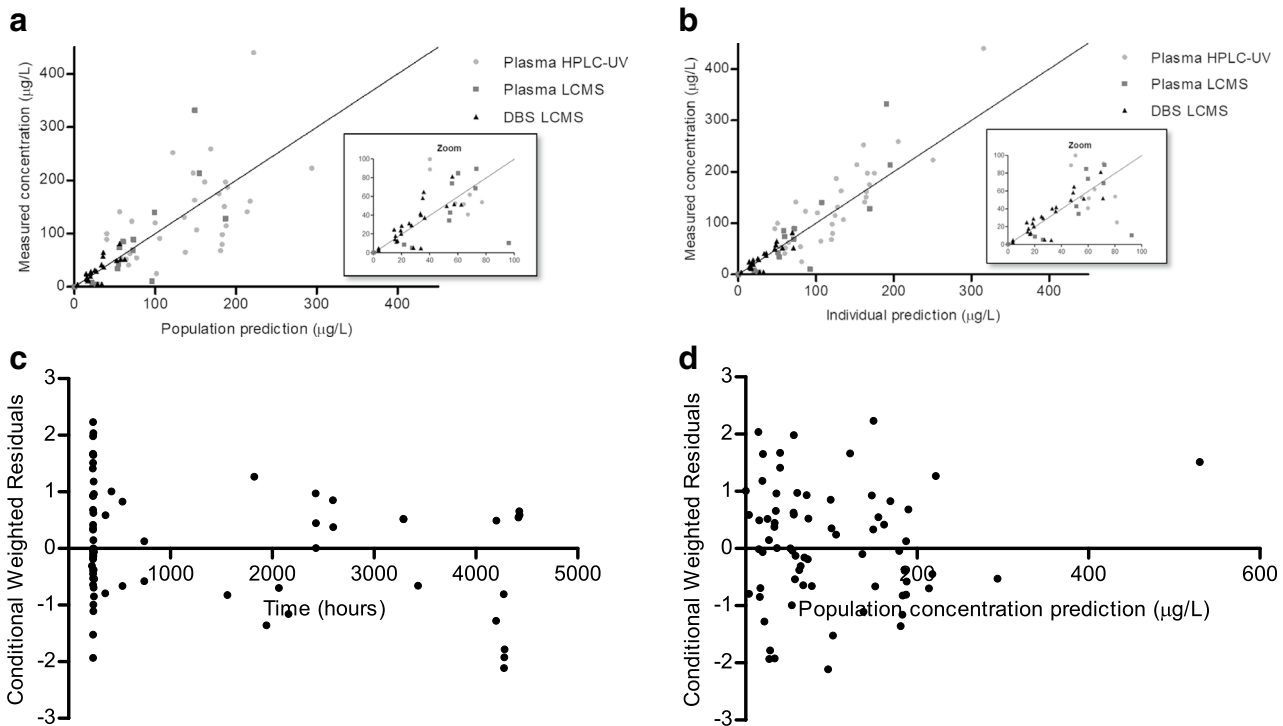
Fig. 2 Goodness-of-fit plots, final model. **a** Measured concentrations vs population predictions. One outlier is not presented for readability of the figure ($x = 529.7$, $y = 1068$). **b** Measured concentrations vs individual predictions. One outlier is not presented for readability of the figure ($x = 755.3$, $y = 1068$). **c** The correlation of conditional weighted residuals (CWRES) with time. One outlier is not shown for readability of the figure (time 38,232.00, CWRES 0.244350). **d** The correlation of CWRES with population-predicted concentrations. *DBS* dried blood spot, *HPLC–UV* high-performance liquid chromatography-ultraviolet, *LCMS* liquid chromatography-mass spectrometry

Table 2 Parameter estimates final model

Parameter	Estimate (RSE %) [shrinkage]	Bootstrap median (90th percentile)
K_a^a (L/h)	2	2
V/F[b] (L/70 kg)	416 (32)	481 (279–2251)
CL/F[b] (L/h/70 kg)	22.1 (12) [34%][3]	22.7 (18.7–31.2)
IPV CL	20.5%	24.0 (11.6–69.7)
Residual variability		
Additional error (µg/L)	0.21 (1)	0.21 (0.11–10.5)
Proportional error	0.39 (19) [7%]	0.33 (0.15–0.46)
Additional error HPLC–UV (µg/L)	26.6 (40) [7%]	25.6 (8.5–39.1)
DBS correction: $y = ax + b$		
a (µg/L)	0.33 (8)	0.31 (0.19–0.40)
b (µg/L)	3.90 (15)	3.87 (3.42–14.84)

CL clearance, *DBS* dried blood spot, *HPLC–UV* high-performance liquid chromatography-ultraviolet, *IPV* inter-patient variability, K_a absorption rate constant, *RSE* relative standard error, *V* volume of distribution

[a]Fixed

[b]Allometric scaling with exponent 1 for V and 0.75 for CL

[c]90th percentile based on bootstrap with $n = 772$ successful runs

[14.91–105.5], $n = 5$), but this difference was non-significant ($p = 0.14$) (see Fig. 3a).

For the total sample of patients with a CGI improvement score ($n = 35$), pipamperone trough concentrations were also predicted based on the pharmacokinetic model. The median [25th–75th percentile] predicted trough concentration for responders was higher than in non-responders: 80.0 µg/L [63.0–136.6] vs 51.3 µg/L [43.4–78.8], with a trend towards significance ($p = 0.07$) (see Fig. 3b). The predicted median AUC_{24h} in responders (3448.0 µg*h/L) was also higher than in non-responders (1811.0 µg*h/L), $p = 0.05$.

When patients with ADHD and concurrent ADHD comedication (methylphenidate, amphetamine, or atomoxetine) were excluded from the analyses, the results remained the same. The median [25th–75th percentile] pipamperone trough concentration was higher in responders (113.5 µg/L [62.0–180.5], $n = 20$) than in non-responders (58.0 µg/L [14.91–105.5], $n = 5$), $p = 0.10$, as was the predicted trough concentration (83.5 µg/L [66.5–136.6], $n = 24$, vs 51.3 µg/L [43.4–78.8], $n = 7$), $p < 0.05$, and the AUC_{24h} (3486 µg*h/L vs 1811 µg*h/L), $p < 0.05$.
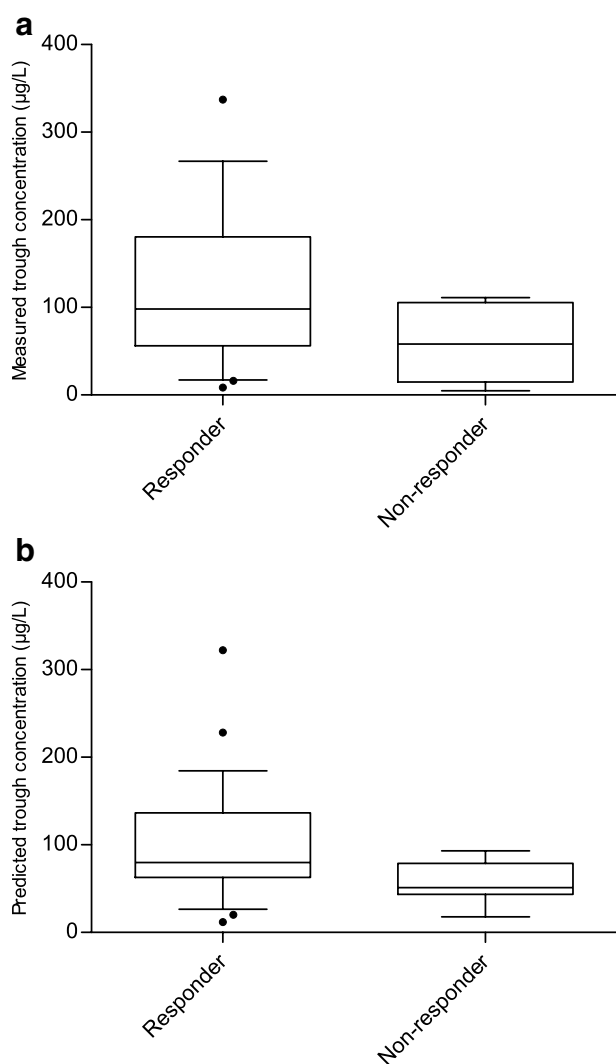
Fig. 3 Pipamperone trough concentrations and clinical improvement. **a** Measured trough concentrations vs response based on the Clinical Global Impression Scale. Data available for $n=29$ subjects. In responders, the measured trough concentration at the time of the first response was used. In non-responders, the highest measured trough concentration during the follow-up was used. Whiskers indicate 10th–90th percentiles. **b** Predicted trough concentrations vs response based on the Clinical Global Impression Scale. Data available for $n=35$ subjects. In responders, the predicted trough concentration at the time of the first response was used. In non-responders, the highest predicted trough concentration during the follow-up was used. Whiskers indicate 10th–90th percentiles

3.2.2 Extrapyramidal Symptoms

In four patients, EPS were observed (8% of 50 patients with EPS scores). All these four patients came from the Dutch sample. For two of these patients, and 44 of the patients without EPS, measured trough concentrations were available. The median [25th–75th percentile] pipamperone trough concentration was lower in patients with EPS (25.74 μg/L [8.6–42.9]) than in patients without EPS (109.5 μg/L [62.0–174.5]). Predicted pipamperone trough concentrations (median [25th–75th percentile]) were also lower in patients with EPS (46.4 μg/L [22.2–77.1], $n=4$) than in patients without (99.6 μg/L [57.7–166.8], $n=46$), $p=0.06$. The AUC_{24h} was significantly lower in patients with EPS (1583.0 μg*h/L) than in patients without EPS (3633.0 μg*h/L), $p=0.03$.

3.2.3 Sedation

Sedation scores were available for 50 patients; nine of whom had sedation at least once. For 46 of these patients, measured trough concentrations were available. The median [25th–75th percentile] pipamperone trough concentration was 77.0 μg/L [36.7–132.5] in patients with sedation ($n=6$) vs 114.0 μg/L [59.0–174.5] in patients without sedation ($n=40$), $p=0.32$. The median [25th–75th percentile] *predicted* trough concentration was also non-significantly lower in patients with sedation (61.9 μg/L [38.1–88.9], $n=9$) than patients without sedation (103.8 μg/L [59.9–166.9], $n=41$), $p=0.08$. The AUC_{24h} was significantly lower in patients with sedation than patients without sedation (2050 vs 3852 μg*h/L, $p=0.02$). All patients using benzodiazepines as comedication were not rated as having sedation.

3.2.4 Biochemical Laboratory Parameters

A total of 15 biochemical laboratory measurements were available for $n=8$ patients (all Dutch patients). The median duration (range) of pipamperone use of these patients was 34 months (1–54). During pipamperone treatment, the median (range) prolactin level was 0.3 U/L (0.03–0.46); two patients had decreased levels (both did not have prior treatment with another antipsychotic), while no patients had elevated prolactin levels. The median (range) total cholesterol level was 4.2 mmol/L (3.5–5.1); no patients had elevated total cholesterol levels. The median (range) triglyceride level was 0.71 mmol/L (0.38–2.06); one patient had elevated triglyceride levels (no baseline levels known). Fasting glucose and glycosylated hemoglobin were normal in all patients; the median (range) glucose level was 4.7 mmol/L (4.2–5.6); the median (range) glycosylated hemoglobin level was 32.5 mmol/mol (31–37).

3.3 Predictions

Predicted concentrations with 95% confidence intervals using a twice-daily 30-mg dosing scheme in steady state for a patient of 25 kg, 50 kg, and 75 kg are shown in Fig. 4a. The means (95% confidence intervals) of the predicted pipamperone trough concentrations (population prediction) after a 30-mg dose were 163.2 (67.3–268.9) μg/L for a patient of

25 kg, 103.9 (49.0–167.2) μg/L for a patient of 50 kg, and 79.3 (38.4–124.4) μg/L for a patient of 75 kg. The same predictions were performed with a 0.6-mg/kg dosage in a twice-daily dosing scheme, showing less variability in pipamperone concentrations and better attainment of the pipamperone trough concentration range that was found to be associated with response (Fig. 4b). The means (95% confidence intervals) of the predicted pipamperone trough concentrations (population prediction) after a 0.6-mg/kg dosage were 81.6 (33.6–134.5) μg/L for a patient of 25 kg, 103.9 (49.0–167.2) μg/L for a patient of 50 kg, and 119.0 (57.6–186.7) μg/L for a patient of 75 kg.

4 Discussion

This is the first study that describes the population pharmacokinetics of pipamperone in children and adolescents, and investigates the relationships between pipamperone concentrations, effectiveness, and side effects in this young population. The pediatric pipamperone pharmacokinetics in this study are comparable to adult values found in a previously

Fig. 4 Simulations. **a** Fixed 30-mg dose. Curves represent population predictions with 95% confidence intervals using a twice-daily pipamperone 30-mg dosing scheme in steady state for a child of 25, 50, and 75 kg. **b** 0.6-mg/kg dose. Curves represent population predictions with 95% confidence intervals using a twice-daily pipamperone 0.6-mg/kg dosing scheme in steady state for a child of 25 kg (15 mg), 50 kg (30 mg), and 75 kg (45 mg)

published study by Potgieter et al. [21]. This study found a mean maximum concentration of 263–266 μg/L after a 120-mg dose for three pipamperone products in healthy volunteers (mean weight 76.8 kg), corresponding to a calculated mean volume of distribution of 451–456 L assuming a bioavailability of 100%. In our pediatric study sample, the mean apparent volume of distribution was estimated at 416 L/70 kg. Both in our sample and in the study by Potgieter et al., a high variability was found. Strikingly, another study performed in adults found relatively low pipamperone concentrations after a 40-mg dose, corresponding to a more than two-fold larger calculated volume of distribution of 908 L [22]. Possibly, the bodyweight of the subjects in this latter study was higher, but patient characteristics were not provided. It could also be hypothesized that non-linear pharmacokinetics underlie these differences; however, this was not seen in our sample.

Although well-established reference ranges are lacking for pipamperone, the Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology recommend a therapeutic range between 100 and 400 μg/L for adults with psychotic symptoms [40]. In the absence of studies correlating pipamperone concentrations to clinical effects, this range is based on expected concentrations at an approved dose and derived from the previously mentioned pharmacokinetic study by Potgieter et al. [21].

However, ideally, reference ranges are defined by well-documented concentration–effect relationships in the relevant population [40]. Recently, it has been suggested that the Q1–Q3 (25th–75th percentile) range of psychotropic drug concentrations in responders would be the most optimal means to define preliminary therapeutic ranges based on observationally collected data [41]. In our study, this would result in a suggested pipamperone reference range for children and adolescents of 56.0–180.5 μg/L. Although the indications for use were mostly unknown, it is expected that the main indication concerned behavioral problems associated with autism spectrum disorders, attention-deficit/hyperactivity disorder, and mental retardation, given the major share of these diagnoses in our sample. This range is substantially lower than the suggested range in adults, which might be partly explained by different indications for use, as psychotic symptoms and aggressive behavior are associated with different pathomechanisms. However, this needs further confirmation for pipamperone. Furthermore, the therapeutic reference range for children might be different from the optimal range in adolescents owing to developmental pharmacodynamic changes, which should be investigated in larger prospective trials.

Based on the pipamperone concentration range in responders and the population pharmacokinetics within our sample, several dose recommendations for children and adolescents could be made. First, a twice-daily dosing
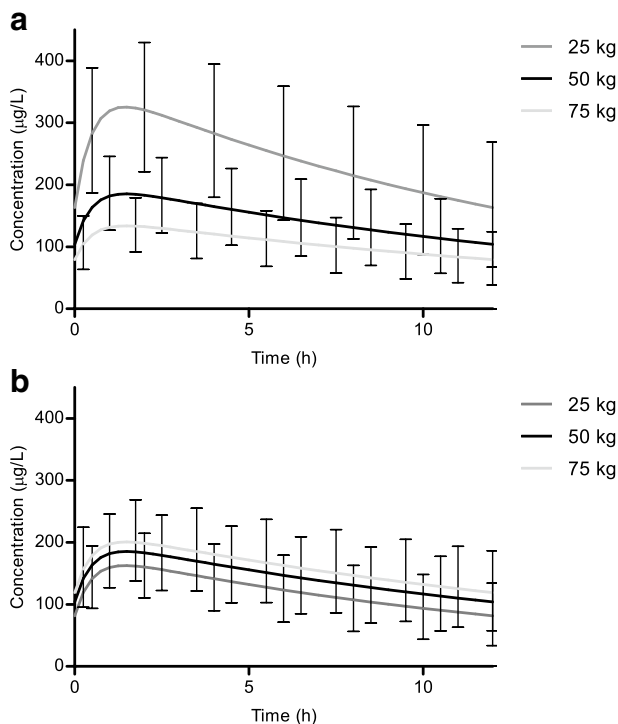
scheme should be sufficient based on the relatively long mean elimination half-life (13 h), as has also been found for adults (12–30 h) [4, 21]. However, current guidelines are not uniform with respect to dosing intervals; while in Germany, a dosing interval of three times per day is advised [15], the Dutch guideline states one to two times a day [16]. Second, a mg/kg dosage seems more appropriate than a fixed dosage, as weight was found to significantly influence the pharmacokinetics. Based on our simulations, a twice-daily 0.6-mg/kg dosage seems appropriate to attain the concentration range that was associated with response. However, given the large variability between patients, some patients might have adequate response with lower dosages, while others need higher dosages. This calls for careful pipamperone dosage titration.

Strikingly, children and adolescents with side effects had lower pipamperone concentrations than subjects without side effects in our study. This is remarkable, as previous studies have found that a higher D_2 receptor occupancy, as a result of higher antipsychotic concentrations, is associated with an increased risk for EPS [42]. Certain children and adolescents might be more susceptible to side effects based on their pharmacodynamic profile, which makes them prone to side effects even at low pipamperone concentrations, preventing a further dosage increase. It might be hypothesized that this is the case for younger children, who have been found to be more vulnerable for other side effects associated with antipsychotic use as well [43]. However, patients with EPS were not generally younger than patients in our sample; neither did patients with EPS have other psychopathology than generally in the sample. Possibly, certain genetic variances underlie the elevated risk, as certain polymorphisms in the dopamine and serotonin receptors have been suggested to be risk factors for antipsychotic-induced side effects in adults [44]. Another explanation is that part of the side effects may be due to the nocebo effect, as with off-label use patients and legal representatives are informed about potential effects and side effects in a very detailed manner. However, it is more likely that side effects have been over-estimated in the Dutch patients, while underestimated in the German patients in our study. While the Dutch patients were enrolled in a clinical trial with structured screening and reporting of side effects, it is expected that in the daily practice of the German TDM service relatively less side effects were reported. As the pipamperone dosages and concentrations were higher in the German sample, this might have led to the finding that higher concentrations are associated with fewer side effects.

In this study, the DBS method was used as pharmacokinetic sampling method next to conventional venipuncture. The DBS method only involves one finger prick for a drug concentration measurement and can be performed in the home setting, which makes it a promising less invasive method for pharmacokinetic sampling in children. The development of a DBS assay requires a thorough validation process before implementation, including the assessment of agreement between DBS samples and simultaneously collected plasma samples in a real-life clinical setting [45]. During this previously performed clinical validation study for pipamperone, the best agreement was found by dividing DBS samples by 0.158 (corresponding to a recovery of ca 16% in DBS) [28]. However, in our model, this conversion of the DBS samples initially led to a clear underestimation of the predicted plasma concentrations. This proportional bias was resolved by a new conversion of DBS concentrations to estimated plasma concentrations, being estimated by the model: DBS/0.33 + 3.90 (see Table 2). However, this finding questions the validity of the clinical validation process in our pediatric population. After consultation with the medical ethics committee, the clinical validation was performed in adults because of ethical concerns.

However, several factors may differentially impact DBS recovery of pipamperone in children vs adults. This could include the amount of interstitial fluid that is collected during the finger prick, which may be more in adults. Furthermore, sampling in children may require more pressure on the finger to collect a full blood spot, and this may have caused hemolysis. Our findings show that results cannot simply be generalized across age groups and performing a clinical validation study in the intended target group should hence be considered. At the same time, in the clinical validation study, a suboptimal agreement was already observed, which was confirmed by the findings in our population.

The results of this study must be considered in the context of its limitations. The pipamperone concentrations were collected in an observational setting with flexible dosing schemes in clinical practice. As has been suggested earlier, this study design is suboptimal to demonstrate concentration–effect relationships [41, 46]. Placebo responders, who generally represent a substantial share of the patients in psychiatry, are likely to receive lower dosages, while nonresponders might receive higher dosages. Additionally, dosages might be lowered when side effects are observed. Therefore, the observed relationships between clinical effects and pipamperone concentrations could be biased. Furthermore, the analyses were performed with two different datasets. The data were collected in two countries, with different clinical and laboratory assessment methods, different inclusion criteria, and prospectively vs retrospectively collected data. The data in Dutch patients were collected by a screening-based method, with questionnaires and screening tools being applied at fixed time points, while in German patients, improvement was retrospectively scored and side effects were only reported at the time of sampling. Possibly, this might have led to an overestimation of side effects in the Dutch patients and an underestimation in the German patients.

As the pharmacodynamic data on response were mainly retrospectively scored and collected in patients with various indications for use, these data did not allow for a more extensive exposure–response analysis. Despite combining the two datasets, the total number of patients was relatively low, and the relatively sparse amount of non-trough pipamperone concentrations might have limited the pharmacokinetic model development. As pipamperone is relatively lipophilic, it is expected to distribute to peripheral tissues. However, our data were possibly too sparse to support a two-compartment model, although a one-compartment model reflected the observed data best. Furthermore, different matrices and analytical methods were used to determine pipamperone concentrations, further increasing variability despite the corrections within the error model for these influences. Last, the influence of metabolizing enzymes such as cytochrome P450 could not be tested. Although the metabolism of pipamperone is assumed to take place in the liver, it is unknown which cytochrome P450 enzyme(s) are involved [40].

5 Conclusions

This study presents the pharmacokinetics and pharmacodynamics of pipamperone in children and adolescents, based on concentrations measured in a real-life clinical setting. Based on our findings, we recommend a twice-daily dosing scheme for pipamperone in this population. Furthermore, bodyweight should be taken into account when dosing pipamperone in children and adolescents. Although more research is needed for the routine application of TDM in children and adolescents, we suggest considerably lower reference ranges than suggested for adults.

Compliance with Ethical Standards

Conflict of interest Teun van Gelder has received lecture fees and study grants from Chiesi and Astellas, in addition to consulting fees from Roche Diagnostics, Vitaeris, Astellas, Aurinia Pharma, and Novartis. Sanne M. Kloosterboer, Karin M. Egberts, Brenda C.M. de Winter, Manfred Gerlach, Manon H.J. Hillegers, Gwen C. Dieleman, Soma Bahmany, Catrien G. Reichart, Emma van Daalen, Mirjam E.J. Kouijzer, Bram Dierckx, and Birgit C.P. Koch have no conflicts of interest that are directly relevant to the content of this article.

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