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A Compilation of Serum Concentrations of 12 Antipsychotic Drugs in a Therapeutic Drug Monitoring Setting

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Background: No comprehensive collection of routine therapeutic drug monitoring data for antipsychotic drugs has been published.

Methods: In this compilation, data on 12 antipsychotics are presented. The drugs included are amisulpride (n = 506), aripiprazole (n = 1610), clozapine (n = 1189), flupentixol (n = 215), haloperidol (n = 390), olanzapine (n = 10,268), perphenazine (n = 1065), quetiapine (n = 5853), risperidone (n = 3255), sertindole (n = 111), ziprasidone (n = 1235), and zuclopenthixol (n = 691). Because only one sample per patient is included, the number of patients equals the number of samples. For each drug, median serum concentrations as well as that of the 10th and 90th percentiles are given for a range of daily doses. Comparisons are made between males and females, between patients younger than 65 years and 65 years and older, and between those treated with a low and a high dose of each drug. The concentration-to-dose (C/D) ratio is the primary variable used in these comparisons. Coefficients of variation (CVs) for the serum concentrations of each drug within and between subjects are presented.

Results: In general, the C/D ratios were higher in females than in males, higher in those 65 years and older than in younger subjects, and lower in those treated with higher doses than in those treated with lower doses. CVs between individuals were larger than within subjects, and the CVs were highest for the drugs with short elimination half-lives.

Conclusions: For each antipsychotic drug, the results presented can serve as a reference tool for pharmacokinetic interpretation of the individual patient's serum drug level. The compiled serum concentrations and the C/D ratios can support the physician's decision when individualizing dosing and determining treatment strategies for a specific patient.

Key Words: antipsychotic drugs, TDM, age, sex, dose

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INTRODUCTION

Antipsychotic drugs are used to treat a wide range of disorders including schizophrenia and other psychoses, bipolar disorder, severe anxiety and depression, behavioral disorders, and dementia.[1] A high proportion of patients treated with antipsychotics do, however, not achieve an adequate clinical response and/or experience adverse drug reactions.[1,2] Moreover, differences in response and adverse effects have been reported between men and women.[3–5] Desired and undesired effects of drugs are related to their concentration at the site of action (ie, for antipsychotics in the central nervous system). Plasma concentrations of antipsychotics have been shown to correlate well with the concentration in the brain.[6] By contrast, because drug concentrations are highly variable when administering the same dose of a drug to a group of patients, the dose given to a patient is a poor predictor of clinical effect.[6] Differences in serum concentrations of antipsychotics at a constant dose within and between individuals are caused by an array of factors, including patient adherence, genetic polymorphisms of drug transporters and metabolizing enzymes, age, sex, concurrent disease, hepatic and renal function, and use of concomitant medications.[7]

Therapeutic drug monitoring (TDM) uses the quantification of drug concentrations in plasma or serum to assist the physician in treatment decisions related to an individual patient. By adjusting the dose, a drug concentration associated with the highest probability of response and the lowest risk adverse drug reactions and toxic effects can be achieved. Serum concentrations of drug metabolites are of importance if the metabolites contribute to the overall clinical effect, but can also be used to calculate the ratio between the concentration of the parent drug and the metabolite, thereby providing a measure of the activity of the enzyme(s) involved in the metabolic step in question.[8] By presenting a comprehensive compilation of a large number of serum concentrations for a drug, a reference tool can be created for appropriate pharmacokinetic interpretation of an individual patient's serum drug level. In addition, by compiling serum

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concentration data found in patients in treatment situations, reference levels for toxicological assessments can be established.[9]

The primary aim of the this study was to present serum concentrations obtained at different daily doses for commonly used antipsychotic drugs by means of TDM in a naturalistic setting. Secondary aims were to describe the serum concentration variability within and between individuals and to compare serum concentrations in women and men, in patients younger than 65 years and 65 years and older, and in patients using high and low doses of a drug.

METHOD

Samples

In the TDM service at the Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway, serum samples from patients treated with antipsychotic drugs are analyzed on request from the responsible physician. Key patient information and the results of the TDM analyses for all samples received since 1999 are stored in a database.

In this study, samples where the following 12 antipsychotic drugs were detected were assessed: amisulpride, aripiprazole, clozapine, flupenthixol, haloperidol, olanzapine, perphenazine, quetiapine, risperidone, sertindole, zuclopenthixol, and ziprasidone. Alimemazine, chlorpromazine, chlorprothixene, dixyrazine, levomepromazine, and thioridazine were not included in this compilation because these antipsychotic drugs are used mainly as needed with uncertain information related to the dose actually ingested. Samples analyzed from October 1999 to 2015 were included. The principles of collection were the same as used in a previously published compilation for antidepressants.[10] In brief, after excluding intramuscular depot injections, one sample per patient was included in the final data set (Table 1). The sample chosen was the first sample from each patient where the daily dose was known. Information on whether the sample was a trough sample obtained under steady state-conditions or not could, in most cases, be derived from the running text found on the requisition forms. Information on concomitant medication was not possible to retrieve. Deliberate or unintentional overdoses were excluded. For the calculations of the coefficient of variation (CV) within and between individuals, data were retrieved from the original database.

The study was approved by the Regional Committee for Medical Research Ethics, Northern Norway, approval number 2016/994-3. According to Norwegian law, it is not necessary to obtain informed consent in scientific studies like the present. As far as the data are retrieved from laboratory routine sample database and anonymized before evaluation and compilation.

Analytical Methods

All antipsychotic drugs were analyzed with liquid chromatography-mass spectrometry methods described

TABLE 1. The Original Database and the Final Data Set Comprising the Number of Patients and Samples Included in the Analyses, Demographic Data of the Patients Evaluated, and Median Daily Doses and Serum Concentrations

	The Original Database*		The Final Data Set†						
Drug	Total No. of Samples	Total No. of Patients	No. of Samples and Patients	Median Age, yrs (Range)	No. of Women (%)	Number of Patients ≥65 years (%)	Median Dose, mg/d (10%–90%)	Median Serum Concentration, nmol/L (10%–90%)	Conversion Factor‡
Amisulpride	1928	636	506	36 (10–85)	206 (41)	24 (4.7)	400 (200–800)	529 (134–1576)	2.71
Aripiprazole	5118	2105	1610	33 (8–92)	799 (50)	64 (4.0)	15 (10–30)	401 (151–915)	2.23
Clozapine	17,592	2038	1189	38 (16–84)	474 (40)	59 (5.0)	350 (150–600)	1067 (341–2348)	3.06
Flupenthixol	1196	507	215	46 (19–91)	126 (58)	25 (11.6)	3 (1–16)	4.3 (1.1–19.3)	2.30
Haloperidol	1429	690	390	50 (0–97)	202 (51)	101 (25.9)	4 (1–20)	6.9 (1.4–34.7)	2.66
Olanzapine	36,400	11,727	10,268	39 (1–98)	4732 (46)	1109 (10.8)	10 (5–20)	82 (29–193)	3.20
Perphenazine	7613	2772	1065	45 (14–95)	595 (56)	185 (17.4)	16 (6–32)	2.0 (0.6–10.3)	2.48
Quetiapine	18,675	7015	5853§	38 (8–99)	3328 (57)	593 (10.1)	400 (100–800)	198 (37–756)	2.61
Risperidone	17,858	6073	3255	40 (6–98)	1585 (49)	532 (16.3)	4 (1–6)	70 (26–166)¶	2.44/2.35‖
Sertindole§	652	255	111	31 (16–64)	51 (46)	0 (0)	16 (8–20)	90 (30–182)	2.27
Ziprasidone	3580	1377	1235	35 (12–84)	674 (55)	39 (3.2)	120 (40–160)	113 (37–300)	2.55
Zuclopenthixol	5765	2013	691	46 (16–95)	332 (48)	106 (15.3)	18 (4–40)	18 (5–65)	2.49

*Includes all available administration forms, that is, intramuscular depot injections as well as oral administration.

†Includes oral administration only. One sample was included per patient; the first sample for which the daily dose was stated on the request form and the serum concentration was quantifiable.

‡To convert from nmol/L to ng/mL, divide the given concentration by the conversion factor.

§The oral depot formulation was introduced in 2007. From the requisition form, it is usually not possible to distinguish between the oral depot and immediate-release formulations. Hence, both formulations are included.

¶The active moiety risperidone + 9-hydroxyrisperidone.

‖For risperidone (2.44) and 9-hydroxyrisperidone (2.35), respectively.

previously.[11–14] In brief, after addition of the internal standards, the drugs were extracted from serum by organic solvents, the extracts were evaporated to dryness with air, and the residuals were reconstituted in methanol. Thereafter, the analytes were separated on C18 columns and quantified on an Agilent MSD 1100 system (Agilent, Palo Alto, CA). Internal standards, usually deuterated, were used. Together with the unknown patient samples, each analytical series contained 7 calibrators covering therapeutic, subtherapeutic, and toxic concentrations. In addition, 6 quality control samples with representative target levels were always included.

The limits of quantitation for the analytes were as follows: Amisulpride 25 nmol/L, aripiprazole and its main metabolite dehydroaripiprazole 25 nmol/L, clozapine and its main metabolite desmethylclozapine 25 nmol/L, flupenthixol 1 nmol/L, haloperidol 1 nmol/L, olanzapine 5 nmol/L, perphenazine 0.5 nmol/L, quetiapine 10 nmol/L, risperidone and its main metabolite 9-hydroxyrisperidone 2.5 nmol/L, sertindole 10 nmol/L, zuclopenthixol 2.5 nmol/L, and ziprasidone 10 nmol/L. Accuracy was controlled routinely with external control samples and precision was calculated from the quality control samples. In general, the interassay CVs were less than 10%. The methods were linear in the concentration ranges achieved by therapeutic use of the drug.

Statistical Analysis

All concentrations are given in nmol/L. To convert from nmol/L to ng/mL, conversion factors for each drug are presented in Table 1. For most calculations, serum concentrations were normalized for daily dose by calculating the concentration–dose (C/D) ratio, that is, the drug concentration (in nmol/L) per milligram drug administered daily.

Parameters used for group comparisons (women vs. men; patients <65 versus ≥ 65 years; patients using a high versus a low dose) were the median parent compound concentration and the median metabolite/parent compound (M/P) concentration ratio at the most common daily doses used in the population. For comparisons between groups, the Mann–Whitney *U* test was used. The daily dose–serum concentration correlation and, when appropriate, daily dose–M/P concentration ratio correlation were analyzed by linear regression.

The CVs for serum concentration and M/P concentration ratio within and between subjects were estimated using a components-of-variance model[15] performed on $\log_{10}$-transformed data here schematically and briefly outlined: The between-subjects mean sum of squares (M) and the within-subject error component (E) based on the number of repeated samples per patient (n) were calculated using analysis of variance. Thereafter, the respective variations were calculated:

1. Between-individual variation = $\sqrt{(M-E)}/n$
2. Within-individual variation = $\sqrt{E}$

To achieve approximate CVs within and between individuals, the respective square root was multiplied by the natural logarithm of 10 (ln 10).

The computer software GraphPad PRISM, version 7.04 (GraphPad Software, La Jolla CA) and IBM SPSS Statistics 24 for Windows (IBM, Armonk, NY) were used for the statistical computations. *P* values < 0.05 were considered statistically significant.

RESULTS

Numbers of samples retrieved from the original database and included in the final data set are presented in Table 1. The 3 drugs with the largest number of patients (and samples) were olanzapine (n = 10,268), quetiapine (n = 5853), and risperidone (n = 3255). Key demographic data for the patients included and overall median daily doses and serum concentrations can be found in Table 1. The concentrations measured (expressed as 10th percentiles, medians, and 90th percentiles) at various daily doses of the drugs are displayed in Table 2.

Comparisons of C/D ratios between men and women and between those younger and $\geq$65 years of age are shown in Table 3. With the exception of sertindole, women had significantly higher C/D ratios than men. Patients 65 years and older had significantly higher C/D ratios than younger ones for all drugs except flupenthixol and ziprasidone. When comparing C/D ratios for the 12 drugs at 2 common dose levels where the higher dose was twice the lower dose, the C/D ratios were in most cases significantly increased at the lower dose level as compared to the higher dose level (Table 4). The relationship between daily doses and M/P ratios for aripiprazole, clozapine, and risperidone is illustrated in Figure 1. The slopes of all regression lines were significantly different from zero ($r^2 = 0.075$; $P = 0.0008$ for dehydroaripiprazole/aripiprazole; $r^2 = 0.171$; $P < 0.0001$ for desmethylclozapine/clozapine; $r^2 = 0.070$; $P < 0.0001$ for 9-hydroxyrisperidone/risperidone).

CVs within and between individuals for the concentrations of the parent antipsychotic drug at the most common daily dose and, when applicable, for the metabolite/parent antipsychotic drug ratio are shown in Table 5. For most drugs, the within-individual CVs were in the range of 30%–50%, with a notable exception for quetiapine, where it was 76%. The between-individual CVs were for most drugs even higher than the corresponding within-individual CVs (Table 5).

DISCUSSION

In this study, we present the most comprehensive compilation of TDM reference concentrations of antipsychotic drugs in a naturalistic setting. The AGNP (Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie) group has recently published updated consensus guidelines for TDM in psychopharmacology.[6] In that review, therapeutic reference ranges of antipsychotics have been recommended when used for their primary indication. A rough comparison with the serum concentrations found in our TDM population shows that most of these concentrations were within the recommended ranges. Concentrations outside these intervals could be caused by numerous factors including noncompliance, genetically determined or disease-related excessively slow (or ultrarapid) drug metabolism, pharmacokinetic interactions, use of doses higher or lower than those

TABLE 2. Parent Substance and Main Metabolite Serum Concentrations in nmol/L (10th Percentile, Median, and 90th Percentile) at Different Daily Doses.

Amisulpride								
Dose	50 mg	100 mg	200 mg	400 mg	600 mg	800 mg	1000 mg	1200 mg
Number of samples	12	23	75	123	64	89	15	15
10th percentile	23	24	96	206	378	382	569	660
Median	64	159	281	443	705	764	1417	1570
90th percentile	361	649	874	1124	1755	1828	3311	6343
Aripiprazole								
Dose	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg		
Number of samples	128	418	568	207	32	215		
10th percentile	73	134	206	247	406	371		
Median	166	285	415	527	685	792		
90th percentile	365	613	764	973	1235	1392		
Dehydroaripiprazole								
10th percentile	42	48	68	84	91	110		
Median	54	95	136	165	191	235		
90th percentile	72	175	231	297	306	396		
Clozapine								
Dose	100 mg	200 mg	300 mg	400 mg	500 mg	600 mg	700 mg	
Number of samples	51	128	178	158	90	87	31	
10th percentile	155	368	380	547	599	545	1000	
Median	549	833	1026	1243	1373	1437	1391	
90th percentile	1276	1644	2060	2333	2547	3275	3108	
N-desmethylclozapine								
10th percentile	85	222	312	337	407	407	655	
Median	323	492	641	803	1017	1082	1082	
90th percentile	784	1247	1306	1555	1816	1956	2364	
Flupenthixol								
Dose	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	10 mg	20 mg
Number of samples	33	33	35	21	17	13	14	7
10th percentile	0.9	1.3	2.1	1.1	1.9	2.2	0.4	0.9
Median	1.8	2.8	4.4	5.4	12.2	6.5	12.1	18.3
90th percentile	3.4	9.7	7.4	11.5	31.0	26.1	35.7	69.3
Haloperidol								
Dose	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg	16 mg	20 mg
Number of samples	50	61	24	43	20	17	20	13
10th percentile	1.0	2.5	3.9	3.5	7.3	7.9	15.5	10.7
Median	2.8	5.7	7.9	11.2	14.7	14.4	21.5	27.0
90th percentile	8.2	11.4	26.3	28.2	59.4	30.2	56.9	75.8
Olanzapine								
Dose	2.5 mg	5 mg	7.5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Number of samples	245	1194	675	3190	1853	2139	229	409
10th percentile	10	18	28	31	48	56	60	77
Median	21	39	59	70	98	119	137	166
90th percentile	40	83	113	141	197	241	290	336
Perphenazine								
Dose	4 mg	8 mg	12 mg	16 mg	20 mg	24 mg	32 mg	40 mg
Number of samples	62	194	129	281	41	138	73	19
10th percentile	0.4	0.4	0.5	0.6	0.6	1.2	1.1	2.3
Median	1.1	1.3	1.2	1.9	2.6	3.7	5.4	6.7
90th percentile	4.8	4.6	6.2	8.2	8.9	12.3	19.4	75.0
Quetiapine								
Dose	50 mg	100 mg	200 mg	300 mg	400 mg	600 mg	800 mg	1000 mg
Number of samples	252	474	633	718	888	832	495	110
10th percentile	16	27	36	59	60	90	89	157

(*continued on next page*)

TABLE 2. (*Continued*) Parent Substance and Main Metabolite Serum Concentrations in nmol/L (10th Percentile, Median, and 90th Percentile) at Different Daily Doses.

Median	46	85	140	205	217	328	335	430
90th percentile	151	272	499	573	693	1053	952	1406
Risperidone								
Dose	0.5 mg	1 mg	2 mg	4 mg	6 mg	8 mg		
Number of samples	95	332	660	886	409	125		
10th percentile	3	3	3	3	3	3		
Median	6	9	12	16	21	43		
90th percentile	23	32	50	84	132	173		
9-hydroxyrisperidone								
10th percentile	4	8	12	22	29	42		
Median	12	21	33	56	77	92		
90th percentile	36	54	73	103	150	183		
Risperidone + 9-hydroxyrisperidone								
10th percentile	10	16	25	42	52	76		
Median	20	33	50	81	121	157		
90th percentile	47	81	107	155	227	280		
Sertindole								
Dose	8 mg	12 mg	16 mg	20 mg				
Number of samples	12	36	32	21				
10th percentile	22	39	30	57				
Median	51	95	82	130				
90th percentile	101	155	231	252				
Ziprasidone								
Dose	40 mg	60 mg	80 mg	100 mg	120 mg	160 mg	200 mg	240 mg
Number of samples	118	76	343	33	233	320	26	18
10th percentile	22	27	32	48	45	56	76	69
Median	57	83	97	124	126	156	162	211
90th percentile	149	183	227	371	316	389	360	669
Zuclopenthixol								
Dose	4 mg	8 mg	10 mg	12 mg	16 mg	20 mg	30 mg	40 mg
Number of samples	57	28	104	26	28	141	53	36
10th percentile	2.0	4.9	6.5	3.7	6.9	7.0	10.4	13.0
Median	7.0	10	16	20	22	22	36	47
90th percentile	15	45	40	39	50	54	95	127

Doses with few available samples are excluded from the table.

recommended for the main indication of the drug, and concentrations not representing trough levels of the drugs.

Dose-adjusted serum concentrations were significantly higher in women than in men for all drugs except sertindole and quetiapine. For sertindole, the difference in the median C/D ratio was about the same numerically as for the other drugs. Because there is no biological rationale that sertindole should be an exception with this respect, we consider this nonsignificant result to be caused by a power issue due to the low number of patients (n = 111) included. Several factors might explain the generally higher concentrations in women than in men, including differences in hepatic clearance of drugs, caused by a lower liver volume in women and/or by differential expression of cytochrome P-450 (CYP) and uridine diphosphate glucuronosyltransferase (UGT) enzymes.[16,17] Interestingly, the differences were numerically larger for typical CYP1A2 substrates (eg, clozapine and olanzapine) than for typical CYP2D6 substrates (eg, perphenazine), consistent with the larger difference in expression between sexes for CYP1A2 than for CYP2D6. A factor adding to the CYP1A2 difference could be that males more often than females are smokers. Notably, quetiapine was the only drug for which the concentration was lower in women than in men. This is consistent with the fact that, in contrast to other CYP enzymes, the activity of CYP3A4 has been found to be higher in women than in men, and quetiapine is the most typical CYP3A4 substrate among the drugs included in this study. The same general pattern as in our study has been observed in previous studies of the most commonly used second-generation antipsychotics,[3,5,18–21] although studies on ziprasidone, amisulpride, and aripiprazole have not been able to demonstrate any sex-related differences.[5,22–24] Finally, it should be taken into account that possible variations in compliance for antipsychotics between males and females[13] could add complexity to the understanding of the sex differences observed.

TABLE 3. Median Concentration/Dose (C/D) Ratios in (nmol/L)/(mg/D) for all Subjects, Men and Women, and Subjects Younger and Older Than 65 Years.

Drug	All Patients	Men	Women	*P*, Women versus men	Patients <65 yrs	Patients ≥65 yrs	*P*, ≥65 versus <65 yrs
Amisulpride	1.19	1.09	1.47	**<0.0001**	1.15	2.29	**<0.0001**
Aripiprazole	27.9	26.5	29.2	**0.0002**	27.8	32.2	**0.01**
Clozapine	3.12	2.72	3.82	**0.03**	3.04	4.95	**<0.0001**
Flupenthixol	1.44	1.18	1.60	**0.0007**	1.43	1.60	0.18
Haloperidol	1.45	1.32	1.60	**0.004**	1.40	1.58	**0.049**
Olanzapine	6.80	4.95	7.87	**<0.0001**	6.47	9.40	**<0.0001**
Perphenazine	0.15	0.13	0.17	**<0.0001**	0.14	0.25	**<0.0001**
Quetiapine	0.61	0.63	0.59	**0.04**	0.58	0.88	**<0.0001**
Risperidone*	23.1	21.0	26.0	**<0.0001**	21.7	36.0	**<0.0001**
Sertindole	6.50	6.32	7.50	0.25	6.50	—†	—†
Ziprasidone	1.13	1.07	1.24	**0.002**	1.13	1.30	0.33
Zuclopenthixol	1.35	1.25	1.50	**0.01**	1.25	1.71	**0.001**

For numbers of samples included in the different groups, see Table 1. *P* values <0.05 are shown in bold.
*For the active moiety risperidone + 9-hydroxyrisperidone.
†No patients were older than 65 years.

Dose-adjusted serum concentrations were significantly higher in patients 65 years and older for all antipsychotic drugs except flupenthixol and ziprasidone (for sertindole, no subjects older than 65 years were included in the study). Again, we consider these apparent exceptions caused by a type II error due to the low number of elderly included (n = 25 for flupenthixol and n = 39 for ziprasidone). The fact that elderlies have higher C/D ratios is generally consistent with the results from previous studies.[18–20,25,26] The most comprehensive previous study of age effects on clozapine, olanzapine, risperidone, and quetiapine concentrations has been published by our group, using information from the same database as in this study.[21] That study illustrates that "elderly" should not be viewed as a homogenous group and that the increases in concentrations are particularly prominent from about 80 years of age. The age effect was most pronounced for clozapine, where subjects aged 80 and 90 years, respectively, on average had dose-adjusted concentrations 2-fold and 3-fold higher than those aged 40 years. Thus, in patients of advanced age, dose reductions should be even larger than what could be anticipated based on the differences in C/D ratios between younger and older subjects presented in Table 3.

All drugs except aripiprazole, flupenthixol, haloperidol, and sertindole displayed lower C/D ratios at the higher dose levels compared with the lower dose levels. Again, we suspect that the nonsignificant differences for these 4 drugs are related to type II errors. For drugs exhibiting linear (first-order) kinetics, including those included in this study, the C/D ratio should principally be the same irrespective of dose. In general, for drugs with zero-order kinetics, the C/D ratio should increase and not decrease with increasing dose. As the C/D ratio expresses the inverse value of the oral clearance, what we have found is an increased clearance with higher

TABLE 4. Comparison of Concentration/Dose (C/D) Ratios for the Parent Substances at Two Common Dose Levels Where the Higher Daily Dose is Twice the Lower

Drug	Doses Compared	C/D Ratio, Lower Dose	C/D Ratio, Higher Dose	*P*
Amisulpride	200 and 400 mg	1.41	1.11	**0.049**
Aripiprazole	10 and 20 mg	28.5	26.4	0.053
Clozapine	200 and 400 mg	4.17	3.11	**<0.0001**
Flupenthixol	2 and 4 mg	1.43	1.35	0.35
Haloperidol	4 and 8 mg	1.43	1.40	0.93
Olanzapine	10 and 20 mg	7.00	5.95	**<0.0001**
Perphenazine	8 and 16 mg	0.16	0.12	**0.0002**
Quetiapine	300 and 600 mg	0.68	0.55	**<0.0001**
Risperidone*	2 and 4 mg	25.0	20.3	**<0.0001**
Sertindole	8 and 16 mg	6.38	5.10	0.71
Ziprasidone	80 and 160 mg	1.21	0.98	**0.0001**
Zuclopenthixol	10 and 20 mg	1.60	1.10	**<0.0001**

All C/D ratios are given in (nmol/L)/(mg/d). *P* values <0.05 are shown in bold.
*For the active moiety risperidone + 9-hydroxyrisperidone.

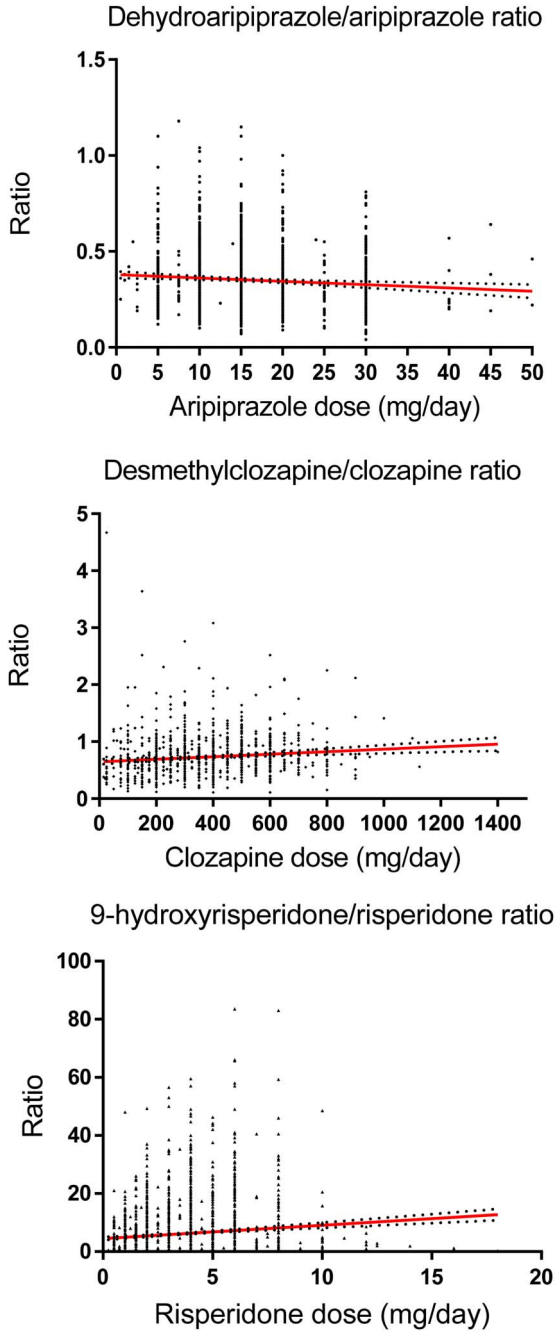

FIGURE 1. The daily dose–metabolite/parent substance ratios for aripiprazole, clozapine, and risperidone correlation were analyzed by linear regression (regression lines with 95% confidence intervals). Two extreme ratios (3.71 and 1.52, respectively) were excluded from the dehydroaripiprazole/aripiprazole figure, one ratio (36.5) was excluded from the desmethylclozapine/clozapine figure, and one ratio (300) was excluded from the 9-hydroxyrisperidone/risperidone figure. The slopes of the regression lines were significantly different from zero ($r^2 = 0.007$; $P = 0.0008$ for dehydroaripiprazole/aripiprazole; $r^2 = 0.01$ $P < 0.0001$ for desmethylclozapine/clozapine; $r^2 = 0.01$; $P < 0.0001$ for 9-hydroxyrisperidone/risperidone).

dose (C_{ss} = (dose/Δt)/Cl; where C_{ss} is the concentration in steady state, Δt is the time interval between 2 doses, and Cl is clearance). We consider this effect to be a logical consequence of the naturalistic and nonrandomized design of our study, where those having an inherent higher clearance tend to be treated with a higher dose just to compensate for their increased clearance, thereby achieving the same therapeutic effect as in those having a lower clearance. It can also be speculated whether the use of TDM in fact could amplify this effect as it might be tempting to adjust the dose when the serum concentration of a drug is outside what could be considered as "normal".

The correlation between daily dose and the M/P ratio for an antipsychotic drug is expected to be zero when linear pharmacokinetics prevails. In our study, however, the M/P ratio decreased with dose for aripiprazole, whereas it increased for clozapine and risperidone. As increased clearance of the parent antipsychotic drug causes a decrease in the M/P ratio, the effect seen for clozapine and risperidone could be caused by the same phenomenon as described above. It is harder to explain the effect on aripiprazole, but is should be noted that although statistically significant, the slopes were close to zero.

The within-individual variations in the serum concentrations were generally lower than the between-individual variations. Moreover, for aripiprazole and clozapine, the variability of the M/P ratio was lower than that of respective parent drug. A larger-than-normal within-individual variation has previously been suggested as a tool to identify noncompliant patients.[8] The within-individual perspective is also useful when a possible interacting medication is introduced or stopped in a patient, or if somatic comorbidity occurs. Not surprisingly, the variability was largest for drugs with short elimination half-lives such as quetiapine and ziprasidone (about 7 hours for both). The even shorter elimination half-life of risperidone (about 3 hours) is not mirrored in the variability of this drug, as the CV presented in Table 5 is based on the sum of risperidone and its active metabolite 9-hydroxyrisperidone, which have a considerably longer elimination half-life. However, these differential elimination half-lives also explained the high variability in the M/P ratio of risperidone because risperidone itself is found in the denominator of this ratio.

This study has some strengths and weaknesses that should be addressed. One of the main limitations is that no structured or detailed information were available on time intervals from last dose to sampling, concomitant medication used, or whether steady state was achieved. Other shortcomings are the lack of information on body weight and smoking habits of the patients. Information on ethnic background and CYP enzyme genotype could also have added interesting data. It is also unknown whether the subjects included are representative for the whole population of patients using antipsychotic drugs, and it is not known to what degree the patients were adherent to the treatment. However, the naturalistic design of this study could also be considered an advantage, and the study included more than 26,000 patients in the final data set, which may

TABLE 5. Coefficients of Variation Within and Between Individuals for the Concentrations Found at the Most Typical Dose Used for Each of the Antipsychotic Drugs Included

Drug (Dose) [Metabolite/Parent Substance Ratio]	Patients (n)/Samples (n)	Within-Patient CV (%)	Between-Patient CV (%)
Amisulpride (400 mg/d)	20/47	39	63
Aripiprazole (15 mg/d)	699/1311	32	43
[Dehydroaripiprazole/aripiprazole]	699/1311	21	36
Clozapine (300 mg/d)	424/1195	39	52
[Desmethylclozapine/clozapine]	424/1195	32	23
Flupenthixol (3 mg/d)	46/61	37	49
Haloperidol (4 mg/d)	81/119	45	54
Olanzapine (10 mg/d)	4348/8134	41	50
Perphenazine (16 mg/d)	435/660	45	80
Quetiapine (400 mg/d)	1351/2010	76	67
Risperidone (4 mg/d)	1301/2181	37	43
[9-hydroxyrisperidone/risperidone]	1301/2181	68	126
Sertindole (12 mg/d)	80/123	41	46
Ziprasidone (160 mg/d)	459/831	55	42
Zuclopenthixol (20 mg/d)	255/379	42	69

When applicable (ie, for aripiprazole, clozapine, and risperidone), CVs for the metabolite/parent substance ratios are also included.

counterbalance the possible impact the inaccuracies mentioned above would have on the principal results found. We also consider it a strength that only one sample per patient has been included because this would reduce the influence of outliers, which could otherwise be expected to be represented with a higher number of samples than the average patient.

Although we had a large total sample, it would have been advantageous to have more samples for some drugs, such as sertindole and flupenthixol. However, the few samples for these drugs reflect that they are infrequently used, thereby reducing the impact of the uncertainties related to the results for these drugs in clinical practice. Nevertheless, for most drugs, there were too few subjects of advanced age to be able to subdivide elderly patients according to exact age. No data were available for the antipsychotics approved most recently, such as paliperidone and lurasidone. However, data for these drugs are emerging, as exemplified by the recently published preliminary report from our group on 310 TDM samples obtained after administration of the long-acting injectable formulation of paliperidone.[27]

CONCLUSIONS

The data shown in this study represent a naturalistic population of patients using antipsychotics comprising both sexes, all ages, various comorbidities, and all possible concomitant medications. For each of the 12 antipsychotic drugs evaluated, the results presented can serve as a reference tool for pharmacokinetic interpretation of an individual patient's drug level. The compiled serum concentrations and the C/D ratios can thus support the physician when individualizing dosing and determining treatment strategies for a specific patient.

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