Effect of Co-medication on the Serum Concentrations of Aripiprazole and the Main Metabolite Dehydroaripiprazole

Thesis submitted for the degree Candidate Pharmaciae at
Department of Pharmaceutical Biosciences, School of Pharmacy,
The Faculty of Mathematics and Sciences,
University of Oslo

Ragnhild Birkeland Waade
November 2007

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Work performed at Department of Psychopharmacology,
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Ragnhild Birkeland Waade

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Abbreviations

ARI – aripiprazole

AUC – area under the plasma concentration versus time curve

C/D ratio – serum concentration/dose

CYP 450 – cytochrome P450

DARI – dehydroaripiprazole

EDTA – ethylenediaminetetraacetic acid

EM – extensive metabolizer

EPS – extrapyramidal symptoms

HEM – heterozygous extensive metabolizer

LC – liquid chromatography

MS – mass spectrometry

PCR – polymerase chain reaction

PM – poor metabolizer

SDS – sequence detection software

SNP – single nucleotide polymorphism

SPC – summary of product characteristics

TDM – therapeutic drug monitoring

UGT – UDP-glucuronosyltransferase

UM – ultrarapid metabolizer

Abstract

Background: Aripiprazole is a relatively new antipsychotic drug with a partial dopamine agonist activity. It is metabolized by cytochrome P450 2D6 (CYP2D6) and CYP3A4 to an active metabolite, dehydroaripiprazole. Studies on pharmacokinetic drug interactions are so far limited. Thus, the aim of the present study was to investigate the impact of different co-medications on the serum concentration of aripiprazole and the active metabolite dehydroaripiprazole in psychiatric patients in a clinical setting.

Method: Psychiatric patients that had routine drug monitoring of aripiprazole performed at the Department of Psychopharmacology, Diakonhjemmet Hospital, as part of clinical follow-up and control of drug treatment were included in the study. A total of 360 patient samples were distributed in different co-medication groups according to information of co-medication given on the requisition forms. Patient samples with no co-medication constituted the control group. Steady state dose-adjusted serum concentrations (concentration/dose ratios) of aripiprazole, dehydroaripiprazole and the sum of aripiprazole and dehydroaripiprazole, and the metabolic ratio (dehydroaripiprazole/aripiprazole) in the different co-medication groups were compared to the control group.

Results: The present analysis showed that co-administration of a CYP3A4 inducer decreased the mean concentration/dose ratio (C/D ratio) of aripiprazole, dehydroaripiprazole and the sum of aripiprazole and dehydroaripiprazole by 69% ($p<0.01$), 75% ($p<0.001$) and 70% ($p<0.001$), respectively. Further, combination with a CYP2D6 inhibitor increased the C/D ratio of aripiprazole by 35% ($p<0.05$), with a corresponding decrease in dehydroaripiprazole by 26% ($p<0.05$). When aripiprazole was co-administered with lithium, a 43% ($p<0.05$) increase in aripiprazole C/D ratio was obtained, whereas there was no effect on the C/D ratio of dehydroaripiprazole. Olanzapine, perphenazine, risperidone injection, escitalopram and lamotrigine also obtained statistically significant effects on aripiprazole disposition, but to a lesser extent. The other psychotropic drugs assessed (clozapine, quetiapine, risperidone tablets, mirtazapine, sertraline, venlafaxine, clonazepam and valproate) did not show an apparent effect on aripiprazole disposition.

Conclusion: In the present study, the drugs most commonly used in combination with aripiprazole were investigated with respect to possible pharmacokinetic drug interactions. The only co-medications which appeared to require dosage adjustments for aripiprazole were

the CYP3A4 inducers and, surprisingly, lithium. The other drug interactions observed were of uncertain clinical importance.

1. Introduction

1.1 Variation in drug response

Inter-individual variability in drug response for two patients on the same drug dosage may be significant. This variability may be caused by variation in pharmacokinetics and/or pharmaco-dynamics. Patient factors, such as sex, age, organ function and co-morbidity, and also environmental factors like smoking, diet and an individual's belief in treatment (placebo/ nocebo) may potentially contribute to this variation (Sirot 2006). Genetic factors, especially in drug metabolizing enzymes, may account for up to 95 percent of inter-individual differences in serum concentration of drugs (Kalow 1998). Another important contribution to pharmaco-kinetic variability is concomitant medication which can cause pharmacokinetic interactions, e.g. by affecting drug metabolizing enzymes or transporters (Sirot 2006). Identification of patient characteristics and other factors contributing to variation in drug response is of great importance in order to achieve a more individualized drug therapy.

1.2 Drug metabolism

Drugs may be metabolized by many different sequential and/or competitive chemical processes, which comprise phase I metabolism by oxidative, reductive or hydrolytic reactions and/or phase II metabolism (e.g. glucuronidation and acetylation).

The cytochrome P-450 (CYP) enzyme system

The cytochrome P-450 (CYP) enzyme system is a superfamily of metabolic phase I enzymes (isoenzymes). CYP enzymes oxidise endogenous and exogenous compounds, including many drugs, making them less lipid soluble and preparing them for phase II metabolism and finally for excretion. The most important CYP enzymes in the metabolism of psychotropic drugs are CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (Dahl 2002). The activity of the different CYP-enzymes shows great inter- and intra-individual variation. For CYP3A4 and CYP1A2 this variation is mostly due to environmental factors, while for CYP2D6, CYP2C9 and CYP2C19 a majority of the inter-individual variability may be explained by genetic variability (Dahl 2002; Ingelman-Sundberg 2004). Genes that exist in different variants, because of evolutionary mutations, are termed polymorphic. Genetic polymorphism refers to a genetic variant of a gene that occurs with a frequency of at least 1% in a population (Ma 2004).

A population can be divided into four different subgroups reflecting the number of functional genes encoding an isoenzyme. The different genotypes will contribute to different capacity of metabolism and thereby different drug exposure, which may involve risks for side effects or failure of drug therapy. Extensive metabolizers (EM) have no mutations and therefore have two active alleles (wild type), producing fully active enzyme. About 50% of Caucasians are CYP2D6 EM (Bradford 2002). Individuals with one active allele and one defective allele are denominated heterozygous extensive metabolizers (HEM). HEM appear with a frequency of about 41% among Caucasians (Bradford 2002), and most often display a slightly reduced metabolic capacity. Poor metabolizers (PM) comprise individuals carrying zero active alleles, and therefore do not produce active enzyme. This results in a complete lack of metabolic capacity through this enzyme, and thereby increased exposure of parent drug and decreased exposure of metabolite if the parent drug and not the metabolite is metabolized by the polymorphic enzyme. This results in an increased risk of overdose and side effects with standard dosing of a drug that is mainly metabolized by this enzyme. About 8% of Caucasians are CYP2D6 PM (Bradford 2002). Ultrarapid metabolizers (UM) carrying more than two active alleles due to the presence of a replicating mutant are only described for CYP2D6 (Johansson 1993). UM metabolize drugs faster than EM, and need higher doses of drug to avoid failure of drug therapy if the parent drug, and not the metabolite, is responsible for the pharmacological activity. Subjects with up to 13 gene copies have been identified (Dalén 1999). The frequency of CYP2D6 UM is about 1% in Caucasians (Dahl 1995). Until recently, UM were only described for the CYP2D6 enzyme. However, in 2006 a novel gene variant of CYP2C19, denominated CYP2C19*17, resulting in an ultrarapid phenotype in patients carrying this mutation, was reported (Sim 2006).

UDP-glucuronosyltransferase (UGT) enzymes
The UDP-glucuronosyltransferase (UGT) enzymes are a superfamily of metabolic phase II enzymes, which catalyze the glucuronidation of various endogenous substances (e.g. bilirubin) and exogenous compounds (e.g. drugs), making them more water-soluble (Tukey 2000). UGT-catalyzed glucuronidation reactions are responsible for about 35% of all drugs metabolized by phase II enzymes (Evans 1999). The human UGT superfamily is comprised of 2 families (UGT1 and UGT2) and 3 subfamilies (UGT1A, UGT2A, and UGT2B) (Mackenzie 1997), thus being classified in the same way as the CYP enzyme superfamily. Genetic polymorphism has also been described for several of the human UGT genes (Miners 2002).

1.3 Tools for individualized drug treatment

Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring (TDM) is a frequently used tool to optimize pharmacotherapy and the measured serum concentrations aids physicians in performing rational drug dosage adjustments to reduce the risk of side effects or therapeutic failure. The fundamental basis for TDM is the hypothesis that the serum concentration of a drug reflects the concentration at the site of action better than the dose. TDM is also based on the assumption that there is a definable relationship between serum concentration and clinical effects (therapeutic effects, adverse effects and toxicity) (Sirot 2006). Drug dosage, time interval between last drug intake and sample withdrawal and information on co-medications are key parameters in order to achieve interpretable results that can lead to informed dose adjustments based on measured serum levels (Sirot 2006). Trough steady state concentrations are generally the basis for reference serum levels. Blood sampling should therefore be performed at least 4-5 drug elimination half-life periods after initiation of aripiprazole treatment or after any change in dose, and during the terminal elimination phase after drug administration. The appropriate sampling time for most drugs in clinical practice is immediately before the next dose (12-24 hours after the last drug intake) (Sirot 2006). The reference concentration interval is preferably a therapeutic concentration window providing a beneficial response in most patients or alternatively a concentration range that most patients obtain at therapeutically documented doses (Baumann 2004b).

Metabolism of a drug gives pharmacologically active or pharmacologically inactive metabolites, or both. When drug and metabolite display similar pharmacologic activity, the reference interval is usually based on the concentration sum of both agents. Even when the metabolites do not contribute to the pharmacological effect of a drug, the analysis of the metabolites may give useful information on the metabolic state of the patient, or on his compliance (Baumann 2004b).

TDM is frequently applied in psychiatry because of the existence of a large inter-individual pharmacokinetic variability for most psychotropic drugs (Preskorn 1993). In addition, indications for TDM of psychotropic drugs frequently encountered in clinical situations include suspected noncompliance, therapy failure or insufficient response even if doses are considered adequate, drugs with a small therapeutic range (e.g. lithium), adverse effects

despite the use of generally recommended doses, known drug interactions in combination treatment and suspected drug interactions (Baumann 2004a). TDM is also beneficial for patient groups like the elderly, children and adolescents, patients with pharmacokinetically relevant co-morbidities (hepatic and renal insufficiency), lactating and pregnant women.

CYP genotyping

Psychiatric patients are in many cases receiving psychotropic drugs for a long period of time or for life. The pharmacological treatment frequently comprises several concomitant drugs and the treatment regimen is often changed during the progression of the disease. In addition, several of the antipsychotic drugs are metabolized by polymorphic enzymes (Dahl 2002). For these reasons, CYP genotyping may be beneficial in psychiatric patients. In clinical practice CYP genotyping is frequently used to explain observations of unexpected serum concentrations in relation to a given dose, failure of drug therapy and/or side effects in patients already receiving drugs. However, knowledge of a patient's genotype prior to initiation of drug therapy gives the opportunity to better choose a suitable medication and starting dose. CYP genotyping prior to drug treatment therefore provides a better chance of avoiding failure of drug therapy or side effects and, thus, may decrease the risk of poor compliance (Kirchheiner 2001).

1.4 Schizophrenia

Schizophrenia affects about 1% of the population (Lewis 2000), and is associated with disturbances in dopamine pathways of the mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular tracts (Keltner 2002). The main clinical features of the disease are positive symptoms (delusions, hallucinations, thought disorder and abnormal behaviour) and negative symptoms (loss of motivation, withdrawal from social contacts and flattening of emotional responses). In addition, deficits in basic cognitive functions (e.g. attention, memory) are often present, together with depression and anxiety (Lewis 2000).

1.5 Aripiprazole

Pharmacodynamics of aripiprazole

All antipsychotics, both traditional and atypical, up to the year 2002, created their antipsychotic effect by dopamine 2 (D_2) receptor antagonism. Aripiprazole (Abilify®), launched in the United States in 2002 and in Europe in 2004, is a new atypical antipsychotic

drug developed for the treatment of schizophrenia (Travis 2005). Like the other atypical antipsychotics, aripiprazole displays antagonistic action at serotonin 2A ($5HT_{2A}$) receptors (Davies 2004). However, aripiprazole differs from other atypical antipsychotics by a partial agonism at D_2 and $5HT_{1A}$ receptors. A partial agonist can act as an agonist or as an antagonist, depending on the target receptor population and the local concentrations of the natural neurotransmitter (Tamminga 2002). Thus, a dopamine partial agonist will stimulate dopamine receptors at low dopamine levels, and inhibit dopamine receptors at high dopamine levels (Stahl 2001).

Due to the mechanism of action aripiprazole has been described as "a dopamine-serotonin system stabilizer" (Davies 2004) and "the first next generation atypical antipsychotic" (Keltner 2002; Winans 2003; Mauri 2007). Its unique pharmacologic profile includes a lower $5HT_{2A}/D_2$ affinity ratio (Roth 2003) and a different side effect profile (Kane 2002; Marder 2003) from all other atypical antipsychotic drugs. Aripiprazole treatment is associated with a low potential for sedation, EPS (extrapyramidal symptoms), hyperprolactinemia, cardiovascular and metabolic side effects, and observed side effects appear to be due mainly to partial agonism at D_2 receptors (e.g. nausea, vomiting, agitation, insomnia, exacerbation of psychosis) (Kane 2002; Marder 2003).

Pharmacokinetics of aripiprazole

Aripiprazole is extensively metabolized by CYP3A4 and the polymorphic enzyme CYP2D6 in the liver (Figure 1.1) and the major metabolite, dehydroaripiprazole, has similar D_2 activity as the parent drug (Mauri 2007). Dehydroaripiprazole is a substrate for CYP3A4 (Citrome 2007). Involvement of other enzymes or alternative metabolic pathways of aripiprazole have not yet been described. The influence of genetic polymorphism in CYP2D6 on the disposition of aripiprazole has recently been described (Hendset 2007). This study showed that CYP2D6 PM obtained an increase in systemic exposure of both aripiprazole and the active sum of aripiprazole and dehydroaripiprazole in psychiatric patients compared to CYP2D6 EM. At steady state approximately 40% of the plasma aripiprazole concentration is represented by dehydro-aripiprazole (Mauri 2007), and the active metabolite may therefore be relevant for the clinical effect of aripiprazole treatment. In TDM the active sum of aripiprazole and dehydro-aripiprazole is monitored.

The mean elimination half-lives of aripiprazole and dehydroaripiprazole are about 75 and 94 hours, respectively. Aripiprazole is well absorbed and the oral bioavailability of the tablet formulation is approximately 90%, with peak plasma concentrations being reached within 3-5 hours. Effective clinical doses are usually between 10 to 30 mg/day (SPCa), and a linear pharmacokinetic profile has been observed at doses between 5 and 30 mg/day (Mallikaarjun 2004). At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to plasma proteins, primarily to albumin (SPCa; DeLeon 2004).

Aripiprazole

CYP2D6

CYP3A4

Dehydroaripiprazole
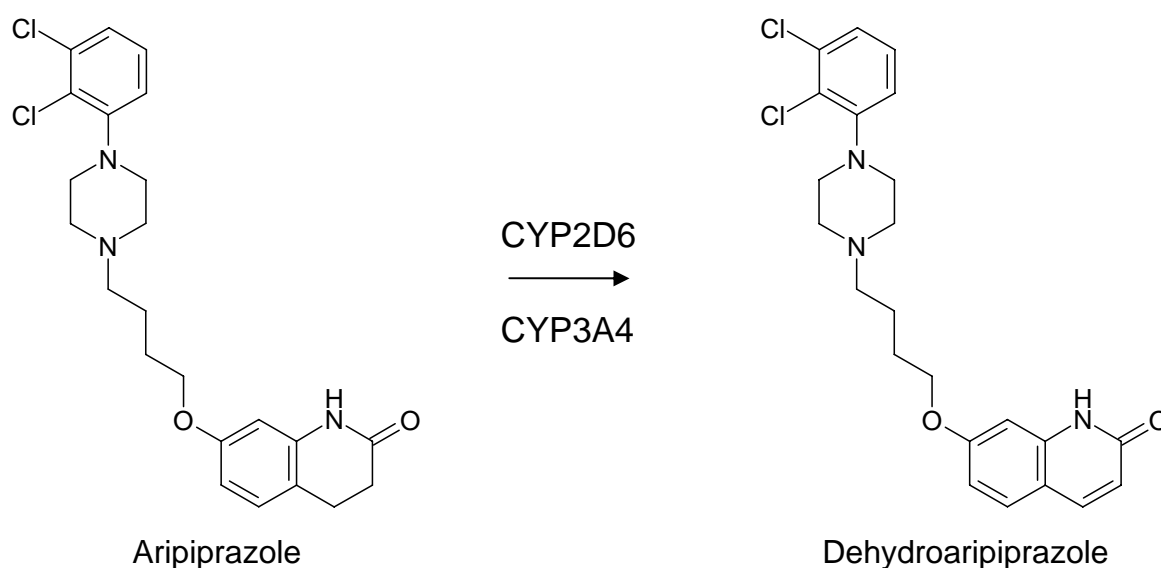
Figure 1.1 Chemical structure of aripiprazole and dehydroaripiprazole, and the metabolizing enzymes responsible for dehydroaripiprazole formation.

Aripiprazole is a relatively new drug, and therefore very few studies on possible drug interactions have been conducted so far. Although data is limited, the possible influence of drugs affecting CYP2D6 and CYP3A4-mediated metabolism on aripirazole disposition have been investigated to some extent. Concomitant use of aripiprazole and the CYP3A4 inducer carbamazepine decreased the systemic exposure of both aripiprazole and dehydroaripiprazole by 70% (Citrome 2007). Correspondingly, administration of the CYP3A4 inhibitor itraconazole with aripiprazole resulted in an increase of the systemic exposure of aripiprazole and dehydroaripiprazole by 48% and 39%, respectively. This implies that both aripiprazole and dehydroaripiprazole are metabolized by CYP3A4. Drug interactions are also observed for aripiprazole and the CYP2D6 inhibitor quinidine. This study revealed an increase of

aripiprazole systemic exposure by 110%, whereas that of dehydroaripiprazole decreased by 35% (SPCa). Two studies on aripiprazole and concomitant lithium demonstrated an increased systemic exposure of aripiprazole by 15% (Citrome 2005) and 34% (Castberg 2007). Further, concomitant use of aripiprazole and valproate resulted in a 24% reduction in systemic exposure of aripiprazole (Citrome 2005; Castberg 2007).

1.6 Aim

Published data on drug interactions with aripiprazole are so far limited. The purpose of the present study was therefore to investigate the impact of different co-medications on the serum concentration of aripiprazole and the active metabolite dehydroaripiprazole in psychiatric patients in a clinical setting.

2. Material and methods

2.1 Patient population and study design

The material was collected from a routine TDM service database at Department of Psychopharmacology, Diakonhjemmet Hospital. The TDM database was screened for all patients receiving aripiprazole as part of their clinical treatment. All patients with serum analysis of aripiprazole performed in the period October 2005 to April 2007 were included in the study. Multiple samples available from the same patient were also included. The serum samples were taken as part of standard clinical follow-up and routine control of drug treatment. The Department of Psychopharmacology, Diakonhjemmet Hospital, also performs CYP genotyping as a routine service. For patients that had CYP genotyping performed as part of their clinical follow-up, the genotyping results were recorded.

Prior to exclusion, the number of serum samples was 1189. Exclusion criteria were as follows: sample withdrawal less than 10 hours or more than 30 hours after last drug intake, steady state conditions not confirmed and high probability of poor compliance. Steady state condition was defined as stable dose of aripiprazole for at least 10 days prior to blood sampling. This was confirmed from information given on the requisition forms or from the patient history in the TDM database. If there were previously performed serum samples of aripiprazole on the same dose as given on the requisition form, and if it was not likely that the dose had changed in between samplings, it was regarded as steady state conditions. Poor compliance was defined when this was stated on the requisition forms or detected from review of the patients' TDM history.

After exclusion, 360 samples were included for further analysis. Information regarding serum concentrations of aripiprazole and dehydroaripiprazole, CYP2D6 genotype, time interval between last drug intake and sample withdrawal, drug dosage, sex and age was recorded. The requisition forms were reviewed in order to identify currently prescribed co-mediacation. The study was approved by the Regional Committee for Medical Research Ethics.

2.2 Analysis of aripiprazole and dehydroaripiprazole

The method was developed for routine TDM analysis at Department of Psychopharmacology, Diakonhjemmet Hospital, and has previously been described in detail (Molden 2006). Briefly,

serum samples were purified by protein precipitation at 4°C (0.5 ml serum and 1.0 ml acetonitrile:methanol/90:10 including the internal standard in a concentration of 1 µmol/L). Determination of aripiprazole and dehydroaripiprazole in 10 µL of the purified samples was performed by liquid chromatographic (LC) separation and tandem mass spectrometric (MS/MS) detection. The instrument consisted of an Alliance HT 2795 HPLC pump and a Quattro Micro triple quadrupole mass spectrometer (both Waters, Milford, MA). Separation was obtained on a C18 analytical column (Ace 3 AQ 100 x 2.1 mm, 3 µm, Advanced Chromatography Technologies, Aberdeen, Scotland) by gradient elution (20-80% acetonitrile in 10 mM ammonium acetate buffer pH 4.5; flow rate 0.25 mL/min). The gradient continued for 7.5 minutes followed by a 2 minute isocratic column wash (80% acetonitrile phase) and a 5 minute isocratic column re-equilibriation (20% acetonitrile phase). Retention times of aripiprazole and dehydroaripiprazole were approximately 6.0 and 6.6 minutes, respectively. The m/z transitions 448 → 285 (aripiprazole) and 446 → 285 (dehydroaripiprazole) were detected in the positive electrospray ionization mode.

Calibration curves for aripiprazole and dehydroaripiprazole were linear in the ranges 40 to 1600 nmol/L and 20 to 600 nmol/L, respectively, with imprecision and deviation of 6% or less (Hendset 2007). The lower limit of quantification, defined as a peak-noise ratio greater than 10, was 2 nM for both aripiprazole and dehydroaripiprazole. All samples were above the lower limit of quantification. One patient had a serum concentration of aripiprazole outside the range of the calibration curve (2921 nmol/L).

Reference material of aripiprazole was provided by Bristol-Myers Squibb (Oslo, Norway), while dehydroaripiprazole was synthesized by Synthetica (Oslo, Norway). The internal standard promazine (not registered for clinical use in Norway) was purchased from SigmaAldrich, St. Louis, MO.

2.3 CYP2D6 genotyping

CYP2D6 genotyping is a routine service at Department of Psychopharmacology, Diakonhjemmet Hospital. For CYP genotyping, blood samples were collected in tubes containing EDTA as anticoagulant. Genomic DNA was extracted from leucocytes by E.Z.N.A® Blood DNA Kits II (Omega Bio-tek, Doraville, GA 30362, USA). All the polymerase chain reaction (PCR) amplification was carried out using an Applied Biosystem 7500 Real-Time PCR instrument with Sequence Detection Software (SDS), Version 1.3

(Applied Biosystem, CA 94404, USA). Copynumber (duplication and deletion) analysis was performed by PCR using a specific set of allele amplification primers (Schaeffeler 2003). CYP2D6*3, *4, *6, *7 and *8 mutations were determined by use of a long-range PCR amplifying the whole CYP2D6 gene, followed by multiplex allele specific PCR. The pre-amplification was diluted with water and used as template for two separate PCR reactions in the multiplex allele-specific PCR. The PCR reaction mix for each reaction was containing genomic DNA, specific primers, nucleoside triphosphates (dATP, dGTP, dCTP and dTTP), $MgCl_2$ or $Mg(OAc)_2$, buffer and ddH_2O. AmpliTaq Gold DNA Polymerase was used in the multiplex PCR. High fidelity DNA Polymerase was used in the copynumber reactions, and the rTth DNA Polymerase was used in the long-range PCR. The samples were separated by electrophoresis, and the fragments were compared with albumin as a molecular weight marker, an internal reference gene which was co-amplified simultaneously in a single-tube biplex assay. Single nucleotide polymorphism (SNP) analysis positive controls representative of each genotype and negative or no template controls were included in each assay. For analysis of CYP2D6 copynumber, patient samples with known genotype (normal, duplication and deletion) were used as controls.

2.4 Data analysis and statistical methods

SPSS® Software version 15.0 (SPSS Inc., Chicago, USA) was used for statistics, and GraphPad Prism version 4 was used as software for graphics. The patient samples were distributed in different co-medication groups denominated aripiprazole + escitalopram, aripiprazole + lithium, aripiprazole + olanzapine etc. Aripiprazole combined with CYP2D6 inhibitors and CYP3A4 inducers, respectively, constituted separated co-medication groups. Some of the samples appeared in several different co-medication groups, as patients often received multiple combinations of drugs. Samples from patients co-medicated with drugs known or highly suspected to interact with aripiprazole (the CYP2D6 inhibitors fluoxetine, paroxetine and levomepromazine (dose>200 mg/day), and the CYP3A4 inducers carbamazepine, phenytoin and phenobarbital) were excluded from the other groups of co-medication, to control bias. Patient samples with no co-medication constituted the control group. Levomepromazine has been reported to be an inhibitor of CYP2D6 (Syvalahti 1986; Brøsen 1991), though not in low doses (Yoshimura 2005). In this study levomepromazine in high doses (>200 mg/day) (SPCb) was regarded as a CYP2D6 inhibitor.

All serum concentrations of aripiprazole, dehydroaripiprazole and the sum of aripiprazole and dehydroaripiprazole were dose-adjusted (C/D ratios; nM/mg per day) as the patients received different doses of aripiprazole, ranging from 5 to 45 mg. Differences in all C/D ratios (aripiprazole, dehydroaripiprazole and the sum of aripiprazole and dehydroaripiprazole) and in the metabolic ratio (dehydroaripiprazole/aripiprazole) between the control group and the different co-medication groups were evaluated by mixed model analysis. The C/D ratios and the metabolic ratio were log-transformed prior to analysis, and then transformed back to original scale after analysis to be presented as geometric mean values with 95% confidence intervals. A comparison of the distribution of sex between the control group and the different co-medication groups was not performed, as the male/female distribution previously was shown not to significantly influence on aripiprazole pharmacokinetics (Molden 2006). Differences in distribution of age, dose and time interval between last drug intake and sample withdrawal between the control group and the different co-medication groups with eight samples or more were evaluated by a two-tailed, nonparametric Mann-Whitney test. Statistical significance was considered as $p<0.05$.

3. Results

A total of 360 samples from 222 patients were included, and the male/female sample distribution was 193/167. The mean age among the samples was 33.4 (range 12-86). Among the 59 of the 222 patients (27%) that had been genotyped the distribution of CYP2D6 polymorphism was as follows: EM: 36 (61%); HEM: 17 (29%); PM: 5 (8%); UM: 1 (1.7%). This was more or less in accordance with the distribution of genetic polymorphism in CYP2D6 among Caucasians (Bradford 2002). In 72% of the patients, aripiprazole was co-administered with other psychotropic drugs. The remaining 28% constituted the control group, with a total of 94 samples. Among the 360 samples, 138 combinations of co-medication were recorded and the mean number of co-medications was 1.5 (range 0-8). No patients received CYP3A4 inhibitors. All co-medication groups consisting of 10 samples or more, with the exception of CYP3A4 inducers (n=2) and lithium (n=8), were evaluated.

3.1 Combination of aripiprazole and CYP2D6 inhibitors

A total of 10 patients (14 samples) received aripiprazole in combination with a CYP2D6 inhibitor (fluoxetine n=9, paroxetine n=3 and levomepromazine >200 mg/day, n=2). There was a significant difference in distribution of age ($p<0.05$) between the CYP2D6 inhibitor group and the control group (Table 3.1). On average, the C/D ratio of aripiprazole was 35%

Table 3.1 Characteristics of patients receiving aripiprazole monotherapy or aripiprazole in combination with CYP2D6 inhibitors.

	ARI	ARI + SUM CYP2D6 inhibitors
Subjects (male/female)	62 (36/26)	10 (4/6)
Samples (male/female)	94 (56/38)	14 (4/10)
Age (year)[1]	33 ± 11	27* ± 11
Dosage (mg/day)[1]	18 ± 8	16 ± 9
Sample time (h)[1, 2]	19 ± 6	22 ± 5
C/D ratio ARI (nM/mg)[3]	26.8 (24.2-29.5)	36.3* (28.4-46.6)
C/D ratio DARI (nM/mg)[3]	9.3 (8.4-10.1)	6.9* (5.4-8.7)
C/D ratio ARI + DARI (nM/mg)[3]	36.6 (33.5-40.0)	43.3 (34.6-54.1)
DARI/ARI[3]	0.35 (0.32-0.38)	0.19** (0.15-0.23)
EM[4]	13 (6)	1 (1)
HEM[4]	3 (3)	0
PM[4]	1 (1)	0
UM[4]	1 (1)	0

[1]Data are presented as mean of samples ± SD; [2]Time interval between last drug intake and sample withdrawal; [3]Data are presented as geometric mean (95% confidence interval); [4]Data are presented as number of samples with number of subjects in parenthesis.
* Significantly different ($p<0.05$) from the control group; ** Significantly different ($p<0.001$) from the control group.
C/D, dose-adjusted serum concentrations; ARI, aripiprazole; DARI, dehydroaripiprazole; EM, extensive metabolizers; HEM, heterozygous extensive metabolizers; PM, poor metabolizers; UM, ultrarapid metabolizers.

higher in patients receiving aripiprazole and a CYP2D6 inhibitor compared to the control group ($p<0.05$) (Table 3.1, Figure 3.1 a). Correspondingly, the C/D ratio of dehydro-aripiprazole and the metabolic ratio (dehydroaripiprazole/aripiprazole) was approximately 26% ($p<0.05$) and 46% ($p<0.05$) lower, respectively, in patients receiving aripiprazole and a CYP2D6 inhibitor compared to the control group (Figure 3.1 b and d). In addition, the C/D ratio of the sum of aripiprazole and dehydroaripiprazole was 18% higher compared to the control group, but the difference was not statistically significant (Figure 3.1 c).
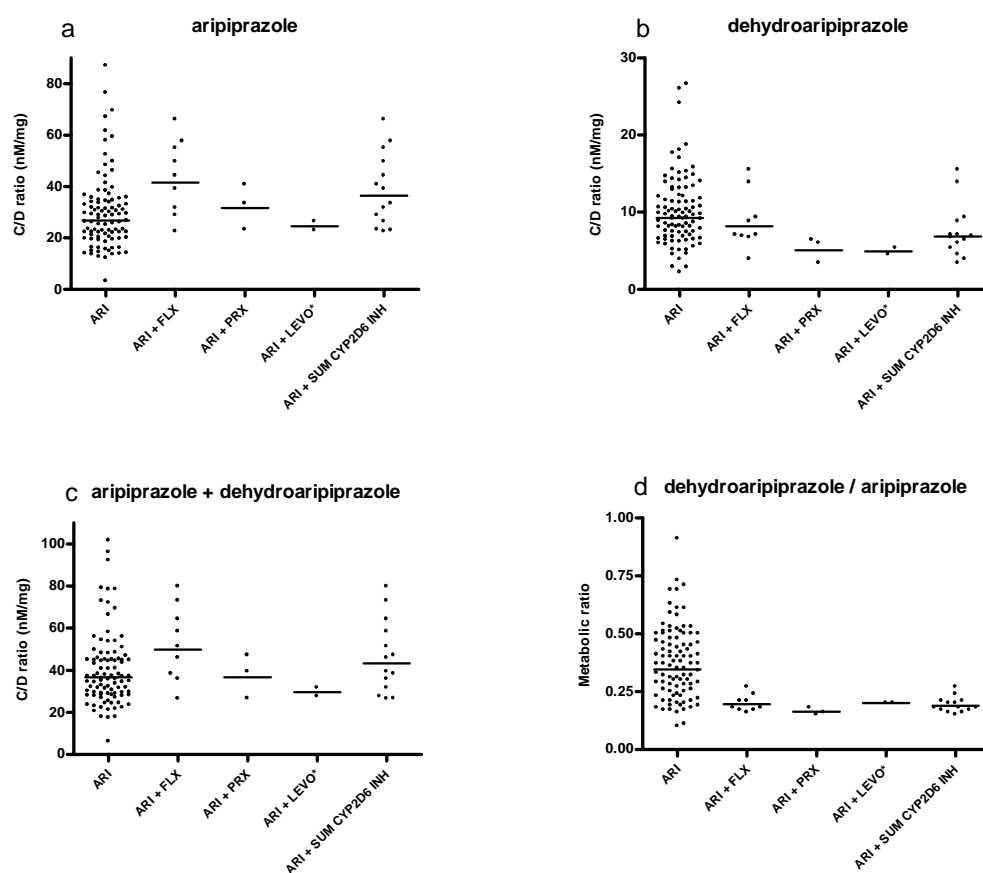
Figure 3.1 Steady state serum concentration-to-dose (C/D) ratios of **(a)** aripiprazole, **(b)** dehydroaripiprazole, **(c)** aripiprazole + dehydroaripiprazole and **(d)** metabolic ratio (dehydroaripiprazole/aripiprazole) for aripiprazole alone and aripiprazole combined with CYP2D6 inhibitors. The horizontal lines indicate the geometric mean values in each group estimated in mixed model analyses; see **Table 3.1** for details and statistics. ARI: aripiprazole; FLX: fluoxetine; PRX: paroxetine; LEVO: levomepromazine; INH: inhibitors. *dose > 200 mg/day.

3.2 Combination of aripiprazole and lithium

There were 8 samples from 6 patients receiving aripiprazole combined with lithium. A significant difference in distribution of time interval between last drug intake and sample
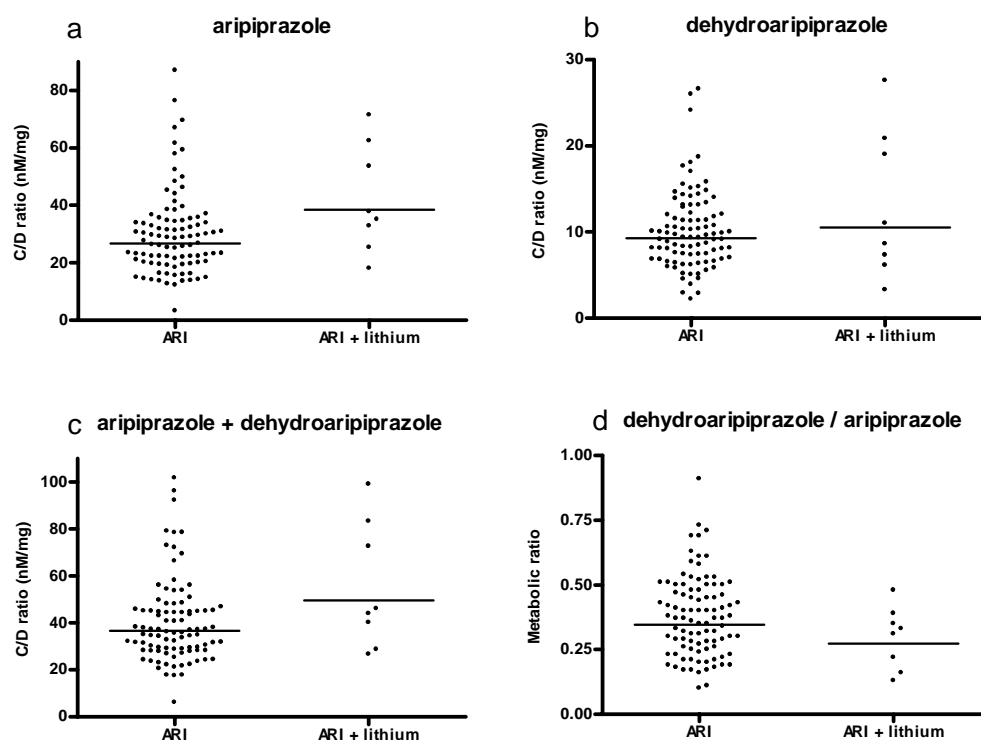
Table 3.2 Characteristics of patients receiving aripiprazole monotherapy or aripiprazole in combination with lithium.

	ARI	ARI + lithium
Subjects (male/female)	62 (36/26)	6 (1/5)
Samples (male/female)	94 (56/38)	8 (1/7)
Age (year)[1]	33 ± 11	39 ± 10
Dosage (mg/day)[1]	18 ± 8	16 ± 4
Sample time (h)[1, 2]	19 ± 6	14* ± 4
C/D ratio ARI (nM/mg)[3]	26.8 (24.2-29.5)	38.4** (27.4-53.8)
C/D ratio DARI (nM/mg)[3]	9.3 (8.4-10.1)	10.6 (7.6-14.7)
C/D ratio ARI + DARI (nM/mg)[3]	36.6 (33.5-40.0)	49.7 (36.7-67.2)
DARI/ARI[3]	0.35 (0.32-0.38)	0.27 (0.20-0.37)
EM[4]	13 (6)	0
HEM[4]	3 (3)	1 (1)
PM[4]	1 (1)	0
UM[4]	1 (1)	0

[1]Data are presented as mean of samples ± SD; [2]Time interval between last drug intake and sample withdrawal; [3]Data are presented as geometric mean (95% confidence interval); [4]Data are presented as number of samples with number of subjects in parenthesis.
* Significantly different ($p<0.01$) from the control group; ** Significantly different ($p<0.05$) from the control group.
C/D, dose-adjusted serum concentrations; ARI, aripiprazole; DARI, dehydroaripiprazole; EM, extensive metabolizers; HEM, heterozygous extensive metabolizers; PM, poor metabolizers; UM, ultrarapid metabolizers.

Figure 3.2 Steady state serum concentration-to-dose (C/D) ratios of **(a)** aripiprazole, **(b)** dehydroaripiprazole, **(c)** aripiprazole + dehydroaripiprazole and **(d)** metabolic ratio (dehydroaripiprazole/aripiprazole) for aripiprazole alone and aripiprazole combined with lithium. The horizontal lines indicate the geometric mean values in each group estimated in mixed model analyses; see **Table 3.2** for details and statistics. ARI: aripiprazole.

withdrawal ($p<0.01$) between the lithium group and the control group was observed (Table 3.2). On average, the C/D ratio of aripiprazole was approximately 43% higher in patients receiving a combination of aripiprazole and lithium compared to the control group ($p<0.05$) (Table 3.2, Figure 3.2 a).

3.3 Combination of aripiprazole and CYP3A4 inducers

There were only 2 samples from 2 patients receiving aripiprazole in combination with CYP3A4 inducers (carbamazepine n=1, phenytoin and phenobarbital n=1). A comparison of the distribution of age, dose or time interval between last drug intake and sample withdrawal between the CYP3A4 inducer group and the control group was not performed due to few samples in the CYP3A4 inducer group (n=2). On average, the C/D ratios of aripiprazole,
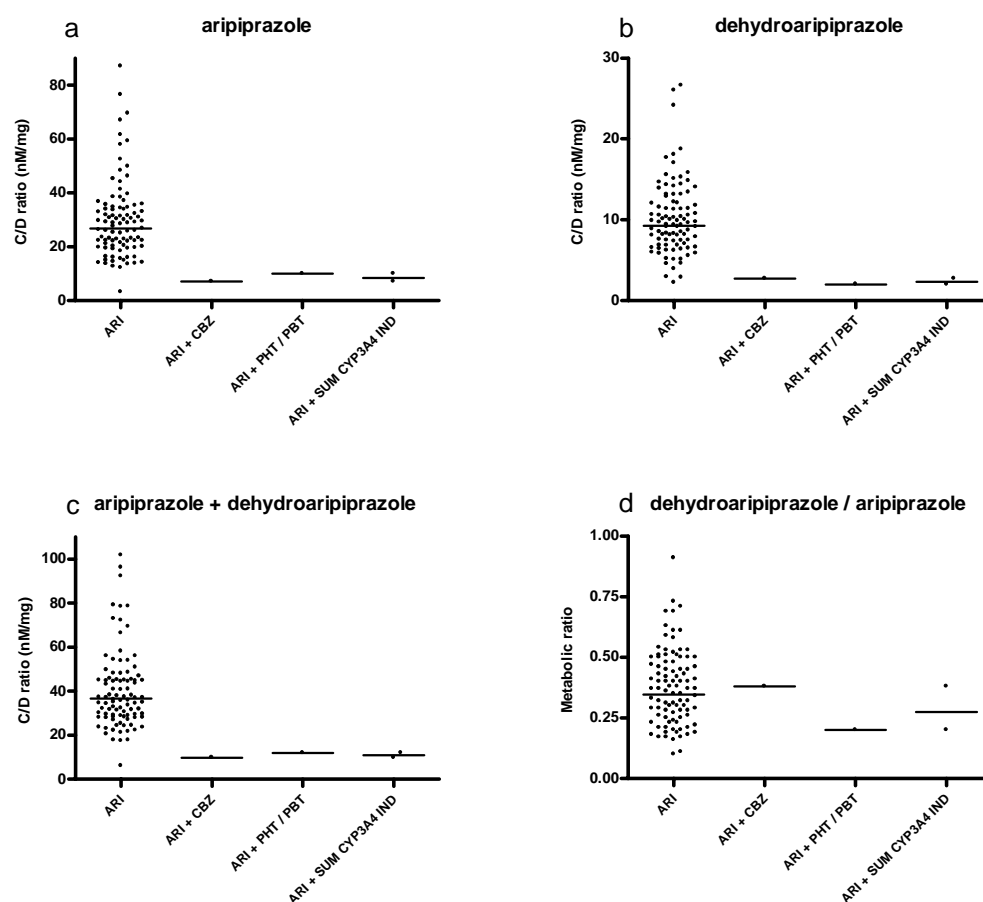

Figure 3.3 Steady state serum concentration-to-dose (C/D) ratios of **(a)** aripiprazole, **(b)** dehydroaripiprazole, **(c)** aripiprazole + dehydroaripiprazole and **(d)** metabolic ratio (dehydroaripiprazole/aripiprazole) for aripiprazole alone and aripiprazole combined with CYP3A4 inducers. The horizontal lines indicate the geometric mean values in each group estimated in mixed model analyses; see **Table 3.3** for details and statistics. ARI: aripiprazole; CBZ: carbamazepine; PHT: phenytoin; PBT: Phenobarbital; IND: inducers.

dehydroaripiprazole and the sum of aripiprazole and dehydroaripiprazole were approximately 69% ($p<0.01$), 75% ($p<0.001$) and 70% ($p<0.001$) lower, respectively, in patients receiving aripiprazole and a CYP3A4 inducer compared to the control group (Figure 3.3, Table 3.3).

Table 3.3 Characteristics of patients receiving aripiprazole monotherapy or aripiprazole in combination with CYP3A4 inducers.

	ARI	ARI + SUM CYP3A4 inducers
Subjects (male/female)	62 (36/26)	2(2/0)
Samples (male/female)	94 (56/38)	2(2/0)
Age (year)[1]	33 ± 11	37 ± 10
Dosage (mg/day)[1]	18 ± 8	20 ± 14
Sample time (h)[1,2]	19 ± 6	25 ± 1
C/D ratio ARI (nM/mg)[3]	26.8 (24.2-29.5)	8.4* (4.3-16.5)
C/D ratio DARI (nM/mg)[3]	9.3 (8.4-10.1)	2.3** (1.2-4.3)
C/D ratio ARI + DARI (nM/mg)[3]	36.6 (33.5-40.0)	10.9** (6.0-19.7)
DARI/ARI[3]	0.35 (0.32-0.38)	0.28 (0.15-0.51)
EM[4]	13 (6)	0
HEM[4]	3 (3)	0
PM[4]	1 (1)	0
UM[4]	1 (1)	0

[1]Data are presented as mean of samples ± SD; [2]Time interval between last drug intake and sample withdrawal; [3]Data are presented as geometric mean (95% confidence interval); [4]Data are presented as number of samples with number of subjects in parenthesis.
* Significantly different ($p<0.01$) from the control group; ** Significantly different ($p<0.001$) from the control group.
C/D, dose-adjusted serum concentrations; ARI, aripiprazole; DARI, dehydroaripiprazole; EM, extensive metabolizers; HEM, heterozygous extensive metabolizers; PM, poor metabolizers; UM, ultrarapid metabolizers.

3.4 Combination of aripiprazole and antipsychotics

A total of 175 samples included aripiprazole in combination with at least one other antipsychotic drug (clozapine n=42, olanzapine n=52, perphenazine n=10, quetiapine n=28, risperidone injection n=21 and risperidone tablets n=11). There was a significant difference in distribution of dose for the clozapine ($p<0.01$) and risperidone injection ($p<0.001$) groups, respectively, compared to the control group (Tables 3.4 and 3.5). Further, there was a significant difference in distribution of time interval between last drug intake and sample withdrawal ($p<0.01$) between the perphenazine group and the control group (Table 3.4). On average, the metabolic ratio (dehydroaripiprazole/aripiprazole) was 23% lower in patients receiving aripiprazole combined with olanzapine compared to the control group ($p<0.001$) (Table 3.4, Figure 3.5 d), but no significant differences were detected in the C/D ratios between the two groups. Concomitant intake of clozapine or quetiapine did not significantly affect the disposition of aripiprazole (Table 3.4). On average, the C/D ratios of aripiprazole and the sum of aripiprazole and dehydroaripiprazole was approximately 75% ($p<0.01$) and 60% ($p<0.01$) higher, respectively, in patients receiving aripiprazole and perphenazine compared to the control group (Table 3.4, Figure 3.6 a and c). Correspondingly, the metabolic

ratio (dehydroaripiprazole/aripiprazole) was 31% lower in patients receiving aripiprazole and perphenazine compared to the control group ($p<0.01$) (Figure 3.6 d).

Table 3.4 Characteristics of patients receiving aripiprazole monotherapy or aripiprazole in combination with the antipsychotics clozapine, olanzapine, perphenazine or quetiapine.

	ARI	ARI + CLOZ	ARI + OLA	ARI + PPZ	ARI + QUE
Subjects (male/female)	62 (36/26)	20 (11/9)	37 (17/20)	8 (5/3)	21 (7/14)
Samples (male/female)	94 (56/38)	42 (27/15)	52 (27/25)	10 (7/3)	28 (10/18)
Age (year)[1]	33 ± 11	37 ± 11	35 ± 11	42 ± 16	31 ± 10
Dosage (mg/day)[1]	18 ± 8	15* ± 5	18 ± 7	16 ± 6	17 ± 8
Sample time (h)[1,2]	19 ± 6	20 ± 6	18 ± 6	25* ± 2	19 ± 6
C/D ratio ARI (nM/mg)[3]	26.8 (24.2-29.5)	26.1 (22.7-30.0)	30.1 (26.3-34.5)	47.0* (34.3-64.5)	28.1 (23.6-33.6)
C/D ratio DARI (nM/mg)[3]	9.3 (8.4-10.1)	9.5 (8.4-10.7)	8.0 (7.0-9.1)	11.1 (8.3-15.0)	8.5 (7.2-10.1)
C/D ratio ARI + DARI (nM/mg)[3]	36.6 (33.5-40.0)	36.0 (31.8-40.7)	38.6 (34.1-43.7)	58.6* (44.1-77.8)	37.1 (31.7-43.5)
DARI/ARI[3]	0.35 (0.32-0.38)	0.36 (0.32-0.41)	0.27** (0.24-0.30)	0.24* (0.18-0.31)	0.30 (0.26-0.36)
EM[4]	13 (6)	5 (3)	8 (6)	2 (2)	6 (4)
HEM[4]	3 (3)	2 (1)	12 (6)	1 (1)	5 (4)
PM[4]	1 (1)	0	2 (2)	2 (1)	2 (1)
UM[4]	1 (1)	0	0	0	0

[1]Data are presented as mean of samples ± SD; [2]Time interval between last drug intake and sample withdrawal; [3]Data are presented as geometric mean (95% confidence interval); [4]Data are presented as number of samples with number of subjects in parenthesis.
* Significantly different ($p<0.01$) from the control group; ** Significantly different ($p<0.001$) from the control group.
C/D, dose-adjusted serum concentrations; ARI, aripiprazole; DARI, dehydroaripiprazole; CLOZ, clozapine; OLA, olanzapine; PPZ, perphenazine; QUE, quetiapine; EM, extensive metabolizers; HEM, heterozygous extensive metabolizers; PM, poor metabolizers; UM, ultrarapid metabolizers.
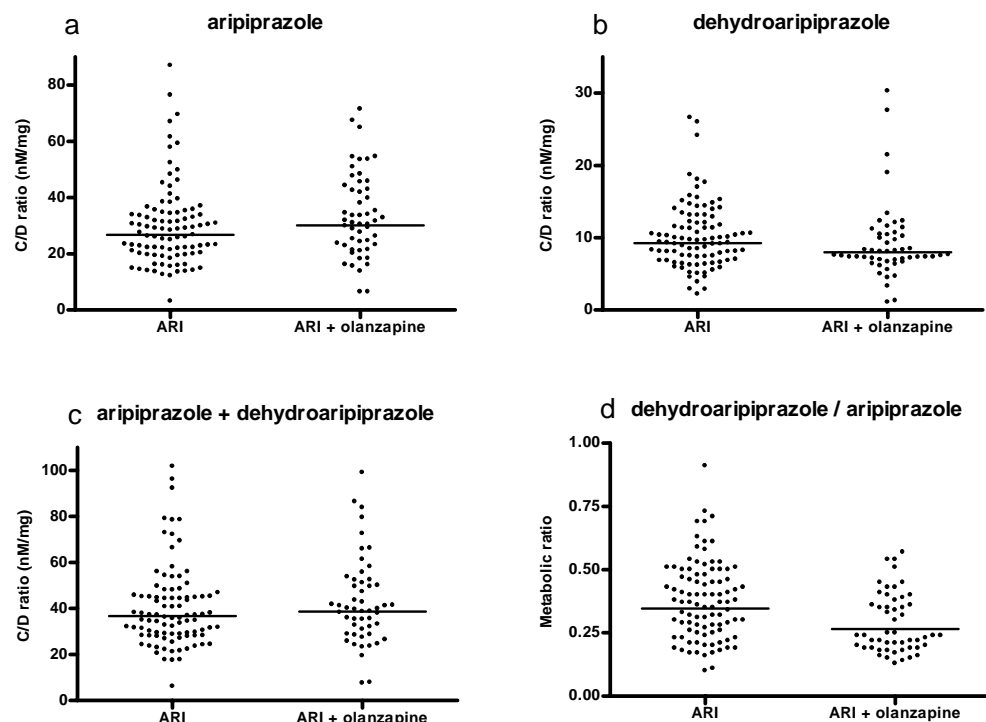
Figure 3.5 Steady state serum concentration-to-dose (C/D) ratios of **(a)** aripiprazole, **(b)** dehydroaripiprazole, **(c)** aripiprazole + dehydroaripiprazole and **(d)** metabolic ratio (dehydroaripiprazole/aripiprazole) for aripiprazole alone and aripiprazole combined with olanzapine. The horizontal lines indicate the geometric mean values in each group estimated in mixed model analyses; see **Table 3.4** for details and statistics. ARI: aripiprazole.
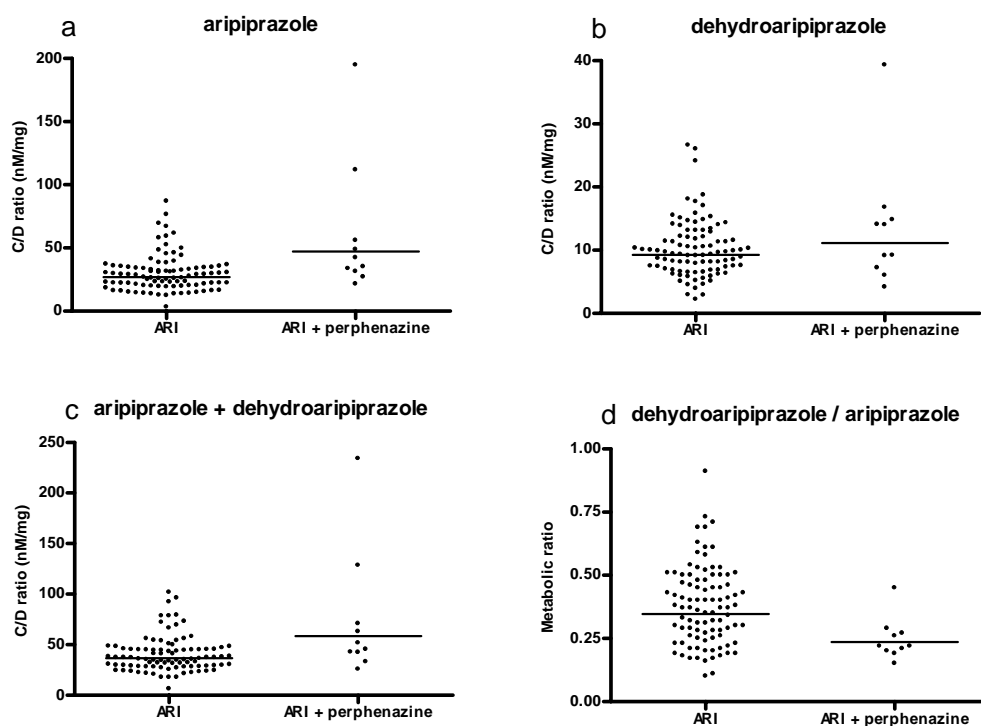
Figure 3.6 Steady state serum concentration-to-dose (C/D) ratios of **(a)** aripiprazole, **(b)** dehydroaripiprazole, **(c)** aripiprazole + dehydroaripiprazole and **(d)** metabolic ratio (dehydroaripiprazole/aripiprazole) for aripiprazole alone and aripiprazole combined with perphenazine. The horizontal lines indicate the geometric mean values in each group estimated in mixed model analyses; see **Table 3.4** for details and statistics. ARI: aripiprazole.

Table 3.5 Characteristics of patients receiving aripiprazole monotherapy or aripiprazole in combination with the antipsychotics risperidone injection or risperidone tablets.

	ARI	ARI + risperidone injection	ARI + risperidone tablets
Subjects (male/female)	62 (36/26)	10 (8/2)	10 (9/1)
Samples (male/female)	94 (56/38)	21 (17/4)	11 (10/1)
Age (year)[1]	33 ± 11	34 ± 11	35 ± 15
Dosage (mg/day)[1]	18 ± 8	27* ± 9	19 ± 9
Sample time (h)[1, 2]	19 ± 6	20 ± 6	19 ± 6
C/D ratio ARI (nM/mg)[3]	26.8 (24.2-29.5)	22.6 (18.3-27.8)	27.1 (20.4-36.0)
C/D ratio DARI (nM/mg)[3]	9.3 (8.4-10.1)	6.7** (5.6-8.1)	9.6 (7.4-12.5)
C/D ratio ARI + DARI (nM/mg)[3]	36.6 (33.5-40.0)	29.6*** (24.5-35.7)	37.3 (29.0-47.9)
DARI/ARI[3]	0.35 (0.32-0.38)	0.30 (0.25-0.36)	0.35 (0.27-0.46)
EM[4]	13 (6)	5 (3)	7 (6)
HEM[4]	3 (3)	10 (3)	1 (1)
PM[4]	1 (1)	0	0
UM[4]	1 (1)	0	0

[1]Data are presented as mean of samples ± SD; [2]Time interval between last drug intake and sample withdrawal; [3]Data are presented as geometric mean (95% confidence interval); [4]Data are presented as number of samples with number of subjects in parenthesis.
* Significantly different ($p < 0.001$) from the control group; ** Significantly different ($p < 0.01$) from the control group; *** Significantly different ($p < 0.05$) from the control group.
C/D, dose-adjusted serum concentrations; ARI, aripiprazole; DARI, dehydroaripiprazole; EM, extensive metabolizers; HEM, heterozygous extensive metabolizers; PM, poor metabolizers; UM, ultrarapid metabolizers.

The C/D ratios of dehydroaripiprazole and the sum of aripiprazole and dehydroaripiprazole were 28% ($p<0.01$) and 19% ($p<0.05$) lower, respectively, in patients receiving aripiprazole and risperidone injection compared to the control group (Table 3.5, Figure 3.8 b and c). In addition, the C/D ratio of aripiprazole was 16% lower compared to the control group, but the difference was not statistically significant. In patients receiving aripiprazole and risperidone tablets there were no apparent effects on aripiprazole pharmacokinetics (Table 3.5, Figure 3.8).
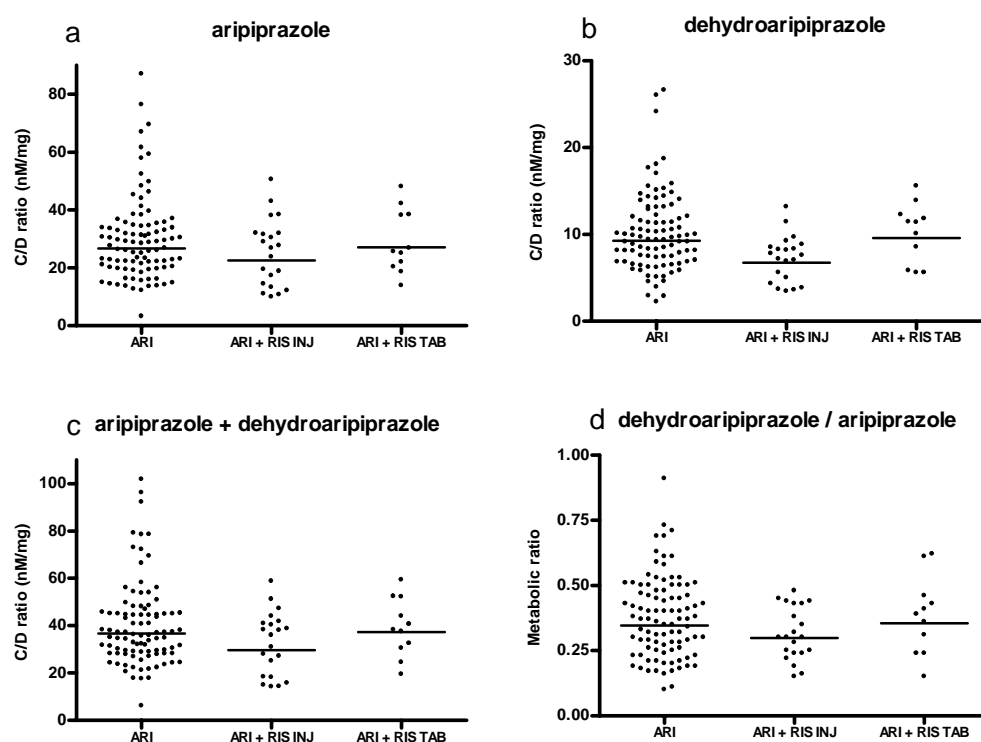
Figure 3.8 Steady state serum concentration-to-dose (C/D) ratios of **(a)** aripiprazole, **(b)** dehydroaripiprazole, **(c)** aripiprazole + dehydroaripiprazole and **(d)** metabolic ratio (dehydroaripiprazole/aripiprazole) for aripiprazole alone, aripiprazole combined with risperidone injection and aripiprazole combined with risperidone tablets. The horizontal lines indicate the geometric mean values in each group estimated in mixed model analyses; see **Table 3.5** for details and statistics. ARI: aripiprazole; RIS: risperidone; INJ: injection; TAB: tablets.

3.5 Combination of aripiprazole and antidepressants

A total of 113 samples (n) included aripiprazole combined with at least one antidepressant (escitalopram n=38, mirtazapine n=19, sertraline n=14 and venlafaxine n=19). There was a significant difference in distribution of dose ($p<0.01$) between the escitalopram group and the control group (Table 3.6). Further, there was a significant difference in distribution of age ($p<0.05$) between the mirtazapine group and the control group (Table 3.6). On average, the

Table 3.6 Characteristics of patients receiving aripiprazole monotherapy or aripiprazole in combination with the antidepressants escitalopram, mirtazapine, sertraline or venlafaxine.

	ARI	ARI + ESCIT	ARI + MIRT	ARI + SERT	ARI + VEN
Subjects (male/female)	62 (36/26)	26 (11/15)	12 (6/6)	11 (7/4)	18 (9/9)
Samples (male/female)	94 (56/38)	38 (15/23)	19 (8/11)	14 (9/5)	19 (9/10)
Age (year)[1]	33 ± 11	32 ± 12	$40** \pm 12$	33 ± 8	36 ± 15
Dosage (mg/day)[1]	18 ± 8	$15* \pm 6$	21 ± 8	16 ± 8	18 ± 10
Sample time (h)[1,2]	19 ± 6	19 ± 6	22 ± 5	20 ± 6	20 ± 6
C/D ratio ARI (nM/mg)[3]	26.8 (24.2-29.5)	33.2** (28.6-38.6)	28.1 (22.7-34.9)	25.1 (19.6-32.1)	28.1 (22.7-34.7)
C/D ratio DARI (nM/mg)[3]	9.3 (8.4-10.1)	10.5 (9.0-12.2)	8.2 (6.6-10.1)	8.0 (6.3-10.1)	8.1 (6.7-9.9)
C/D ratio ARI + DARI (nM/mg)[3]	36.6 (33.5-40.0)	44.1** (38.4-50.7)	36.5 (30.0-44.4)	33.4 (26.8-41.6)	36.6 (30.4-44.2)
DARI/ARI[3]	0.35 (0.32-0.38)	0.32 (0.28-0.36)	0.29 (0.24-0.35)	0.32 (0.25-0.40)	0.29 (0.24-0.35)
EM[4]	13 (6)	4 (3)	2 (2)	3 (2)	5 (5)
HEM[4]	3 (3)	1 (1)	7 (4)	1 (1)	4 (4)
PM[4]	1 (1)	0	0	0	1 (1)
UM[4]	1 (1)	0	0	0	0

[1]Data are presented as mean of samples $\pm$ SD; [2]Time interval between last drug intake and sample withdrawal; [3]Data are presented as geometric mean (95% confidence interval); [4]Data are presented as number of samples with number of subjects in parenthesis.
* Significantly different ($p<0.01$) from the control group; ** Significantly different ($p<0.05$) from the control group.
C/D, dose-adjusted serum concentrations; ARI, aripiprazole; DARI, dehydroaripiprazole; ESCIT, escitalopram; MIRT, mirtazapine; SERT, sertraline; VEN, venlafaxine; EM, extensive metabolizers; HEM, heterozygous extensive metabolizers; PM, poor metabolizers; UM, ultrarapid metabolizers.
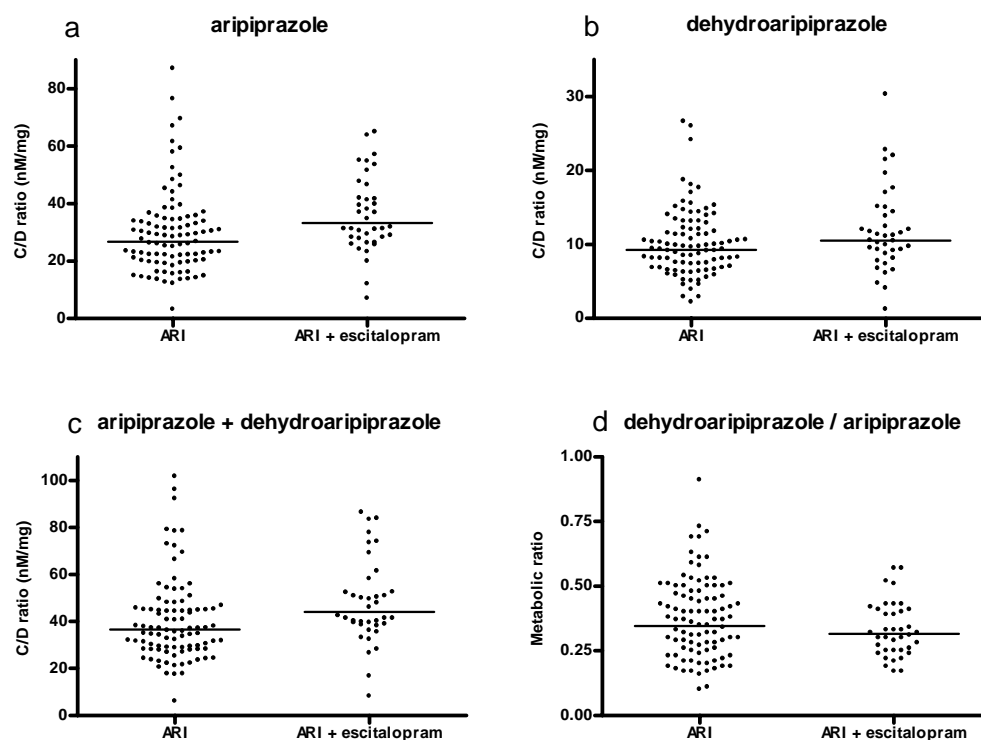
Figure 3.9 Steady state serum concentration-to-dose (C/D) ratios of **(a)** aripiprazole, **(b)** dehydroaripiprazole, **(c)** aripiprazole + dehydroaripiprazole and **(d)** metabolic ratio (dehydroaripiprazole/aripiprazole) for aripiprazole alone and aripiprazole combined with escitalopram. The horizontal lines indicate the geometric mean values in each group estimated in mixed model analyses; see **Table 3.6** for details and statistics. ARI: aripiprazole.

C/D ratio of aripiprazole and the C/D ratio of the sum of aripiprazole and dehydroaripiprazole were 24% ($p<0.05$) and 20% ($p<0.05$) higher, respectively, in patients receiving aripiprazole

in combination with escitalopram compared to the control group (Table 3.6, Figure 3.9 a and c). Concomitant intake of mirtazapine, sertraline or venlafaxine did not significantly affect the disposition of aripiprazole (Table 3.6).

3.6 Combination of aripiprazole and antiepileptics

A total of 103 samples (n) included aripiprazole in combination with at least one antiepileptic drug (clonazepam n=34, lamotrigine n=49 and valproate n=26). There were significant differences in distribution of dose ($p<0.01$) and time interval between last drug intake and sample withdrawal ($p<0.05$) between the lamotrigine group and the control group (Table 3.7). On average, the metabolic ratio (dehydroaripiprazole/aripiprazole) was 17% lower in patients receiving aripiprazole and lamotrigine compared to the control group ($p<0.05$) (Table 3.7, Figure 3.14 d). Further, a minimal effect was observed for concomitant intake of aripiprazole and valproate, giving a decrease in the C/D ratios of aripiprazole, dehydro-aripiprazole and the sum of aripiprazole and dehydroaripiprazole by 14%, 12% and 14%, respectively, although not statistically significant (Table 3.7). Concomitant intake of clonazepam did not significantly influence on the disposition of aripiprazole (Table 3.7).
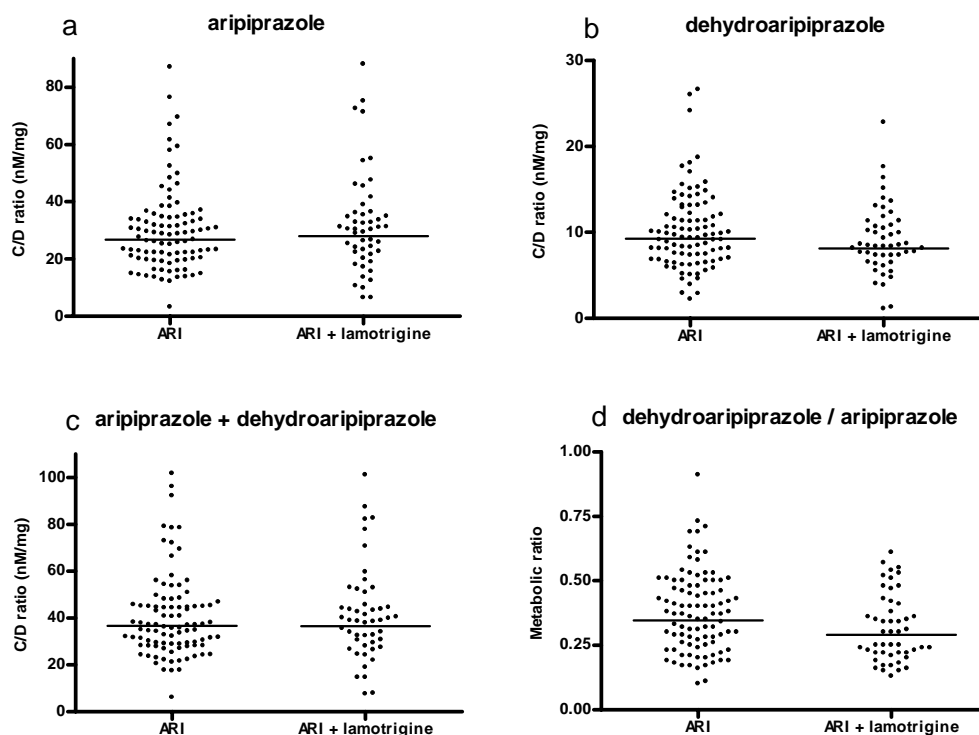
Table 3.7 Characteristics of patients receiving aripiprazole monotherapy or aripiprazole in combination with the antiepileptics clonazepam, lamotrigine or valproate.

	ARI	ARI + clonazepam	ARI + lamotrigine	ARI + valproate
Subjects (male/female)	62 (36/26)	22 (13/9)	31 (8/23)	15 (8/7)
Samples (male/female)	94 (56/38)	34 (18/16)	49 (16/33)	26 (18/8)
Age (year)[1]	33 ± 11	36 ± 10	30 ± 9	38 ± 16
Dosage (mg/day)[1]	18 ± 8	20 ± 8	15* ± 6	20 ± 9
Sample time (h)[1, 2]	19 ± 6	19 ± 6	17** ± 6	20 ± 7
C/D ratio ARI (nM/mg)[3]	26.8 (24.2-29.5)	28.1 (23.8-33.1)	27.9 (24.2-32.3)	23.1 (19.2-27.7)
C/D ratio DARI (nM/mg)[3]	9.3 (8.4-10.1)	9.0 (7.8-10.3)	8.1 (7.1-9.3)	8.2 (6.8-9.7)
C/D ratio ARI + DARI (nM/mg)[3]	36.6 (33.5-40.0)	37.5 (32.4-43.3)	36.6 (32.1-41.7)	31.6 (26.8-37.2)
DARI/ARI[3]	0.35 (0.32-0.38)	0.32 (0.28-0.37)	0.29** (0.26-0.33)	0.35 (0.30-0.42)
EM[4]	13 (6)	5 (5)	9 (5)	6 (5)
HEM[4]	3 (3)	2 (2)	2 (2)	5 (2)
PM[4]	1 (1)	1 (1)	1 (1)	1 (1)
UM[4]	1 (1)	0	0	0

[1]Data are presented as mean of samples ± SD; [2]Time interval between last drug intake and sample withdrawal; [3]Data are presented as geometric mean (95% confidence interval); [4]Data are presented as number of samples with number of subjects in parenthesis.
* Significantly different ($p<0.01$) from the control group; ** Significantly different ($p<0.05$) from the control group.
C/D, dose-adjusted serum concentrations; ARI, aripiprazole; DARI, dehydroaripiprazole; EM, extensive metabolizers; HEM, heterozygous extensive metabolizers; PM, poor metabolizers; UM, ultrarapid metabolizers.

Figure 3.14 Steady state serum concentration-to-dose (C/D) ratios of **(a)** aripiprazole, **(b)** dehydroaripiprazole, **(c)** aripiprazole + dehydroaripiprazole and **(d)** metabolic ratio (dehydroaripiprazole/aripiprazole) for aripiprazole alone and aripiprazole combined with lamotrigine. The horizontal lines indicate the geometric mean values in each group estimated in mixed model analyses; see **Table 3.7** for details and statistics. ARI: aripiprazole.

4. Discussion

Almost three quarters of the patients (72%) received aripiprazole in combination with other psychotropic drugs. This high proportion, in spite of the low age, might be due to the presence of the more complicated cases in need for a closer follow-up with serum monitoring than what is the case for patients receiving monotherapy. Further, there were a total of 138 combinations of co-medication, suggesting a difficulty of treating these patients adequately.

Co-administration with a CYP2D6 inhibitor had a statistically significant effect on the steady state pharmacokinetics of aripiprazole and dehydroaripiprazole. The increase and decrease of aripiprazole and dehydroaripiprazole C/D ratios were 35% and 26%, respectively, and thus the metabolic ratio (dehydroaripiprazole/aripiprazole) was approximately 46% lower compared to the control group. These results were not of equal magnitude as suggested by the aripiprazole product information, where the systemic exposure of aripiprazole increased by 110% whereas that of dehydro-aripiprazole decreased by 35% when co-administered with the potent CYP2D6 inhibitor quinidine in an interaction study (SPCa). Further, in a recent study based on material from a routine therapeutic drug monitoring service concomitant use of aripiprazole and a CYP2D6 inhibitor resulted in a 44% higher systemic exposure of aripiprazole compared to aripiprazole alone (Castberg 2007). The results of the present study were based on 14 samples from 10 patients, where 13 samples were of unknown CYP2D6 genotype. Because CYP2D6 genotype was previously shown to influence on the disposition of aripiprazole (Hendset 2007), the possible differences in distribution of CYP2D6 genotype between the groups in the present study could have affected the results. Nevertheless, the effect of CYP2D6 inhibitors on aripiprazole disposition resembles that of impaired metabolic capacity in CYP2D6 due to genetic polymorphism (PM). The significant difference in distribution of age between the CYP2D6 inhibitor group and the control group was not likely to influence on the results in this study as the mean age was relatively low in both groups, and according to the manufacturer no dose adjustments of aripiprazole are required on the grounds of age (Mauri 2007). The counterbalancing of drug and active metabolite resulted in a minimal difference in the C/D ratio of the sum of aripiprazole and dehydroaripiprazole between the CYP2D6 inhibitor group and the control group in the present study. This suggests that CYP2D6 mediates metabolism of aripiprazole to dehydroaripiprazole without being importantly involved in the elimination of dehydroaripiprazole. Due to the minimal

difference in the C/D ratio of the sum of aripiprazole and dehydroaripiprazole, no dose adjustment of aripiprazole is necessary. However, this is not in accordance with the manufacturer's prescribing information, where a 50% dose reduction of aripiprazole is recommended when co-administered with CYP2D6 inhibitors (SPCa).

The effect of perphenazine on the pharmacokinetics of aripiprazole have not been studied previously, but perphenazine was shown to inhibit the CYP2D6 metabolism of dextro-methorphan *in vitro* (Shin 1999). Concomitant intake of aripiprazole and perphenazine increased the C/D ratios of aripiprazole and the sum of aripiprazole and dehydroaripiprazoley by approximately 75% and 60%, respectively, and decreased the metabolic ratio by 31% compared to aripiprazole monotherapy. Two of the samples in the perphenazine group were taken from a patient with no functional alleles encoding CYP2D6 (PM). Excluding these samples, the C/D ratios of aripiprazole and the sum of aripiprazole and dehydroaripiprazole were approximately 32% and 22% higher, respectively, and the metabolic ratio was 26% lower compared to the control group, but none of these effects were statistical significant. Escitalopram is reported to be a weak inhibitor of CYP2D6 *in vitro* (von Moltke 2001). This weak inhibitory action might be reflected in the C/D ratios of aripiprazole and the sum of aripiprazole and dehydroaripiprazole in the present study, being increased by 24% and 20%, respectively, in patients co-medicated with escitalopram compared to the control group. Correspondingly, in a recent study concomitant intake of aripiprazole and citalopram or escitalopram increased the C/D ratio of aripiprazole by 39% (Castberg 2007). However, the effects of perphenazine and escitalopram on aripiprazole disposition are not totally in accordance with the impact of a CYP2D6 inhibitor previously shown (SPCa; Castberg 2007), where co-administration of aripiprazole and a CYP2D6 inhibitor resulted in a decrease of the C/D ratio of dehydroaripiprazole, whereas co-medication with perphenazine or escitalopram did not show such a decrease. As CYP2D6 is thought not to be importantly involved in the elimination of dehydroaripiprazole, and as the systemic exposure of both aripiprazole and dehydroaripiprazole increased when co-administered with perphenazine or escitalopram, this suggests the possibility of aripiprazole and dehydroaripiprazole to be metabolized by a not yet identified enzyme, which might be inhibited by perphenazine and escitalopram. Studies are needed to explore this proposed metabolism pathway of aripiprazole.

A pharmacokinetic interaction between aripiprazole and lithium is unexpected because lithium is neither metabolized nor bound to plasma proteins, and is almost entirely excreted

unchanged in urine (Wang 2002). Nevertheless, in the present study concomitant use of aripiprazole and lithium increased the C/D ratio of aripiprazole by approximately 43% (n=8). Correspondingly, previous studies demonstrated an increase in the systemic exposure of aripiprazole of 15% (n=7) (Citrome 2005) and 34% (n=6) (Castberg 2007) when co-administered with lithium. The low number of samples studied may indicate the findings to be coincidental, yet the studies published so far points in the same direction. One might also speculate that the uneven distribution of male/female samples (1/7) in the lithium group in the present study influenced on the results, however according to a previous study sex is of no significance to aripiprazole disposition (Molden 2006). There is no obvious pharmacokinetic explanation of the observed effects on the pharmacokinetics of aripiprazole, but perhaps, as suggested by Castberg and co-worker, the effects might be due to non-pharmacological factors, such as the possibility of a better adherence to aripiprazole treatment among patients receiving mood stabilizers than average (Castberg 2007). In total, these findings indicate a dose reduction of aripiprazole of about one quarter of the usual dose, but more studies are needed to explore these issues further.

Among the co-medications investigated the CYP3A4 inducers had the greatest influence on aripiprazole disposition, where the C/D ratios of aripiprazole, dehydroaripiprazole and the sum of aripiprazole and dehydroaripiprazole obtained were approximately 69%, 75% and 70% lower, respectively, compared to the control group. This is consistent with a recent study of aripiprazole and concomitant intake of carbamazepine, where the systemic exposure of aripiprazole and dehydroaripiprazole were 71% and 69% lower, respectively (Citrome 2007). Similarly, Castberg and co-worker observed an 88% reduction of aripiprazole systemic exposure (Castberg 2007). As expected, the metabolic ratio did not differ significantly between the 3A4 inducer group and the control group in the present study, as the reduction of aripiprazole and dehydroaripiprazole C/D ratios were of the same magnitude. The findings could reflect the fact that both aripiprazole and dehydroaripiprazole are substrates for CYP3A4 (Citrome 2007) which is known to be induced by carbamazepine, phenytoin and phenobarbital (Cloyd 2000; Sandson 2005). In addition, dehydroaripiprazole might be a substrate for an inducible enzyme other than CYP3A4, as carbamazepine is also known to induce CYP1A2 and some of the UGT enzymes (Cloyd 2000; Sandson 2005) and as the systemic exposure of dehydroaripiprazole decreased when aripiprazole was co-administered with CYP2D6 inhibitors. In total, these studies suggest a dose increase of aripiprazole of

about three times the usual dose when co-administered with CYP3A4 inducers, but careful interpretation is in order due to few samples.

Due to a slightly increased C/D ratio of aripiprazole and a slightly decreased C/D ratio of dehydroaripiprazole, although not statistically significant, the metabolic ratio was 23% lower in patients receiving aripiprazole combined with olanzapine compared to the control group. Olanzapine is metabolized primarily by CYP1A2 and UGT1A4 enzymes in addition to flavin mono-oxygenase (FMO) and, to a lesser extent, CYP2D6 (Callaghan 1999; Linnet 2002). Olanzapine is also highly bound to albumine (90%), but protein binding displacement is not a likely explanation for the effect of olanzapine on aripiprazole pharmacokinetics as the C/D ratio of aripiprazole would be expected to decrease and not increase. The effects on aripiprazole and dehydroaripiprazole C/D ratios in the present study slightly resemble the results obtained for aripiprazole co-administered with a CYP2D6 inhibitor, but are not of equal magnitude. In a previous interaction study with imipramine, olanzapine did not show a metabolic drug interaction involving CYP2D6 (Callaghan 1997). The effect of olanzapine on aripiprazole disposition has not been studied previously, and the mechanism of this interaction is not obvious. Perhaps olanzapine inhibits an UGT enzyme responsible for a not yet explored metabolism pathway of aripiprazole.

Previous studies have shown differences in metabolite/parent drug ratio of risperidone when using injections compared to tablets (Nesvåg 2006). In theory, it is possible that the parent drug and the metabolite influence on the metabolism of other drugs differently. Therefore, the results of concomitant use of aripiprazole and risperidone are separated in two groups; risperidone injection and risperidone tablets. In the present study, aripiprazole combined with risperidone tablets showed no apparent effect on aripiprazole pharmacokinetics. In contrast, concomitant use of aripiprazole and risperidone injection decreased the C/D ratios of dehydroaripiprazole and the sum of aripiprazole and dehydroaripiprazole by 28% and 19%, respectively, compared to the control group. In addition, the C/D ratio of aripiprazole decreased by 16%, but this was not statistically significant. We have not been able to find reports regarding induction of drug metabolism by risperidone, and therefore a non-pharmacological explanation of the observed effect on aripiprazole disposition in the risperidone injection group might be more likely. Treatment with expensive injection formulations are primarily prescribed to patients with an established problem of poor compliance. A more pronounced problem of poor compliance with respect to aripiprazole

treatment might therefore be an explanation for the lower C/D ratios in the risperidone injection group compared to the control group.

Due to a slightly decreased C/D ratio of dehydroaripiprazole, although not statistical significant, the metabolic ratio (dehydroaripiprazole/aripiprazole) was 17% lower in patients receiving aripiprazole and lamotrigine compared to the control group. There was no apparent effect on the C/D ratio of aripiprazole, not consistent with a recent study reporting a 51% increase of aripiprazole systemic exposure (Castberg 2007). This difference might be a result of a higher number of samples in the present study (n=49 versus n=4). Because lamotrigine is not highly bound to plasma proteins, clinically significant drug–drug interactions through competition for protein binding are unlikely (Tidwell 2003). Further, lamotrigine is metabolized by UGT1A4 and UGT2B7 (Rowland 2006), and does not have any known effects on the activity of CYP enzymes (Tidwell 2003). The decrease in the metabolic ratio was mainly due to the decrease in the C/D ratio of dehydroaripiprazole. Thus, as lamotrigine appears to be a weak inducer of UGTs (Benedetti 2000) this might suggest that dehydroaripiprazole is metabolized by UGT enzymes. More studies are needed to confirm this speculation.

Concomitant intake of valproate did not significantly influence on aripiprazole disposition, but the decrease in the C/D ratios of aripiprazole and dehydroaripiprazole by 14% and 12%, respectively, shared the same tendency as reported in other studies. Citrome and co-workers observed a 24% and 8% reduction of aripiprazole and dehydroaripiprazole systemic exposure, respectively (Citrome 2005). Correspondingly, Castberg and co-worker demonstrated a 24% reduction of aripiprazole systemic exposure (Castberg 2007). Valproate and/or its metabolites may displace other highly plasma protein-bound drugs (Anderson 1998). Thus, the reason for the non-significant decrease in the C/D ratios of aripiprazole and dehydroaripiprazole in the present study might be that valproate displaces bound aripiprazole as valproate and aripiprazole share the same plasma protein-binding site II (Panjehshahin 1991; Imamura 1996). As aripiprazole is not a high extraction ratio drug, given its high bioavailability (Mauri 2007), the increase in the free fraction of aripiprazole may lead to increased oral clearance and therefore a decrease in plasma concentrations of total drug, with no change in unbound plasma drug concentration, and apparently no change in clinical effect will be observed.

The clinical impact of minor changes in the systemic exposure of aripiprazole and dehydro-aripiprazole is uncertain. An increase or decrease in serum concentrations of 20% is within the limits of what is considered bioequivalent (Steinijans 1991), but this does not account for possible clinical effects due to significant changes in the metabolic ratio. In TDM, it is common practice to monitor the active sum of aripiprazole and dehydroaripiprazole as these are considered to have similar pharmacological activities. Due to different physio-chemical characteristics of parent drug and active metabolite (e.g. lipid solubility) and thus potential differences in brain distribution, a significantly higher serum concentration of aripiprazole may theoretically change the clinical effect to a greater extent than reflected by the sum of the active compounds (Hendset 2006).

The distribution of dose and time interval between last drug intake and sample withdrawal were different for some of the co-medication groups in the present study. Concerning dose, C/D ratio was applied. The use of C/D ratio assumes linear kinetics and this was shown for aripiprazole (Mallikaarjun 2004). Accordingly, differences in distribution of dose for some of the co-medication groups compared to the control group are supposed to be of no importance to the interpretation of the results. Concerning time interval between last drug intake and sample withdrawal, this was not likely to influence on the results in the study due to the long elimination half-lives of aripiprazole and dehydroaripiprazole (SPCa).

The naturalistic clinical setting in the present study has several obvious limitations of methodological nature, such as potential poor compliance, lack of information on the requisition forms with respect to concomitant medication and clinical relevant conditions (e.g. somatic disease), potential food consumption affecting aripiprazole metabolism (e.g. grapefruit juice), and false information on the requisition forms regarding time interval between last drug intake and sample withdrawal. Moreover, single samples as opposed to AUC also contribute to the uncertainty of the results obtained. In addition, only 27% of the included patients were genotyped, and the possibility of uneven distribution of CYP2D6 genotype between the different co-medication groups and the control group was present. On the other hand, the study was conducted in a clinical setting with patients already receiving medical treatment. The results achieved are therefore more likely to reflect true conditions opposed to studies with healthy individuals. In addition, this approach resulted in a relatively high number of samples for the drugs most frequently used in combination with aripiprazole. Further, with such an approach the possibility to discover unexpected interactions, not likely

to happen in regular interaction studies, are present (e.g. lithium). Moreover, there are also ethical questions attached in conducting a regular interaction study with healthy individuals receiving antipsychotic treatment for a period of time and then add a potent CYP inhibitor or inducer and observe the effects on the systemic exposure of the drug of interest. In the present study the relatively high number of samples included was thought to counterbalance the uncertainty of the methodological limitations.

5. Conclusion

The majority of psychiatric patients with serum measurements performed as part of their clinical follow-up were also treated with other drugs. Among the co-medications investigated the CYP3A4 inducers had the greatest impact on aripiprazole pharmacokinetics, suggesting a dose increase of aripiprazole of about three times the usual dose. As the CYP2D6 inhibitors caused a significant change in the C/D ratio of aripiprazole, whereas there was a minimal change in the C/D ratio of the sum of aripiprazole and dehydroaripiprazole, the clinical effect of this is uncertain. Surprisingly, the impact of lithium on aripiprazole disposition was of such a magnitude that dosage adjustments should be assessed. Several drugs, including es-citalopram, olanzapine, perphenazine, risperidone injection and lamotrigine resulted in minor interactions with aripiprazole. The clinical importance of these interactions is uncertain.

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