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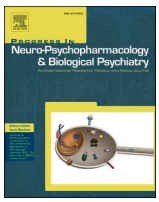

Role of *CYP2D6* and *CYP3A4* polymorphisms on aripiprazole and dehydroaripiprazole concentrations in patients undergoing long-acting treatment

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ABSTRACT

Aripiprazole once-monthly (AOM) exhibits an important interindividual pharmacokinetic variability with significant implications for its clinical use. CYP2D6 and CYP3A4 highly contributes to this variability, as they metabolize aripiprazole (ARI) into its active metabolite, dehydroaripiprazole (DHA) and the latter into inactive metabolites.

This study aims to evaluate the effect of *CYP2D6* and *CYP3A4* polymorphisms in combination and the presence of concomitant inducers and inhibitors of this cytochromes on ARI and DHA plasma concentrations in a real clinical setting.

An observational study of a cohort of 74 Caucasian patients under AOM treatment was conducted. Regarding CYP2D6, higher concentrations were found for active moiety (ARI plus DHA) (AM) (67 %), ARI (67 %) and ARI/DHA ratio (77 %) for poor metabolizers (PMs) compared to normal metabolizers (NMs). No differences were found for DHA.

PMs for both CYP2D6 and CYP3A4 showed a 58 % higher AM and 66 % higher plasma concentration for ARI compared with PMs for CYP2D6 and NMs for CYP3A4. In addition, PMs for both CYP2D6 and CYP3A4 have 45 % higher DHA concentrations than NMs for both cytochromes and 41 % more DHA than PMs for CYP2D6 and NMs for CYP3A4, suggesting a significant role of CYP3A4 in the elimination of DHA.

Evaluating the effect of CYPD26 and CYP3A4 metabolizing state in combination on plasma concentrations of ARI, DHA and parent-to-metabolite ratio, considering concomitant treatments with inducers and inhibitor, could optimize therapy for patients under AOM treatment.

1. Introduction

Aripiprazole (ARI) is an atypical antipsychotic whose efficacy may be mediated through a combination of partial agonist activity at D2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors (Aihara et al., 2004; Argo et al., 2004). Binding affinity and functional selectivity

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of ARI at dopamine D2 receptors are essential to its mechanism of action. As a partial agonist, it has a moderate intrinsic activity at D2 receptors, which is lower than that of dopamine itself, suggesting a nuanced modulation of dopaminergic neurotransmission (Aihara et al., 2004). Moreover, the ability to act as a dopamine system stabilizer is thought to be mediated through its action at presynaptic D2 autoreceptors, decreasing dopamine release, while also serving as an antagonist at postsynaptic D2 receptors at higher doses. This dual activity helps to modulate dopamine levels more finely than typical antipsychotics, which are known for their strong antagonistic effects on dopamine receptors (Argo et al., 2004).

The pharmacokinetics of aripiprazole, particularly its plasma concentrations, exhibit considerable inter-individual variability, which has significant implications for its clinical use. One of the key factors contributing to ARI variability is the polymorphic nature of the cytochromes P450 family (CYP2D6 and CYP3A4), responsible for metabolizing ARI into its active metabolite, dehydroaripiprazole (DHA) (Toja-Camba et al., 2021). DHA is also a ligand at the D2 receptor and has similar pharmacological properties to the original compound (Tadori et al., 2011). According to the Neuropsychopharmacology Therapeutic Drug Monitoring Consensus Guidelines, the therapeutic reference range is 100–350 ng/mL for ARI and 150–500 ng/mL for ARI plus DHA, called active moiety (AM) (Hiemke et al., 2018).

The introduction of aripiprazole long-acting injectable once-monthly (AOM) dosing has improved the treatment compliance of this drug. AOM is the polymorphic monohydrate form of ARI; currently, 400 mg and 300 mg formulations are approved for the induction treatment of schizophrenia and maintenance therapy (SmPC Abilify Maintena, Otsuka Pharmaceuticals, 2024). Due to low solubility, AOM is slowly absorbed into the systemic circulation after intramuscular injection. Maximum plasma concentrations under steady-state conditions are reached 4 days after deltoid injection and 5–7 days after gluteal injection. The mean apparent half-life is 29.9 days for 300 mg and 46.5 days for 400 mg; according to the manufacturer, steady-state concentrations are achieved with the fourth injection at both injection sites (Mallikaarjun et al., 2013).

As a member of the cytochrome P450 family, CYP2D6 is responsible for catalyzing several metabolic reactions that ARI undergoes, specifically its metabolization into the active metabolite DHA. In addition, this cytochrome also takes part in the conversion of the DHA into inactive metabolites (Soria-Chacartegui et al., 2021; Swainston Harrison and Perry, 2004). Consequently, genetic polymorphisms in the *CYP2D6* gene could significantly influence the plasma concentrations and pharmacokinetics of both ARI and DHA. Today, 163 alleles of CYP2D6 have been described have different functions, frequencies, and clinical metabolic effects in different populations (Friedrich et al., 2014; Sistonen et al., 2024). Depending on the combination of alleles, the following metabolizer states can be distinguished in different phenotypes: Normal metabolizer (NM), Intermediate Metabolizer (IM), Poor metabolizer (PM) and ultrarapid metabolizers (UM) (Caudle et al., 2020).

Regarding CYP3A4, it is known that it plays a certain role in the metabolization of ARI to DHA and the latter into inactive metabolites. A recent study has described that the variant CYP3A4*22 produces reduced enzyme activity and may affect the metabolism of antipsychotics (Van Der Weide and Van Der Weide, 2015). On the other hand, CYP3A4*20 polymorphism produces a non-functional protein that may result in elevated drug concentrations in individuals carrying this allele, present in 1.2 % of the Spanish population(Apellániz-Ruiz et al., 2015). However, no studies have examined the effect of CYP3A4*20 on the pharmacokinetics of ARI. In addition to genetics, concomitant drugs can influence drug metabolism (Zanger and Schwab, 2013). In this sense, phenoconversion is the mismatch between the genotype-based prediction of CYP450-mediated drug metabolism and the true capacity of an individual to metabolize drugs (phenotype) due to nongenetic factors (Klomp et al., 2020). Accordingly, Lisbeth et al. found phenoconversion to be the limiting factor for predicting an accurate dose based on CYP2D6 genotype (Lisbeth et al., 2016). The genotype–phenotype mismatch of CYP2D6 could have significant consequences in the clinical setting and may result in suboptimal treatment of patients (Klomp et al., 2020). The Summary of Product Characteristics (SmPC) approved by the Food and Drug Administration (FDA) and Dutch Pharmacogenetics Working Group recommend dose adjustment of AOM if concomitant treatments with CYP2D6 and CYP3A4 inhibitors or CYP34 inducers (Table of Pharmacogenetic Associations, FDA, 2024). However, recommendations for dose reductions based on cytochrome phenotype are only established for CYP2D6 PMs, but not for CYP3A4. In addition, FDA SmPC states that DHA represents about 29 % of the ARI exposure in plasma without specifying the metabolizer phenotype for CYP2D6 or CYP3A4 (SmPC Abilify Maintena, Otsuka Pharmaceuticals, 2024).

Based on the above, pharmacokinetics and pharmacogenetics play a key role in the personalized prescription of AOM. This study evaluates the effect of the CYP2D6-CYP3A4 metabolizing state in combination on AOM pharmacokinetics. The aim of the present work is to study the effect of CYP2D6 and CYP3A4 polymorphisms and the presence of concomitant inducers and inhibitors of this cytochromes on ARI and DHA plasma concentrations in a real clinical setting.

2. Methods

2.1. Study design and procedures

An observational study of a cohort of patients under AOM treatment was conducted to evaluate the effect of *CYP2D6* and *CYP3A4* genetic polymorphisms on plasma concentrations of ARI and DHA. The authors declare that all procedures performed were in accordance with the ethical standards of the relevant national and institutional committees on human experimentation and with the 1975 Declaration of Helsinki (as revised 2008). All procedures involving patients were approved by the Drug Research Ethics Committee of Galicia (2020/486) and written informed consent was obtained from all subjects. The study included patients who received at least four doses of AOM and a starting regimen of 400 plus concomitant oral aripiprazole for 14 days (Abilify Maintena®; Otsuka, Tokyo, Japan). Exclusion criteria were age < 18 years, pregnancy, and cognitive impairment. Three blood samples were obtained from each patient, one for pharmacokinetic analysis, one for genotyping and one for evaluation of biochemical data. Demographic characteristics and biochemical data including gender, age, height, weight, dosage, concomitant medication, liver, and kidney function were recorded.

2.2. Pharmacokinetic analysis

Blood samples for pharmacokinetic analysis were collected in EDTA tubes immediately prior to AOM administration (Ctrough). All samples were centrifuged at 3.500 rpm for 10 min at 4 °C to obtain the plasma. A volume of 180uL of plasma sample was spiked with 20ul of aripiprazole-d8 (internal standard) and 500uL of acetonitrile and centrifuged. The supernatant was evaporated to dryness and the dry residue was reconstituted with 500uL of 10 mM Ammonium Formate/ Acetonitrile (85:15). Concentrations of ARI and DHA in plasma were measured with an ultra-high performance liquid chromatography-tandem mass spectroscopy (UHPLC-MS/MS) Xevo TQD® triple quadrupole mass spectrometer (LLOQ: 25 ng/mL and LLOD: 5 ng/mL) (Waters, Massachusetts, USA), using a validated method previously published (Toja-Camba et al., 2024).

2.3. Genotype and phenotype

Genetic analysis was performed for single nucleotide polymorphic variants (SNPs) or insertion-deletions (indels) for CYP2D6 and CYP3A4 genes. Analyses were performed using Taqman assays on the QuantStudio 12 K Flex (Applied Biosystems, Foster City, California). For

CYP2D6, the following variants were analyzed: rs1065852, rs201377835, rs5030862, rs5030865, rs774671100, rs28371706, rs16947, rs1135840, rs59421388, rs35742686, rs72549356, rs267608319, rs3892097, rs28371725, rs72549346, rs1135822, rs79292917, rs5030655, rs5030867, rs5030865, rs769258, rs5030656. Copy number variations in the *CYP2D6* gene were also determined. For CYP3A4 the presence or absence of the alleles *22 (rs35599367) and *20 (rs67666821) were evaluated. After genotyping CYP2D6, each allele is assigned an activity value corresponding to the activity value described by Caudle et al. Individuals with activity score (AS) 0 are classified as PMs, individuals with AS 0.25–1 are classified as IMs, individuals with AS 1.25–2.25 are classified as NMs, and individuals with AS >2.25 are classified as UMs (Caudle et al., 2020).

Regarding CYP3A4, patients with presence of heterozygous *1/*22 and homozygous *22/*22 were grouped under CYP3A4 PM phenotype.

Once phenotyping has been performed, depending on the presence of concomitant CYP2D6 and CYP3A4 inhibitors or inducers, the appropriate phenoconversion was performed for each patient.

2.4. Data analysis

The main statistics analysis afforded two approaches: drug concentrations and dose-adjusted drug concentrations. Adjustment to a normal distribution was not assumed in doses, concentration levels and ratios variables (Kolmogorov-Smirnov with Lilliefors correction normality test), so nonparametric tests were carried out. For comparison of two independent samples the Mann-Whitney tests were performed and for comparison of more than two independent samples the Kruskal-Wallis test were used to test the significance of differences between the different CYP3A4 and CYP2D6 groups. *P* values of less than or equal to 0.05 were considered to be statistically significant. Data were presented as median and interquartile ranges.

3. Results

3.1. Study population

Observational study of a cohort of 74 Caucasian patients under AOM treatment (40 male and 34 female) and no concomitant oral aripiprazole; Median age was 48 years (35–54); Weight 82.15 Kg (68.5–93); BMI 29.82 kg/m^2; Cr: 0.8 mg/dL (0.7–0.97); AST: 23 IU/L (19–30.5); ALT: 30 IU/L (18–43); GGT: 26 IU/L (17–42); Median dose administrated of AOM was 400 mg (300–400); Injection site (28 Deltoid; 46 Gluteus); smoking status (51 smokers; 23 non-smokers). CYP2D6 enzyme genotyping was performed for all the variants. Phenotyping was done according to the activity score of each allele and phenoconversion was performed (10 patients on concomitant treatment with fluoxetine). CYP3A4 genotyping was also performed for all individuals but phenoconversion was not performed due to the absence of inhibitors/inducers for this cytochrome. Obtained frequencies for CYP2D6 and CYP3A4 were depicted in Table 1.

Table 1
Biochemical data and obtained phenotypes frequencies for CYP2D6 and CYP3A4. PM: Poor Metabolizer; IM: Intermediate Metabolizer; NM: Normal Metabolizer; UM: Ultra metabolizer; *Presence of heterozygous *1/*22 and homozygous *22/*22 were grouped under CYP3A4 PM phenotype.

	PM n (%)	IM n (%)	NM n (%)	UM n (%)
CYP2D6 Phenotype	2 (3)	29 (39)	40 (54)	3 (4)
CYP2D6 after phenoconversion	12 (16)	24 (32)	35 (47)	3 (4)
CYP3A4 Phenotype*	5 (7) *1/*22 (3) *22/*22 (2)	–	69 (93)	–

3.2. Effects of CYP2D6 phenotypes on plasma concentrations

After reviewing the concomitant medication, 11 patients were found to have concomitant treatment with strong CYP2D6 inhibitors and none for CYP3A4. Phenoconversion for CYP2D6 was performed following calculator developed by the University of Florida Health Precision Medicine Program (Cicali et al., 2021). To explore the effect of CYP2D6 metabolizer status on plasma concentrations, comparative analyses were performed between the three phenotype groups (PMs, IMs and NMs); since UMs group did not reach a sufficient n, it was discarded from the analysis (Table 2). Significant differences were found between the three groups for AM ($p = 0.0468$) (Fig. 1A), ARI ($p = 0.0302$) (Fig. 1B) and ARI/DHA Ratio ($p = 0.0174$) (Fig. 1C). In addition, group to group comparisons showed a difference in the AM of PMs (327.1 ng/mL) vs NMs (196 ng/mL) $p = 0.0038$; in the case of ARI, PMs (243 ng/mL) showed higher concentrations than IMs (153 ng/mL) $p = 0.0486$ and also with respect to NMs (145 ng/mL) $p = 0.0027$; Differences were also found between the above groups in the case of ARI/DHA ratio for PMs (3.6) vs IMs (2.3) $p = 0.0055$ and PMs vs NMs (2) $p = 0.0015$. No differences were found in the case of DHA. To determine whether these differences were not due to AOM doses, the same analysis was performed correcting each value by the administered dose (Fig. 1A, B, C). After dose-adjusted drug concentrations were calculated, the differences remained statistically significant and, in addition, statistical significance was reached in the comparison of AM of PMs (0.85) vs IMs (0.56) $p = 0.0317$. No differences were found in the case of DHA either. The results of the dose-adjusted analysis are available in Supplementary Table S1.

3.3. Effect of CYP2D6 and CYP3A4 combined on plasma concentrations

Since ARI and DHA are also metabolized via CYP3A4, a stratification of patients was performed considering CYP2D6 and CYP3A4 metabolizer states.

NMs for both cytochromes showed lower AM (197 ng/mL) and ARI (148 ng/mL) (Fig. 2A and B) concentrations than PMs for both cytochromes (344 ng/mL) and (271 ng/mL) respectively, with *p*-values <0.001. DHA concentrations were higher in PM-PM (86 ng/mL) in comparison with PM-NM (61 ng/mL) and NM-NM (59 ng/mL) with p-values <0.05 (Fig. 2C). In the case of the ARI/DHA ratio (Fig. 2D), significant differences were found both between NM-NM vs PM-PM ($P = 0.0304$), NM-NM vs PM-NM ($P = 0.0122$) as well as in the case of IM-NM vs PM-NM ($p = 0–0253$) (Table 3). CYP2D6NM-3A4PM ($n = 1$) and CYP2D6UM-3A4NM ($n = 3$) groups were discarded from the analysis in order not to increase the bias due to random effects.

On the other hand, dose adjusted ratio for AM, ARI and ARI/DHA ratio were calculated (Fig. 2A, B, C). Statistical significance was maintained between the same groups. Furthermore, after adjustment, significant differences were obtained between the PM-CYP2D6-NM-CYP3A4 and PM-CYP2D6-PM-CYP3A4 groups for AM and ARI (Fig. 2A,B,C and D). Results of Dose-adjusted ratios are available in Supplementary Table S2.

4. Discussion

This study explores how the combination of CYP2D6 and CYP3A4 genotypes and their predicted phenotypes affects plasma concentrations of AM, ARI, DHA and parent-to-metabolite ratio in patients under AOM treatment. Also, it takes into account a strict and most validated up to date CYP2D6 phenoconversion (Cicali et al., 2021).

Our results showed a strong effect between different CYP2D6 metabolizer states on AM, ARI and ratio ARI/DHA. Particularly, this trend is observed in PMs that have 1.7-fold concentration of AM compared with NMs. FDA SmPC of AOM warns of the need to adjust the dose to 300 mg in PMs for CYP2D6 as they found 60 % higher AM concentrations in these metabolizers (SmPC Abilify Maintena, Otsuka Pharmaceuticals, 2024). In real world data, we observed 67 % higher

Table 2

Plasma concentrations (ng/mL) and Ratio ARI/DHA among CYP2D6 phenotypes after phenoconversion. Presented as Median (Interquartile Range). AM: Active moiety ARI: Aripiprazole; DHA: Dehydroaripiprazole; PM: Poor Metabolizer; IM: Intermediate Metabolizer; NM: Normal Metabolizer. *: $p < 0.05$; **: $p < 0.01$.

	PM (12)	IM (23)	NM (36)	p	p PM vs IM	p PM vs NM	P IM vs NM
AM	327 (202–353)	216 (171–313)	196 (162–274)	**0.0468***	0.0971	**0.0038****	0.2722
ARI	243 (144–282)	153 (110.5–228.4)	145 (100–182)	**0.0302***	**0.0486***	**0.0027****	0.279
DHA	64 (60–88)	62 (54–77)	58 (42–74)	0.5752	0.6493	0.3375	0.3695
ARI/DHA Ratio	3.6 (2.3–4.2)	2.3 (1.8–3)	2 (1.8–2.9)	**0.0174***	**0.0055****	**0.0015****	0.7162

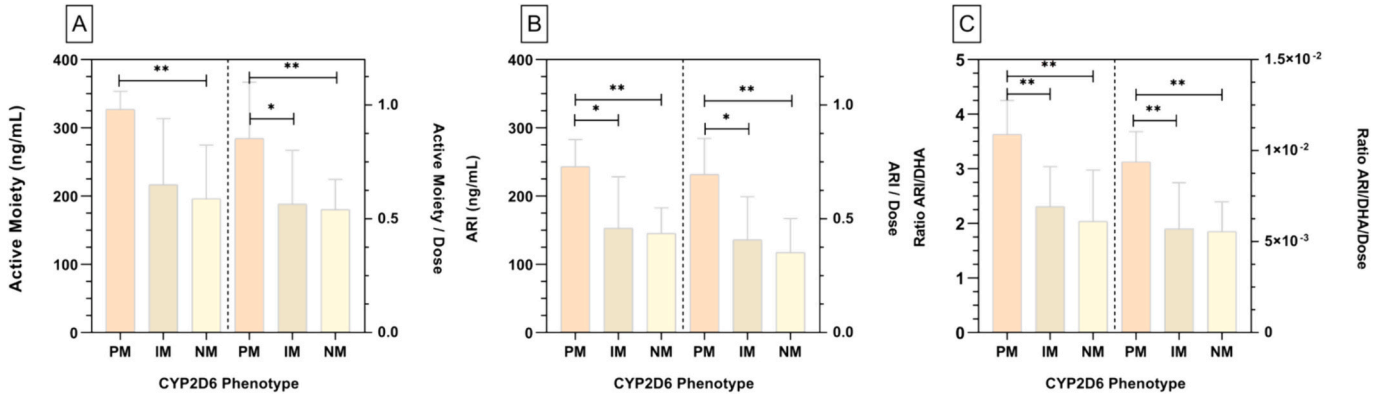

Fig. 1. AM, ARI and ARI/DHA Ratio concentrations and dose-adjusted ratios among the different CYP2D6 Phenotype groups after phenoconversion. *: $p < 0.05$; **: $p < 0.01$.

concentrations in these metabolizers for both AM and ARI and 77 % higher in the case of the ARI/DHA ratio. On the other hand, the SmPC recommends that, with concomitant medication that strongly inhibits CYP2D6, the dose adjustment should also be made to 300 mg, without considering the baseline metabolizer status.

The SmPC does not contemplate recommendations for IMs, nor does the Dutch Pharmacogenetics Working Group (Beunk et al., 2023). In other available works, IMs exhibit higher concentrations of AM and ARI with respect to NMs (Tveito et al., 2020; Zhang et al., 2019), but these non-prospective studies lack information about concomitant drugs and they have not been taken into account for the analysis. In our work, significant differences are obtained between PMs and IMs, although an upward trend is observed in IMs vs NMs, but significance was not reached.

The influence of certain concomitant drugs affecting CYP2D6 on ARI concentrations have been reported by other authors (Kiss et al., 2020; Nemoto et al., 2014). These findings are in line with our results but, in addition, in our study it has been carried out the stratification of patients according to the activity score associated with each allele. Also, it was possible to obtain information about the analysis of more than 20 allelic variants, as well as the number of copies of variants, and a strict phenoconversion was done taking into account the drugs included in the FDA list of CYP2D6 inhibitors, which is one of the most authoritative resources (Table of Substrates, Inhibitors and Inducers, FDA, F, 2024). This influence on ARI concentrations is also observed after dose-adjusted concentrations, where this increase continues to be observed. The adjusted dose-concentrations for AM and ARI in the NMs in our study are practically identical to those observed in other works available in the literature (Hart et al., 2022; Nagai et al., 2012).

In our study, no relationship was found between the metabolizing phenotype for CYP2D6 and plasma DHA concentration, as previously stated by other authors (Tveito et al., 2020). In the present work, we provide the parent-to-metabolite ratio ARI/DHA, where 77 % higher ratios were found for PMs compared to NMs. Therefore, the increase in AM observed is at the expense of ARI concentration. NMs ARI/DHA ratios obtained are in accordance with the AOM SmPC, but a certain inter-variability is observed (SmPC Abilify Maintena, Otsuka Pharmaceuticals, 2024).

With most of the focus remaining on the genetic polymorphisms of CYP2D6 and their consequent effect on the pharmacokinetics of ARI, nonetheless, the role of CYP3A4 cannot be entirely dismissed. Furthermore, observing the constant and unchanging concentration of DHA across the different CYP2D6 metabolizing groups, the role of CYP3A4 should be studied. To study this possible effect, patients were grouped according to predicted activity for CYP2D6 and CYP3A4. We observed 75 % higher AM and 83 % higher ARI concentrations in the PM-CYP2D6-PM-CYP3A4 group compared to the NMs group for both cytochromes. Statistical significance was maintained when the comparison was made using dose-adjusted ratios. On the other hand, when performing this adjustment, PM-CYP2D6-PM-CYP3A4 groups showed a 58 % higher AM and 66 % higher ARI compared with PM-CYP2D6-NM-CYP3A4. All these differences were also observed in the ARI/DHA ratio between the same groups. On the contrary, other studies have explored the influence of CYP3A4 on ARI metabolism without finding a correlation (Belmonte et al., 2018; Saiz-Rodríguez et al., 2020), this could be due to the fact that the combined effects of the two cytochromes were not taken into account and that their samples did not include homozygotes for the *22 allele.

Our analysis also reveals that PMs for both cytochromes have 45 % higher DHA concentration than NMs. This suggests that CYP3A4 plays a more significant role than expected, in the elimination of DHA. In the possible metabolic pathways that can undergo DHA shown in the molecule's FDA approval documents (Review for approval of Aripiprazole, FDA, 2001), CYP3A4 catalyzes up to 3 possible reactions and two of them independently of CYP2D6. Therefore, the reduction in the metabolizing capacity of this pathway could explain the increase in DHA

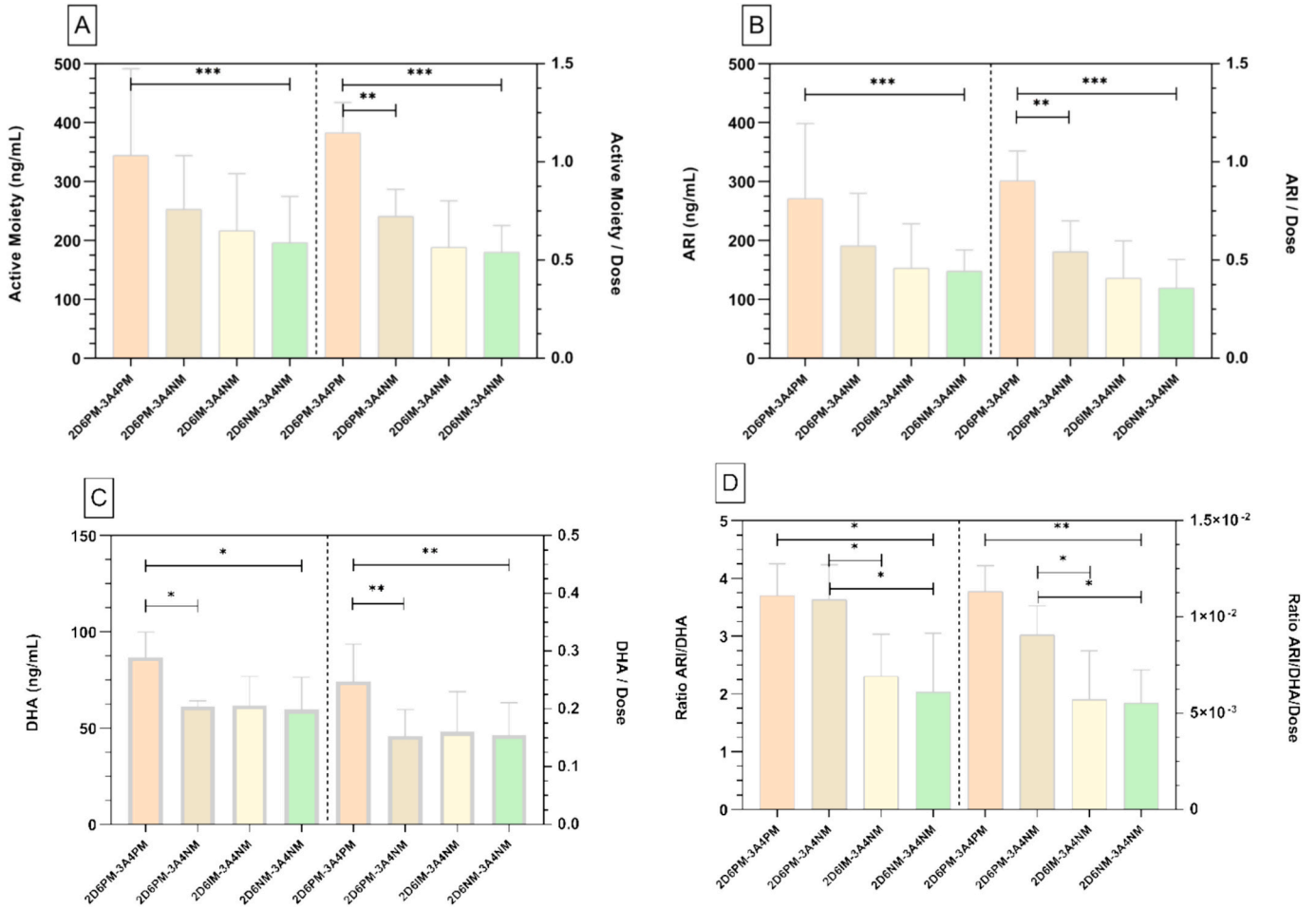

Fig. 2. Active moiety, ARI and ARI/DHA Ratio concentrations and dose-adjusted ratios among the different CYP2D6-CYP3A4 combined phenotypes. *: $p < 0.05$; **: $p < 0.01$; ***:$P < 0.001$.

Table 3
Plasma concentrations and Ratio ARI/DHA corrected among CYP2D6 phenoconverted phenotypes and CYP3A4 phenotypes. AM: Active Moitey; ARI: Aripiprazole DHA: Dehydroaripiprazole; PM: Poor Metabolizer; IM: Intermediate Metabolizer; NM: Normal Metabolizer. *: $p < 0.05$; **: $p < 0.01$; ***:$P < 0.001$.

	2D6NM-3A4NM (34)	2D6IM-3A4NM (24)	2D6PM-3A4NM (8)	2D6PM-3A4PM (4)	p	p NM-NM vs IM-NM	p NM-NM vs PM-NM	p IM-NM vs PM-NM	p PM-NM vs PM-PM	p NM-NM vs PM-PM
AM	197 (160–275)	217 (173–314)	253 (183–344)	344 (324–492)	0.0574	0.2819	0.13	0.5355	0.1535	**0.0003*** **
ARI	148 (100–194)	153 (110–228)	191 (138–280)	271 (231–399)	**0.0485***	0.289	0.0997	0.3132	0.2141	**0.0005*** **
DHA	60 (42–76)	62 (54–77)	61 (45–64)	87 (73–100)	0.2612	0,3925	0,8138	0,5076	**0.0162***	**0,0344***
ARI/DHA Ratio	2 (1.8–3)	2.3 (1.8–3)	3.6 (2.3–4.2)	3.7 (2.5–4.2)	0.0701	0.7333	**0.0122***	**0.0253***	0.901	**0.0304***

concentrations and the increases observed in AM and ARI for this metabolizer states. Furthermore, our analysis reveals that CYP2D6PM-3A4PM have 41 % more DHA than CYP2D6PM-3A4NM, which reinforces this hypothesis.

This study increases the evidence that PMs for CYP2D6 should be treated with lower doses of AOM. On the other hand, a trend towards higher concentrations of AM and ARI in IMs were observed. In addition, the evidence provided by this study shows that considering concomitant drugs is needed to stratify patients when it comes to the clinical implementation of these techniques, and it is probably the cause of the difference in the results found with other studies that do not take this effect into account. On the other hand, CYP3A4 metabolizer status also influences AOM metabolism and affects plasma concentrations of AM, ARI and DHA. Therefore, it would be advisable to be genotyped and combined with CYP2D6 activity.

In relation to the main limitation of this study, it is necessary to highlight the reduce sample size. In this regard, having a larger sample size would have allowed us to obtain more statistically significant differences and create more robust evidence.

Genotyping and phenotyping of CYP2D6 and CYP3A4 as well as consider concomitant drugs may constitute an important tool to obtain optimal concentrations within the therapeutic reference range and,

consequently, maximizing therapeutic efficacy while reducing the potential adverse events. Further studies should be performed to relate our results with clinical outcomes of patients under AOM therapy.

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Ethical statement

The authors declare that all procedures performed were in accordance with the ethical standards of the relevant national and institutional committees on human experimentation and with the 1975 Declaration of Helsinki (as revised 2008). All procedures involving patients were approved by the Drug Research Ethics Committee of Galicia (2020/486) and written informed consent was obtained from all subjects.

CRediT authorship contribution statement

Gonzalo Hermelo Vidal: Investigation, Formal analysis. **María Vidal-Millares:** Methodology, Investigation, Data curation. **María José Durán-Maseda:** Methodology, Investigation, Data curation. **Alicia Rial-Pérez:** Writing – review & editing, Investigation, Data curation. **Olalla Maroñas:** Data curation, Conceptualization. **Angel Carracedo:** Data curation, Conceptualization. **Ana Estany Gestal:** Methodology, Formal analysis. **Francisco Cajade-Pascual:** Writing – review & editing, Data curation. **Irene Zarra-Ferro:** Writing – review & editing, Visualization. **Anxo Fernández-Ferreiro:** Writing – review & editing, Project administration, Investigation, Funding acquisition. **Cristina Mondelo-García:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2024.111134.

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