CYP2C8*3 and *4 define CYP2C8 phenotype: An approach with the substrate cinitapride

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Abstract
Cinitapride is a gastrointestinal prokinetic drug, prescribed for the treatment of functional dyspepsia, and as an adjuvant therapy for gastroesophageal reflux disease. In this study, we aimed to explore the impact of relevant variants in CYP3A4 and CYP2C8 and other pharmacogenes, along with demographic characteristics, on cinitapride pharmacokinetics and safety; and to evaluate the impact of CYP2C8 alleles on the enzyme’s function. Twenty-five healthy volunteers participating in a bioequivalence clinical trial consented to participate in the study. Participants were genotyped for 56 variants in 19 genes, including cytochrome P450 (CYP) enzymes (e.g., CYP2C8 or CYP3A4) or transporters (e.g., SLC or ABC), among others. CYP2C8*3 carriers showed a reduction in AUC of 42% and Cmax of 35% compared to *1/*1 subjects (p = 0.003 and p = 0.011, respectively). *4 allele carriers showed a 45% increase in AUC and 63% in Cmax compared to *1/*1 subjects, although these differences did not reach statistical significance. CYP2C8*3 and *4 alleles may be used to infer the following pharmacogenetic phenotypes: ultrarapid (UM) (*3/*3), rapid (RM) (*1/*3), normal (NM) (*1/*1), intermediate (IM) (*1/*4), and poor (PM) metabolizers (*4/*4). In this study, we properly characterized RMs, NMs, and IMs; however, additional studies are required to properly characterize UMs and PMs. These findings should be relevant with respect to cinitapride, but also to numerous CYP2C8 substrates such as imatinib, loperamide, montelukast, ibuprofen, paclitaxel, pioglitazone, repaglinide, or rosiglitazone.

Study Highlights
WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
CYP2C8 is a poorly described gene from a pharmacogenetic perspective, traditionally assumed to have a minor impact on pharmacotherapy with numerous substrates.
INTRODUCTION

Functional dyspepsia (FD) and gastroesophageal reflux disease (GORD) are associated with significantly increased healthcare costs related to doctor visits, diagnostic examinations, and therapeutic procedures, and a reduced quality of life.\(^1,2\) The prevalence of GORD worldwide is 13.3%, and in Europe is from 15% to 19.1%,\(^3\) whereas the global prevalence of uninvestigated FD is from 6.9% to 17.6%.\(^4\) In Spain, 9.8% of the population manifests typical symptoms of GORD more than once a week, as well as dyspeptic symptoms (39% of patients present it at some time throughout their life).\(^5,6\)

Cinitapride (4-amino-N-[1-(3-cyclohexen-1-yl-methyl)-4-piperidinyl]-2-ethoxy-5 nitrobenzamide) is a gastrointestinal prokinetic drug, developed and commercialized in Spain in 1989. It is prescribed for the treatment of FD, and as an adjuvant therapy for GORD.\(^7\) Due to its procholinergic/serotonergic activity, cinitapride increases the tone of the lower esophageal sphincter with a potent gastrokinetic effect, generating significant evacuation of the bowel. It is also a D2 receptor antagonist which can contribute to the prokinetic effect.\(^8\) The frequencies of some adverse drug reactions (ADRs) are not entirely known, being similar among benzamides. Consistent with its mechanism of action, neurological disorders related to extrapyramidal symptoms (neck, tongue, and face muscle spasm), somnolence (with a prevalence of 0.1% to 1%), gynecomastia, galactorrhea, skin and subcutaneous tissue disorders like rash, pruritus, and angioedema, are described in the drug label.\(^7,9\) Cinitapride is marketed in India, Pakistan, Peru, Argentina, Paraguay, Uruguay, Mexico, Costa Rica, Guatemala, Honduras, Nicaragua, Panama, and El Salvador.\(^10\)

Cinitapride undergoes significant hepatic first-pass metabolism. More than 70% of an oral dose is rapidly absorbed and metabolized by the isoforms of the cytochrome P450 (CYP), CYP3A4 and CYP2C8.\(^7\) After 1 mg single oral dose, cinitapride's area under the curve from 0 to 24h (AUC<sub>0-24</sub>) was from 1580 to 3464 pg*h/ml, while C<sub>max</sub> ranged between 330 and 1398 pg/ml.\(^8,11,12\)

For cinitapride, the lack of articles describing its pharmacogenetics and the absence of clinical guidelines indicates the importance of further research in this area. Likewise, CYP2C8 (the gene coding for CYP2C8) is poorly characterized; Indeed, the impact of CYP2C8 alleles on the enzyme's function is not clearly known.\(^13–15\) Therefore, the assessment of their function on a well-known substrate such as cinitapride represents a valuable model which may be extended to other substrates.

The aim of this candidate gene study was to describe relevant pharmacogenetic biomarkers for cinitapride prescription. In this regard, we aimed to confirm the impact of relevant variants in CYP3A4 and CYP2C8 (i.e., the principal candidate genes) along with demographic characteristics on cinitapride's pharmacokinetics and safety and to evaluate the impact of CYP2C8 alleles on the enzyme's function. Furthermore, we aimed to evaluate in an exploratory manner other variants in other relevant pharmacogenes (i.e., secondary candidates). The reason for including single nucleotide polymorphisms (SNPs) in genes apparently unrelated to cinitapride was the scarcity of information included in its drug label and previous literature. This work is promoted by La Princesa University Hospital Multidisciplinary Initiative for the Implementation of Pharmacogenetics, PriME-PGx.\(^16\)

MATERIALS AND METHODS

Study design and population

The information for this candidate gene pharmacogenetic study was obtained from a bioequivalence clinical trial comprising 36 healthy volunteers, performed at the Clinical Trials...
Unit of Hospital Universitario de La Princesa (UECHUP) (EUDRA-CT: 2018–002444-90). It was a randomized, open-label, one-center, single-dose, crossover bioequivalence clinical trial of two cinitapride 1 mg tablet formulations, under fasting conditions, with a wash-out period of at least 7 days between the administration of both drugs. The reference formulation (R) was Cidine® 1 mg tablets (cinitapride marketed by Almirall, S.A.). In each period, volunteers were randomly assigned to receive one formulation, and in the following period they received the other one. The bioequivalence clinical trial was approved by the Independent Ethics Committee on Clinical Research (IECCR) of the Hospital de La Princesa and the Spanish Drug’s Agency (AEMPS), conducted in accordance with Spanish legislation and following the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines and the Revised Declaration of Helsinki.17,18 Inclusion criteria were as follows: man or woman, aged 18–55 years, with no physical or psychiatric pathology, and normal laboratory tests. Exclusion criteria included: having received prescribed drugs in the previous 15 days, or any kind of medication in the 48 h prior to dosing, except for contraception, a body mass index (BMI) outside the 18.5–30 kg/m² range, history of sensitivity to any drug, lactose intolerance, positive drug screening or alcohol poisoning in the last week before hospitalization, smoking, having donated blood in the last month before hospitalization, pregnant or breastfeeding women, participation in another study in the previous 3 months, inability to collaborate during the study, and history of swallowing difficulties.

Study design and procedures

Twenty-five volunteers gave their informed consent for participation in the pharmacogenetic study. During hospitalization at UECHUP and subsequent controls, 17 samples were obtained for pharmacokinetic profiling, between baseline to 72 h post-dose. Subsequently, EDTA-K2 tubes were centrifuged and plasma was stored at −80°C until drug plasma determinations, which was outsourced to an external analytical laboratory. A high-performance liquid chromatography triple quadrupole mass spectrometer (HPLC-MS/MS) instrument was used for the determinations, using a method fully validated according to Spanish current legislation (i.e., the European Medicine’s Agency’s guideline on bioanalytical method validation16). The lower limit of quantification (LLOQ) of the method was 0.5 pg/ml.

Pharmacokinetic analysis

Cinitapride pharmacokinetic data were analyzed with WinNonLin Professional Edition Version 8 (Pharsight Corporation). The following pharmacokinetic parameters were collected directly from the plasma time-concentration curves: cinitapride’s maximum concentrations (Cmax) and time to reach that concentration (tmax). The AUC from baseline to t, ’t’ being the last time-point (i.e., 72 h) (AUC0–t), was calculated using the linear trapezoidal rule. The drug clearance adjusted for bioavailability (Cl/F) was calculated as dose (D) divided by AUC; the volume of distribution adjusted for bioavailability (Vd/F) was calculated by dividing Cl/F by ke, ke being the apparent terminal elimination rate. The test (T) and R formulations were demonstrated to be bioequivalent; therefore, for each pharmacokinetic parameter, the mean of both formulations was calculated to reduce intraindividual variability.

Genotyping, haplotyping, and phenotyping

DNA was extracted from 500 μl of thawed peripheral blood stored in EDTA-K2 tubes in a Maxwell® RSC Instrument (Promega Biotech Ibérica S.L.). Genotyping was performed by real-time quantitative polymerase chain reaction (RT-qPCR) with TaqMan® hydrolysis probes. A QuantStudio 12 K Flex qPCR instrument (Applied Biosystems, ThermoFisher) was used along with an OpenArray® thermal block and a customized array. The analyzed genes and variants are summarized in Table 1. Alleles were selected based on their prevalence and functional impact. For instance, for CYP2C8, the three most relevant alleles in Madrid’s population are *2, *3, and *4; *2 has a 19% prevalence in Africans and 1.2% in Latin Americans (ethnic groups representing 19% and 62% of the immigrant population of Madrid, respectively) and *3 and *4 have a prevalence of 7%–15% in Iberians.20 Alleles located in genes with available Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines were selected based on CPIC’s allele function and frequency tables. The exploratory analysis of variants in genes apparently unrelated to cinitapride pharmacokinetics follows the same rationale as for previous publications21–23 to describe and discover new associations and clarify pharmacokinetic processes. CYP3A5, CYP2C19, SLC01B1, CYP2B6, CYP2D6 (including a copy number variation assay targeting exon 9), and UGT1A1 variants were used to infer the pharmacogenetic phenotype according to the CPIC guidelines.24–30 CYP3A4 alleles were used to infer the enzyme’s phenotype according to the Dutch Pharmacogenetics Working Group (DPWG) indications.31 The impact of CYP and UGT enzyme or ABC and SLC transporter genotypes or phenotypes on the pharmacokinetics and safety of cinitapride was evaluated; similarly, receptor genes (i.e., ADRA2A, HTR2A, HTR2C, DRD2, DRD3) were analyzed for their potential relationship with ADR incidence.
TABLE 1 Variants/alleles genotyped for this study

| Gene   | Allele (variant) | Gene   | Allele (variant) |
|--------|------------------|--------|------------------|
| CYP1A2 | *1C (rs2069514)  | CYP3A4 | *22 (rs35599367) |
|        | *1F (rs762551)   |        | *2 (rs55785340)  |
|        | *1B (rs2470890)  |        | *6 (rs4646438)   |
| CYP2B6 | *5 (rs3211371)   | ABCB1  | C3435T (rs1045642)|
|        | *9 (rs3745274)   |        | C1236T (rs1128503)|
|        | *4 (rs2279343)   |        | G2677T (rs2032582)|
| CYP2C8 | *2 (rs11572103)  | SLCO1B1| *1B (rs2306283) |
|        | *3 (rs10509681)  |        | *5 (rs4149056)   |
|        | *4 (rs1058930)   |        | rs4149015        |
| CYP2C9 | *2 (rs1799853)   | *3     | rs1057910        |
|        | *4 (rs1057910)   | SLC22A1| *2 (rs7252763)   |
| CYP2C19| *2 (rs4244285)   | *3     | rs12208357       |
|        | *4 (rs4986893)   | *5     | rs34059508       |
|        | *4 (rs28399504)  | COMT   | rs13306278       |
|        | *17 (rs1224850)  |        | rs4680           |
| CYP2D6 | *3 (rs35742686)  | ADRA2A | rs1800544        |
|        | *4 (rs3892097)   | HTR2A  | rs6313           |
|        | *6 (rs5030655)   |        | rs6314           |
|        | *7 (rs5030867)   |        | rs7997012        |
|        | *8 (rs5030865)   | HTR2C  | rs1414334        |
|        | *9 (rs5030656)   |        | rs3813929        |
|        | *10 (rs1065852)  |        | rs518147         |
|        | *14 (rs5030865)  | DRD2   | rs1799732        |
|        | *17 (rs28371706) |        | rs1800497        |
|        | *41 (rs28371725) |        | rs6277           |
| CYP3A5 | *3 (rs776746)    | DRD3   | rs6280           |
|        | *6 (rs10264272)  | ABCC2  | rs2273697        |
| UGT1A1 | *8 (rs878729)    |        | rs717620         |

Statistical analysis

Statistical analysis was conducted with SPSS Statistics Version 21.0. (IBM Corp.). AUC₀–₇ and Cmax were divided by the dose/weight ratio (DW), and CI/F and Vd/F were divided by weight to correct the impact of subject weight on pharmacokinetic variability, which may be variable according to sex or race. All pharmacokinetic data were logarithmically transformed to normalize distributions. Initially, an univariate analysis was conducted, whereby pharmacokinetic parameters were compared according to categorical variables (e.g., sex, race, genotypes, phenotypes) by means of an ANOVA test (for variables with three or more categories) or a t-test (variables with two categories). A Bonferroni post-hoc test was applied after ANOVA tests. Afterwards, all pharmacokinetic parameters were individually analyzed with a multivariate analysis, using linear regression. Only variables with p < 0.05 in the univariate analysis were included as independent variables, transformed into dummy variables when necessary. Moreover, due to the high number of tests and the subsequent high risk for type-1 error, the Bonferroni correction for multiple comparisons was used to adjust the level of significance in the multivariate analysis. The incidence of ADRs could not be analyzed because none of the adverse events reported in the clinical bioequivalence trial showed a causal relationship with drug administration. The Spanish Pharmacovigilance System Algorithm was used for the determination of causality.32

RESULTS

Demographic characteristics

Twelve men and 13 women were enrolled in this study. Weight and height were significantly superior in men compared to women (p = 0.018 and p < 0.001, respectively) but there was no difference in BMI. Moreover, there were no significant differences in age, weight, height, or BMI according to race (Table 2).

Pharmacokinetics

Mean AUC₀–₇ was lower for men (total = 3447.35 ± 1261.56 h*pg/ml, 2764.08 ± 1264.76 h*pg/ml for men, 4078.06 ± 904.94 h*pg/ml for women; p = 0.005) and similar for Caucasians and Latin Americans (3505.33 ± 1387.17 h*pg/ml and 3401.79 ± 1205.37 h*pg/ml, respectively; p = 0.829). Mean Cmax was 980.80 ± 388.93 h*pg/ml lower for men than women (858.90 ± 463.96 h*pg/ml vs. 1264.76 h*pg/ml for men, p = 0.003, p = 0.018 and p = 0.829). After DW correction, no significant differences were found for either AUC/DW or Cmax/DW and other pharmacokinetic parameters concerning sex and race (Table 3).

Table 4 shows the significant relationships observed between genotyped variants or phenotypes and cinitapride pharmacokinetic parameters. Subjects with CYP2C8 *1A/*3 and *3/*3 genotypes showed significantly lower cinitapride AUC/DW and Cmax/DW compared to subjects with the *1A/*1A genotype (decrease of 42% and 35% and 0.042, respectively) and with the *1A/*4 genotype (decrease of 42% and 35% and p = 0.004, p = 0.002, respectively). Conversely, *1A/*4 genotype showed a tendency towards higher AUC/DW and Cmax/DW compared to *1A/*1A genotype (p = 0.422 and p = 0.097). Conversely, significantly higher values of Vd/F and CI/F were observed
TABLE 2 Demographic characteristics of the healthy volunteers who participated in the study

| Sex       | N   | Age (years) Mean | Weight (kg) Mean | Height (cm) Mean | BMI (kg/m²) Mean |
|-----------|-----|-----------------|-----------------|-----------------|-----------------|
|           |     | Mean          | Mean          | Mean          | Mean          |
|           |     | SD            | SD            | SD            | SD            |
| Male      | 12  | 29.58         | 75.29*        | 174.83*       | 24.60          |
|           |     | 8.32          | 9.92          | 5.33          | 2.76           |
| Female    | 13  | 32.54         | 65.38         | 162.61        | 24.64          |
|           |     | 8.21          | 9.59          | 6.26          | 2.66           |
| Total     | 25  | 31.12         | 70.14         | 168.48        | 24.62          |
|           |     | 8.25          | 10.80         | 8.45          | 2.65           |
| Race      |     |                |                |                |                |
| Caucasian | 11  | 29.36         | 74.22          | 170.72        | 25.47          |
|           |     | 7.47          | 10.49          | 8.42          | 3.10           |
| Latin-American | 14 | 32.50         | 66.92          | 167.61        | 23.96          |
|           |     | 8.84          | 10.27          | 8.35          | 2.11           |
| Total     | 25  | 31.12         | 70.14          | 168.48        | 24.62          |
|           |     | 8.25          | 10.80          | 8.45          | 2.65           |

Abbreviations: BMI, body mass index; SD, standard deviation.
*p < 0.05 after t-test compared to the other category.

in subjects with CYP2C8 *1A/*3 and *3/*3 genotypes compared to those with *1A/*1A (p < 0.001, p = 0.003, respectively) and *1A/*4 diploets (p = 0.001, p = 0.004, respectively). In the case of the comparison between *1/*1 and *1A/*4, AUC/DW and C_{max}/DW values were 45% and 63% higher in *1A/*4, although these differences did not reach statistical significance (p = 0.422 and p = 0.097, respectively). Furthermore, CYP2C9 normal metabolizers (NMs) showed significantly higher AUC/DW, C_{max}, and t_{max} and significantly lower Vd/F and Cl/F compared to CYP2C9 intermediate (IM) and poor (PM) metabolizers (p = 0.002, p = 0.003, p = 0.038, p < 0.001, and p = 0.002, respectively). No significantly differences were found between CYP3A4 normal (NMs, n = 23) and intermediate (IMs, n = 2) metabolizers either in AUC/DW and C_{max}/DW (p = 0.719 and p = 0.523, respectively) or in the rest of the pharmacokinetics parameters.

Additionally, volunteers carrying the CYP1A2 *1/*1 diploety were significantly associated with a higher t_{1/2} than volunteers with the*1B/*1B diploety (p = 0.300). Individuals carrying the ABCB1 C1236T T/T genotype presented significantly higher values of t_{1/2} and Vd/F_W than those carrying the C/C diploety (p = 0.020, p = 0.031), while there were no differences in other SNPs of the ABCB1 gene. COMT rs13306278 C/C genotype carriers showed lower t_{1/2} (p < 0.040) and Vd/F (p < 0.01) in comparison with C/T subjects. SLC22A1*1/*1 individuals presented higher AUC/DW and lower Cl/F than *1/*3 (p = 0.027, p = 0.026, respectively). Finally, individuals with ABC2 rs2273697 G/G genotype exhibited a lower t_{1/2} compared with those with G/A and A/A genotypes (p < 0.02). No significant results were observed for variants in the remaining genes.

Regarding multivariate analysis, CYP2C8 *3 genotype and SLC22A1 *3 were significantly related to AUC/DW variability (Table 5); CYP2C8 genotype to C_{max}/DW variability; CYP2C8 genotype, CYP2C9 phenotype, and ABCB1 C1236T to Vd/F_W; and ABCB1 C1236T to t_{1/2} variability; and CYP2C8 genotype and SLC22A1*3 to Cl/F variability. No variables were related to t_{max} variability (Table 5). After Bonferroni correction for multiple comparisons, only CYP2C8 associations with AUC/DW, C_{max}/DW, Vd/F, and Cl/F variability and ABCB1 C1236T with Vd/F variability remained significant (i.e., p < 0.006).

No adverse event was causally related to cinitapride intake; therefore, no ADR was noted. Therefore, the effect of ADRA2A, HTR2A, HTR2C, DRD2, and DRD3 (genes potentially involved in cinitapride pharmacodynamics) polymorphism could not be evaluated concerning cinitapride's tolerability nor the impact of the remaining variants located in genes affecting cinitapride pharmacokinetics.

DISCUSSION

GORD and FD are highly prevalent in the world's population; consequently, the prescription of drugs for their treatment, including cinitapride, is very frequent and usually prolonged in time. To date, few studies have properly characterized cinitapride's pharmacokinetic profile. It is known as a substrate of CYP2C8 and CYP3A4, but the clinical relevance of genetic polymorphisms in these genes on cinitapride's exposure remains unknown. Moreover, no pharmacogenetic guideline has been published to date reporting a clinically relevant phenotype of CYP2C8 that can be inferred based on allele genotyping. Table 6 shows a list of relevant CYP2C8 substrates which may be affected by the presence of gene polymorphisms. Further research should be conducted evaluating the impact of CYP2C8 polymorphisms on the effectiveness, safety, and pharmacokinetics of these drugs. Similarly, only recently a pharmacogenetic guideline on CYP3A4 has been published for the substrate quetiapine. Hence, the present work is a convenient model to interrogate the effects of CYP3A4...
The pharmacokinetic parameters here observed generally resembled those previously reported in the literature. For instance, in Chinese, Mexican and German populations, AUC₀–ₜ and Cₘₚₙₐₓ after 1 mg cinitapride administration to young and healthy volunteers were 1580–3464 pg·h/ml and 330–1398 pg/ml,⁸¹¹,¹² while in the present study, an AUC₀–ₜ of 3447 ± 1261 pg·h/ml and a Cₘₚₙₐₓ of 980 ± 388 pg·h/ml were observed, with significant differences between males and females. Nevertheless, a high pharmacokinetic interindividual variability is observed among studies. Although some of this variability can be explained due to the study design (e.g., depending on fasting or fed condition), a non-negligible part of variability remains unexplained. When AUC₀–ₜ and Cₘₚₙₐₓ were divided by the DW ratio to correct the impact of weight on pharmacokinetic variability, the abovementioned significant sex differences disappeared. It can therefore be concluded that sex does not influence cinitapride’s exposure but weight does.

Concerning pharmacogenetics, CYP2C8 diplotype carriers showed a reduction in AUC of 42% and Cₘₚₙₐₓ of 35% compared to *1/*1 subjects. *4 allele carriers showed a 2.47-fold increase in AUC and a 2.53-fold increase in Cₘₚₙₐₓ compared to *3 allele carriers. Moreover, volunteers with the *1/*4 diplotype showed a 1.45-fold and a 1.63-fold increase in AUC/DW and Cₘₚₙₐₓ/DW compared to *1/*1 volunteers, but these association did not reach the level of significance due to the low sample size (i.e., only two *1/*4 individuals were identified). Accordingly, the following pharmacogenetic phenotypes can be proposed: CYP2C8 UMs (*3/*3), RMs (*1/*3), NMs (*1/*1), IMs (*1/*4), and PMs (*4/*4). To our knowledge, this is the first study to report a pharmacogenetic phenotype for CYP2C8. Since UMs and PMs were not sufficiently represented they could not be properly characterized. Additional studies are warranted to characterize UM and PM phenotypes. Not only are our findings relevant with respect to cinitaipride, but also to numerous additional CYP2C8 substrates such as imatinib, loperamide, montelukast, ibuprofen, paclitaxel, pioglitazone, repaglinide, or rosiglitazone. Potentially, CYP2C8 phenotype may become a clinically relevant pharmacogenetic biomarker to individualize pharmacotherapy with various drugs.

Notwithstanding the current findings, the effect of CYP2C8 alleles should be described further in depth. CYP2C8 is involved in the metabolism of a diverse number of drugs, the prototypical CYP2C8 substrate being paclitaxel.⁷⁸⁸⁸⁷⁸⁸ CYP2C8*2 and *3 alleles were associated with decreased metabolism of paclitaxel and arachidonic acid,⁷⁸⁸⁸⁷⁸⁸ and CYP2C8*3 with increased metabolism of
| Genotype or phenotype | N | AUC/DW (kg*h*pg/ml*mg) | C<sub>max</sub>/DW (kg*pg/ml*mg) | t<sub>max</sub> (h) | t<sub>1/2</sub> (h) | Vd/F (L/kg) | Cl/F (L/h*kg) |
|-----------------------|---|-------------------------|-------------------------------|-----------------|--------------|-------------|---------------|
|                       |   | Median | SD    | Median | SD    | Median | SD    | Median | SD    | Median | SD    | Median | SD    |
| **CYP2C8**             |   |         |       |         |       |         |       |         |       |       |         |       |         |       |
| *1A/*1A               | 12 | 280,762.57 | 85,231.95 | 75,763.43 | 23,803.30 | 0.85 | 0.11 | 48.62 | 10.43 | 261.62 | 62.80 | 3.91 | 1.13 |
| *1/*3 + *3/*3         | 10 | 162,863.15<sup>a</sup> | 63,250.72 | 48,951.85<sup>a</sup> | 14,131.46 | 0.76 | 0.07 | 63.68 | 35.18 | 627.35<sup>a</sup> | 344.41 | 7.13<sup>a</sup> | 2.79 |
| *1/*4                | 2  | 403,033.83 | 40,280.38 | 124,334.12 | 6660.84 | 0.75 | 0.00 | 42.40 | 6.77 | 151.90 | 42.41 | 2.51 | 0.23 |
| **CYP2C9**            |   |         |       |         |       |         |       |         |       |       |         |       |         |       |
| NM                   | 14 | 293,193.04<sup>*a</sup> | 93,972.24 | 81,663.87<sup>*a</sup> | 29,152.95 | 0.85<sup>*a</sup> | 0.11 | 47.45 | 10.35 | 249.25<sup>*a</sup> | 73.57 | 3.78<sup>*a</sup> | 1.19 |
| IM + PM              | 11 | 177,432.25 | 77,041.78 | 50,656.35 | 124,334.12 | 0.76 | 0.07 | 62.66 | 33.54 | 591.66 | 347.53 | 6.76 | 2.91 |
| **CYP1A2**            |   |         |       |         |       |         |       |         |       |       |         |       |         |       |
| *1/*1                | 2  | 214,491.16 | 65,685.21 | 55,649.07 | 7714.45 | 0.75 | 0.00 | 101.71<sup>*a</sup> | 27.97 | 393.54 | 279.82 | 5.13 | 3.45 |
| *1/*1B               | 12 | 270,460.10 | 132,861.33 | 67,668.36 | 33,307.86 | 0.80 | 0.10 | 53.60 | 12.32 | 393.54 | 279.82 | 5.13 | 3.45 |
| *1B/*1B              | 11 | 216,541.25 | 63,129.07 | 70,654.14 | 25,378.17 | 0.83 | 0.12 | 46.10 | 9.08 | 333.34 | 125.55 | 5.08 | 1.57 |
| **ABCB1 C1236T**     |   |         |       |         |       |         |       |         |       |       |         |       |         |       |
| rs1128503            |   |         |       |         |       |         |       |         |       |       |         |       |         |       |
| C/C                  | 10 | 202,527.12 | 92,016.32 | 64,764.72 | 29,073.89 | 0.80 | 0.11 | 46.57 | 11.09 | 395.32 | 207.06 | 5.75 | 2.06 |
| C/T                  | 12 | 287,405.91 | 119,990.45 | 71,141.34 | 31,759.91 | 0.84 | 0.11 | 47.39<sup>*a</sup> | 10.07 | 346.06 | 177.17 | 5.21 | 2.49 |
| T/T                  | 3  | 194,105.06 | 118,163.39 | 48,606.12 | 19,936.73 | 0.75 | 0.00 | 90.41<sup>*a</sup> | 38.67 | 514.34 | 438.18 | 4.85 | 2.87 |
| **ABCC2 rs2273697**  |   |         |       |         |       |         |       |         |       |       |         |       |         |       |
| rs13306278           |   |         |       |         |       |         |       |         |       |       |         |       |         |       |
| C/C                  | 17 | 232,045.46 | 96,946.17 | 66,551.96 | 27,286.33 | 0.81 | 0.11 | 47.38<sup>*a</sup> | 10.07 | 346.06 | 177.17 | 5.21 | 2.49 |
| G/A + A/A            | 8  | 263,960.57 | 119,990.45 | 71,141.34 | 31,759.91 | 0.81 | 0.10 | 46.57 | 11.09 | 395.32 | 207.06 | 5.75 | 2.06 |
| **COMT rs13306278**  |   |         |       |         |       |         |       |         |       |       |         |       |         |       |
| rs12208357           |   |         |       |         |       |         |       |         |       |       |         |       |         |       |
| C/C                  | 12 | 255,124.99<sup>*a</sup> | 99,082.99 | 69,141.44 | 24,925.98 | 0.83 | 0.10 | 55.16 | 25.41 | 371.61 | 272.52 | 4.59<sup>*a</sup> | 1.89 |
| C/T                  | 17 | 147,902.53 | 100,460.33 | 59,800.78 | 53,899.87 | 0.71 | 0.07 | 46.69 | 12.71 | 607.42 | 383.32 | 8.78 | 4.27 |
| **Total**            | 25 | 242,258.29 | 103,421.06 | 68,020.56 | 28,201.75 | 0.81 | 0.10 | 54.15 | 24.21 | 399.91 | 288.70 | 5.10 | 2.56 |

Abbreviations: AUC, area under the curve; C<sub>max</sub>, maximum concentration; Cl/F, drug clearance adjusted for bioavailability; DW, dose/weight ratio; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; SD, standard deviation; t<sub>1/2</sub>, time to reach half maximum concentration; t<sub>max</sub>, time to reach maximum concentration; Vd/F, volume of distribution adjusted for bioavailability.

<sup>a</sup>For the CYP2C8 analysis, one *3/*4 subject was excluded.

<sup>b</sup>CYP2C9 NM phenotype included *1/*1 diplotype; IM phenotype included *1/*2, *2/*2, and *1/*3 diplotypes only one volunteer showed the *2/*3 diplotype (PM phenotype).

*p < 0.05 after ANOVA or t-test; *1 p < 0.05 vs. *1/*1 and *1/*4, after ANOVA and Bonferroni post-hoc test; *2 p < 0.05 vs. *1B/1*B after ANOVA and Bonferroni post-hoc test; *3 p < 0.05 vs. *1/*1; *4 p < 0.05 vs. T/T.
Allele carriers also carry a CYP2C8 *3 allele. Here, the discrepancy (i.e., 96% of 30411A encoding for these alleles (2130G *2. The variants *3 and CYP2C9 (LD) between two ways. First, as a result of the linkage disequilibrium *3 on the enzyme's activity may be explained in CYP2C8 discrepancies encountered concerning the impact of on chromosome 10, and are inherited together very frequent. The variants *3 allele was related to a discrepancy in previous pharmacogenetic observational studies. In fact, the only subject with CYP2C8 *1/*3 and CYP2C9 *2 is a clear confusing factor that may have led to biased conclusions in previous pharmacogenetic observations. In contrast, CYP2C8 *4 allele is generally assumed to cause a reduction in the enzyme's function for drugs such as montelukast and paclitaxel, which is consistent with the findings reported here. We observed an apparent effect of CYP2C9 phenotype on cinatapride exposure variability; however, this association is not consistent as, even if cinatapride was metabolized via CYP2C9, which to our knowledge has not been reported to date, IM and PMs should accumulate the drug in plasma compared to NM, and the opposite effect was observed. Therefore, we confidently conclude that these effects are due to CYP2C8*3. Consistently, it should be emphasized that in the multivariate analysis, the association of CYP2C9 disappeared, supporting the above hypotheses. Second, the effect of CYP2C8*3 allele could be substrate-specific. This effect is well described for other genes and drugs, such as CYP2D6*17, a well-known decreased-function allele, which is related to higher des-brisoquine clearance. Further studies should clarify the effect of CYP2C8*3 allele on cinatapride's or other substrates' pharmacokinetics, but we suggest that the LD with CYP2C9*2 is a clear confusing factor that may have led to biased conclusions in previous pharmacogenetic observational studies. In fact, the only subject with CYP2C9 *1/*3 and CYP2C8 *1/*1 diplo- types exhibited a normal value of AUC/DW and Cmax/DW (data not shown), which confirms that CYP2C9 polymorphism does not impact the pharmacokinetics of cinatapride. In contrast, CYP2C8 *4 allele is generally assumed to cause a reduction in the enzyme's function for drugs such as montelukast and paclitaxel, which is consistent with the effects observed with cinatapride in the present study. Moreover, in a previous study conducted by our group, CYP2C8*3 allele was related to a higher clearance of ibuprofen as compared with individuals with CYP2C9 *1/*1 and CYP2C8 *1/*1 diplo- types, which is consistent with the findings reported here.

One additional variant, ABCB1 C1236T, was related to cinatapride's exposure variability. ABCB1 gene variants determine the activity of the P-glycoprotein, an efflux transporter localized in cell membranes throughout the entire body, which participates in the pharmacokinetics of several substrates. The effect of C1236T variant on the transporter's performance is currently still unknown, therefore further studies are warranted to confirm this association as no good comparators are available in the literature. Concerning CYP3A4, we failed to demonstrate a significant effect of

### Table 5

| Factor | β     | R²   | Significance (p) |
|--------|-------|------|------------------|
| AUC/DW |       |      |                  |
| CYP2C8*3 | *1A/*3 + *3/*3 vs. *1A/*1A + *1A/*4 | 0.57 | 0.557 | <0.001 |
| SLC22A1*3 | *1/*1 vs. *1/*3 | -0.44 | 0.041 |
| Cmax/DW |       |      |                  |
| CYP2C8*3 | 1A/*3 + *3/*3 vs. *1A/*1A + *1A/*4 | 0.51 | 0.376 | 0.001 |
| tmax   |       |      |                  |
| No variables related. |
| t1/2   |       |      |                  |
| ABCB1 C1236T | C/C vs. C/T + T/T | 0.507 | 0.266 | 0.010 |
| Vd/F   |       |      |                  |
| CYP2C8*3 | 1A/*3 + *3/*3 vs. *1A/*1A + *1A/*4 | -1.600 | 0.71 | 0.001 |
| ABCB1 C1236T | C/C vs. C/T + T/T | 0.933 | 0.002 |
| CYP2C9 | NM vs. IM + PM | -0.936 | 0.047 |
| CI/F   |       |      |                  |
| CYP2C8*3 | 1A/*3 + *3/*3 vs. *1A/*1A + *1A/*4 | -0.571 | 0.556 | <0.001 |
| SLC22A1*3 | *1/*1 vs. *1/*3 | 0.45 | 0.041 |

Abbreviations: AUC, area under the curve; Cmax, maximum concentration; CI/F, drug clearance adjusted for bioavailability; DW, dose/weight ratio; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; t1/2, time to reach half maximum concentration; tmax, time to reach maximum concentration; Vd/F, volume of distribution adjusted for bioavailability.

* p < 0.006 after Bonferroni correction for multiple comparisons in multivariate analysis.
its phenotype on cinitapride exposure variability due to the low sample size, as only two *1/*22 (IMs) subjects were identified.25,39

Finally, cinitapride is marketed in a few countries and it is indicated for highly prevalent pathologies. Therefore, patients diagnosed with GORD or FD under treatment with cinitapride may be able to avoid a certain percentage of ADRs and even lack of efficacy. For instance, we speculate that CYP2C8 UMs could require a daily dose increase of 50%–100%, while PMs may require dose reductions to avoid ADRs. Alternatively, another drug may be used. However, the relevance of this work extends beyond the association with cinitapride, as other more relevant substrates could be affected by these phenotypes (e.g., chemotherapy agents like paclitaxel). Having characterized with such clarity the effect of CYP2C8 polymorphisms and identified the methodological problem of LD with CYP2C9 in the literature is a major finding. This opens the door to properly evaluate the impact of CYP2C8 phenotype on the exposure and

### Table 6: Examples of CYP2C8 substrates

| Almotriptan     | Elagolix   | Mavacamten | Roxadustat |
|-----------------|------------|------------|------------|
| Aminophenazone  | Enasidenib | Meloxicam  | Samidorphan |
| Amiodarone      | Enalutamide| Mephenytoin| Selegiline |
| Amitriptyline   | Erlotinib  | Mestranol  | Selalexip |
| Amodiaquine     | Estradiol  | Methadone  | Selumetinib|
| Anastrozole     | Eszopiclone| Mitapivat  | Simvastatin |
| Antipyrine      | Ethinylenediol | Montelukast | Sitagliptin |
| Apalutamide     | Febuxostat | Morphine   | Sorafenib  |
| Apixaban        | Finerenone | Mycofenolate| Sulfadiazine|
| Apomorphine     | Fluorouracil| Nabilone   | Tazarotene  |
| Atorvastatin    | Fluvastatin| Naproksen  | Tegafur    |
| Azelastine      | Fosphenytoin| Nicardipine| Temazepam  |
| Azilsartan medoxomil | Glasdegib | Nicotine  | Tepotinib  |
| Belumosudil     | Halofantrine| Olodaterol | Terbinafine|
| Brigitinib      | Hydroxychloroquine | Ombitasvir | Testosterone|
| Buprenorphine   | Ibuprofen  | Omeprazole | Theophylline|
| Cabazitaxel     | Ilfosamide | Ozanimod   | Tirbanibulin|
| Caffeine        | Imatinib   | Paclitaxel | Tolbutamide |
| Cannabidiol     | Irbesartan | Palovarotene| Torasemide|
| Carbamazepine   | Ixazomib   | Pazopanib  | Treprostinil|
| Celecoxib       | Ketamine   | Perphenazine| Tretinoin   |
| Cerivastatin    | Ketorolac  | Phenprocoumon| Trifarotene|
| Chloroquine     | Lansoprazole| Phenytoin  | Trimethadione|
| Cisapride       | Lapatinib  | Pioglitazone| Trimethoprims|
| Clozapine       | Levomilnacipran | Piroxicam  | Tucatinib   |
| Cyclophosphamide| Lidocaine  | Pitavastatin| Velpatasvir |
| Dabrafenib      | Lonafarnib | Ponatinib  | Verapamil   |
| Dapsone         | Loperamide | Propofol   | Vortioxetine |
| Dasabuvir       | Loratadine | Quinine    | Voxelaprevir|
| Dexibuprofen    | Lorlatinib | Relugolix  | Warfarin    |
| Diazepam        | Lovastatin | Remdesivir  | Zafirlukast |
| Diclofenac      | Lumateperone| Repaglinide| Zidovudine  |
| Diltiazem       | Macitentan | Rosiglitazone| Zopiclone   |
| Eltrombopag     |            |            |            |

Note: List of substrates obtained from DrugBank.35

*aPharmGKB pathway available describing CYP2C8–drug interaction.

*bSubstrates majorly metabolized by CYP2C8.36
safety of other relevant substrates of CYP2C8 such as ibuprofen, paclitaxel, and pioglitazone. Potentially, this will contribute to advancing precision pharmacotherapy with CYP2C8 substrates.

Limitations

The most important limitation of our study is the sample size, which prevented the finding of genotypes of interest (e.g., CYP3A4*22) among the participating population. Moreover, some potentially relevant alleles could be present in our study population but were not genotyped (e.g., CYP3A4*20). In addition, these results are from a single-dose phase I clinical trial, in which healthy volunteers were recruited, therefore we were unable to draw any conclusion about cinitapride’s effectiveness. Moreover, the observed relationships regarding pharmacokinetics may not be extrapolable to patients, whose gastric motility may be affected, and therefore the process of absorption may significantly differ. Likewise, these results may not apply to patients outside the BMI range implemented in the inclusion criteria (e.g., obese patients). Moreover, no ADRs were noted and therefore we could not conclude as to cinitapride’s tolerability. In contrast, this study was performed under strictly controlled conditions, thus it is a good model to address the effects of genetic polymorphism on drug pharmacokinetics without the interference of smoking or other confounding factors.

CONCLUSIONS

CYP2C8*3 and *4 alleles may be used to infer the PM, IM, NM, and UM phenotypes. Not only is this relevant with respect to cinitapride, but also with respect to numerous additional substrates such as imatinib, loperamide, montelukast, ibuprofen, paclitaxel, pioglitazone, repaglinide, or rosiglitazone. Further studies are needed to validate the utility of this phenotype with cinitapride (particularly the impact of UM and PM phenotypes) and other substrates.

AUTHOR CONTRIBUTIONS

D.M.C., P.Z., and F.A.-S. wrote the manuscript. D.M.C., P.Z., and F.A.-S. designed the research. D.M.C., P.Z., P.S.-C., A.C., G.V.-G., M.N.-G., A.G.-F., R.P.G., G.M.-A., M.R., S.M.-V., D.O., and F.A.-S. performed the research. D.M.C., P.Z., and F.A.-S. analyzed the data.

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CONFLICT OF INTEREST

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