Metoprolol, a commonly prescribed β-blocker, is primarily metabolized by cytochrome P450 2D6 (CYP2D6), an enzyme with substantial genetic heterogeneity. Several smaller studies have shown that metoprolol pharmacokinetics is influenced by CYP2D6 genotype and metabolizer phenotype. To increase robustness of metoprolol pharmacokinetic estimates, a systematic review and meta-analysis of pharmacokinetic studies that administered a single oral dose of immediate-release metoprolol were performed. Pooled analysis (n = 264) demonstrated differences in peak plasma metoprolol concentration, area under the concentration–time curve, elimination half-life, and apparent oral clearance that were 2.3-, 4.9-, 2.3-, and 5.9-fold between extensive and poor metabolizers, respectively, and 5.3–, 13–, 2.6–, and 15-fold between ultrarapid and poor metabolizers (all P < 0.001), respectively. Enantiomer-specific analysis revealed genotype-dependent enantio-selective metabolism, with nearly 40% greater R- than S-metoprolol metabolism in ultrarapid and extensive metabolizers. This study demonstrates a marked effect of CYP2D6 metabolizer phenotype on metoprolol pharmacokinetics and confirms enantiomer-specific metabolism of metoprolol.
and PMs, a 2.3-fold difference in $C_{\text{max}}$/dose (90% CI: 2.2–2.4-fold, $P < 0.001$), a 4.9-fold difference in AUC/dose (90% CI: 4.7–5.0-fold, $P < 0.001$), a 2.3-fold difference in $t_{1/2}$ (90% CI: 2.3–2.3-fold; $P < 0.001$), and a 5.9-fold difference in CL/F (90% CI: 5.6–6.1-fold; $P < 0.001$) were found. Between EMs and UMs, a 2.3-fold difference in $C_{\text{max}}$/dose (90% CI: 1.9–2.9-fold; $P = 0.11$), a 2.7-fold difference in AUC/dose (90% CI: 1.9–4.0-fold; $P = 0.17$), a 1.1-fold difference in $t_{1/2}$ (90% CI: 0.7–3.6-fold; $P = 0.94$), and a 2.6-fold difference CL/F (90% CI: 1.9–3.3-fold; $P < 0.001$) were found.

Overall, the observed heterogeneity between the studies, as indicated by the $I^2$ statistics (these range from 0 to 100%; the lower the number, the lower the degree of heterogeneity), was high and ranged between 80 and 95%.

In addition to the gene-dose effect noted in the analysis of racemic metoprolol, a stereoselective metabolism of metoprolol that becomes more pronounced with an increasing number of functional alleles (http://www.cypalleles.ki.se/cyp2d6.htm) was observed in the pooled enantiomer-specific analysis (Table 2). As a result of genotype-dependent metabolism of the S-enantiomer, peak S-metoprolol concentrations and AUC are ~40% higher than those of R-metoprolol in the UM and EM groups (approximate S/R ratios: 1.5 and 1.5, respectively, for UM, and 1.3 and 1.5, respectively, for EM) and are ~20% higher.

Table 1  Pooled analysis of metoprolol pharmacokinetics stratified by CYP2D6 phenotype

| Group     | $n$ | $C_{\text{max}}$/dose (ng/ml/mg) | AUC/dose (μg × h/l/mg) | $t_{1/2}$ (h) | CL/F (l/h) |
|-----------|-----|---------------------------------|------------------------|--------------|------------|
| UM        | 12  | 0.67 (0.55–0.79)                | 2.73 (1.71–3.75)       | 2.8 (0.5–5.1) | 367 (259–474) |
| EM        | 122 | 1.56 (1.25–1.86)                | 7.31 (5.96–8.66)       | 3.1 (2.8–3.4) | 141 (127–157) |
| IM        | 11  | 2.56 (0.88–4.25)                | 18.46 (5.19–31.73)     | 4.8 (4.5–5.2) | 95 (60–130)   |
| PM        | 27  | 3.55 (2.60–4.50)                | 35.53 (28.97–42.09)    | 7.2 (7.0–7.5) | 24 (17–30)   |

Data presented as mean (95% CI).

AUC/dose, area under the curve divided by the dose of metoprolol given; CI, confidence interval; CL/F, oral clearance; $C_{\text{max}}$/dose, peak metoprolol concentration divided by the dose of metoprolol given; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; $t_{1/2}$, elimination half-life; UM, ultrarapid metabolizer.
in the IM group (approximate S/R ratios: 1.1 and 1.3 in IM, respectively). The preference for the metabolism of R-metoprolol is also seen in the different fold changes between the UM and the PM phenotypes regarding different PK parameters (5.3- vs. 3.8-fold difference in peak metoprolol concentration, 14.5- vs. 9.5-fold difference in AUC, and 30.4- vs. 22.4-fold difference in CL/F for R- vs. S-enantiomer, respectively).

Because the EM group has been broadly defined as having “at least one” active allele, an analysis was performed to determine whether a semiquantitative dose effect could be observed among different allele combinations.12,14 After assigning a score of 1 for each fully active allele, 0.5 for alleles with decreased activity, and 0 for inactive alleles/deletions, a clear trend toward decreased metabolism with lower semiquantitative dose was noted regarding peak metoprolol concentration and AUC (Table 3).

Finally, data regarding the influence of CYP2D6 metabolizer phenotype on the clinical effects of metoprolol were extracted. In these studies, exercise-induced heart rates of healthy volunteers were determined before and after the administration of metoprolol. Twenty participants from one study16 were excluded because the data appeared to be duplicated from an earlier study.15 A greater change in heart rate was observed in PMs, an effect that continued virtually unchanged for more than 12 h, while in EMs, the hemodynamic effects of metoprolol markedly decreased (Table 4). This effect was also noted in the 12-h area under the effect curve.

DISCUSSION

This meta-analysis provides more robust evidence of the effects of different CYP2D6 metabolizer phenotypes on metoprolol pharmacokinetics. A clear gene-dose effect was observed regarding metoprolol pharmacokinetics, whereby metabolism of metoprolol was found to be proportional to the number of active CYP2D6 alleles present, as evident in the four PK parameters measured (metoprolol $C_{\text{max}}$, AUC, $t_{1/2}$, and CL/F). In addition, CYP2D6 exhibits a preference toward metabolism of the
Table 3 Extensive metabolizer semiquantitative gene-dose subanalysis of metoprolol pharmacokinetics stratified by CYP2D6 phenotype

| Study          | N   | % Chg HR (1.5 h) | % Chg HR (12 h) | AUC/dose (μg × h/l/mg) | t1/2 (h) | CL/F (l/h) |
|----------------|-----|------------------|-----------------|------------------------|----------|------------|
| Hamelin⁹       | EM 10 | 21%            | 5 ± 7%          | 5.39 (4.28–6.49)       | 3.4 (2.7–4.2) | 168 (136–200) |
| Hemeryck¹⁰     | EM 8  | ND              | ND              | 203 ± 75 (%)          | ND       | ND         |
| Sharma¹⁶       | EM 16 | 24%            | 14 ± 2%         | 34.17                  | 8.2      | ND         |

Data presented as mean ± 95% CI.

Table 4 Effect of metabolizer phenotype on changes in exercise-induced heart rate

| Study          | N   | % Chg HR (1.5 h) | % Chg HR (12 h) | 12 h HR AUC |
|----------------|-----|------------------|-----------------|-------------|
| Hamelin⁹       | EM 10 | 21%            | 5 ± 7%          | ND          |
| Hemeryck¹⁰     | EM 8  | ND              | ND              | ND          |
| Sharma¹⁶       | EM 16 | 24%            | 14 ± 2%         | ND          |

Data presented as mean ± SD where applicable.

EM, extensive metabolizer; HR AUC, heart rate area under the effect curve; ND, not done; PM, poor metabolizer; % Chg HR, percentage change in heart rate.

R-enantiomer of metoprolol. The magnitude of this effect is dependent on the degree of metabolism exerted by the enzyme: PMs show no preference, whereas the difference between the enantiomers increases gradually through the IM, EM, and UM phenotypes. Finally, this pooled systematic analysis shows that these PK differences influence clinical effects of metoprolol such as increase or decrease in heart rate and blood pressure.

With varying degrees of statistical significance, each of the studies included in this meta-analysis demonstrated a gene-dose effect of CYP2D6 metabolizer phenotype on metoprolol pharmacokinetics. Consequently, the pooled analysis also demonstrates this effect, however, with greater statistical robustness, given the substantially larger sample size of 264 participants, while the largest individual study consisted of only 36 participants. In addition, no individual study presented PK data for all four metabolizer groups. Two studies presented oral clearance⁶ and AUC¹⁴ as a semiquantitative gene dose to provide a better understanding of individual allele-specific effects. The pooled analysis, however, now allows for a direct comparison of four PK parameters stratified by four major metabolizer phenotypes, with an additional semiquantitative gene-dose subanalysis of the EM group.

The results of this study have potential implications for clinical practice. First, additional evidence supporting the validity of CYP2D6 genotyping was demonstrated by a clear correlation among genotype, metabolizer phenotype, and metoprolol pharmacokinetics. Genotyping patients before initiating therapy with metoprolol would allow for the identification of PMs and UMs, thus potentially avoiding adverse events such as hypotension, syncope, and bradycardia in the former and a lack of effect in the latter. Armed with this foreknowledge, adjustment of the initial metoprolol dose or the use of alternative drugs that are not major substrates for CYP2D6 may be considered. Alternative β-blockers that do not depend on CYP2D6 metabolism are bisoprolol, a lipophilic drug that has been successfully tested in heart failure, and atenolol, which is hydrophilic but has fewer positive end point studies. Carvedilol, a newer “third-generation” β-blocker with unique vasodilating properties, may also be a good alternative, although carvedilol undergoes some CYP2D6-dependent metabolism. Carvedilol has been shown in several studies (e.g., the COMET trial) to be superior to metoprolol in the treatment of heart failure. Given the significant effects that the CYP2D6 phenotype has on metoprolol pharmacokinetics, as well as the substantial prevalence of CYP2D6 UMs and PMs (combined prevalence probably >10% population), it may be possible that some of the observed differences in clinical trials comparing metoprolol with other β-blockers may have been due to underlying CYP2D6 genotype and metabolizer phenotype. Furthermore, in the future, it may be possible to target and adjust metoprolol dosing according to the CYP2D6 genotype/phenotype.

While this study observed a robust CYP2D6 gene-dose effect on metoprolol pharmacokinetics, it has several limitations. First, the results of any meta-analysis are limited by the parameters of the studies that comprise the meta-analysis. Therefore, several of the limitations inherent to the original studies are carried forward. For example, not all ethnic groups were represented in this study; only white and Asian participants were reported. The lack of diversity in this analysis could limit the generalizability of the results. Second, additional alleles or confounding genetic variation in the form of yet-uncovered haplotypes could influence the conclusions drawn from the data. Finally, the meta-analysis showed a substantial degree of heterogeneity among the pooled studies, which limits the generalizability of the findings.

In summary, this systematic review and meta-analysis provided robust evidence for the importance of CYP2D6 metabolizer phenotype in influencing plasma metoprolol pharmacokinetics and also confirmed the enantiomer-specific metabolism of metoprolol, which is dependent on the degree of metabolism present. These results could have further implications for pharmacogenetics-oriented personalized β-blocker therapy.

METHODS

Data sources and study selection criteria. This study followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. A comprehensive search of the PubMed database was conducted for articles published up to October 2012, using the terms metoprolol and CYP2D6. All articles published in English that evaluated the association between CYP2D6 metabolizer...
phenotype and metoprolol pharmacokinetics were screened. In addition, bibliographies of those articles were scanned in search of further articles. To be included in the systematic review, the articles had to fulfill the following inclusion criteria: (i) study participants must have received a single dose of racemic, immediate-acting metoprolol and not any other medications (prescribed or study drugs), (ii) study participants must have been genotyped for CYP2D6, (iii) metoprolol PK data must have been stratified by metabolizer phenotype, and (iv) at least one of the four PK parameters (peak metoprolol concentration, AUC, half-life, and oral clearance) must have been present. A total of 153 studies were screened, of which 13 met the inclusion criteria.

**Genotype/phenotype data and data compilation.** For each study, participants were assigned to a distinct CYP2D6 metabolizer phenotype according to previously published criteria25–27 using phenotypic data (i.e., debrisoquine or dextromethorphan metabolizer status) and/or genotyping data for CYP2D6. Regarding genotyping for CYP2D6, subjects with a gene duplication resulting in more than two active CYP2D6 alleles (i.e., defined as *1, *2, *33, and *35) were classified as UMs, while those with at least one active allele were classified as EMs. Subjects carrying two alleles of substrate-dependent decreased activity (i.e.,*9, *10, *17, *29, *36, and *41) or compound heterozygotes for one decreased activity allele in combination with a null allele (i.e.,*3–*8, *11–*16, *19, *20, *21, *38, *40, *42, *44, *56, and *62) were termed as IMs. A combination of two null alleles in a homozygous variant or compound heterozygous manner was classified as a PM phenotype.12,28,29

The focus analysis on four common PK parameters: $C_{\text{max}}$, AUC, $t_{1/2}$, and CL/F. Data were acquired from published results and converted to commonly reported units ($C_{\text{max}}$ (ng/ml), AUC (ng × h/ml), $t_{1/2}$ (h), CL/F (l/h)) as needed. Because different doses of metoprolol were administered, $C_{\text{max}}$ and AUC were normalized by dividing by the dose given ($C_{\text{max}}$/dose and AUC/dose).

**Statistical analysis.** The statistical analysis was performed with Comprehensive Meta-Analysis software, version 2.2.064 (Biestat, Englewood, NJ). Because of the substantial heterogeneity between studies, pooled PK parameters were calculated using a random-effects model. The inverse variance method was used for weighing studies. Heterogeneity between studies was formally assessed by the I² statistics. Nonnormality of the data distribution was considered and tested for but found to be not serious enough to warrant special treatment. Comparison of the means of pooled PK parameters between metabolizer phenotype groups was done by one-way analysis of variance (mean and 95% CI). $P$ values were not adjusted for multiple comparisons. The calculation for the quotient between two means and its corresponding 90% CI was done using Fieller’s method,30 which was incorporated in an online calculator (http://www.graphpad.com/quickcalcs). A $P$ value of <0.05 was considered statistically significant. GraphPad Prism 6.0.2 (GraphPad, La Jolla, CA) was used for additional statistical analyses.

**SUPPLEMENTARY MATERIAL** is linked to the online version of the paper at http://www.nature.com/cpt

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**AUTHOR CONTRIBUTIONS**

C.M.B., P.N., E.D.K., and M.S. wrote the manuscript. C.M.B., P.N., E.D.K., and M.S. designed the research. C.M.B. performed the research. C.M.B. and P.N. analyzed the data.

**CONFLICT OF INTEREST**

P.N. has received research support from Roche Diagnostics (Indianapolis, IN) and Express Scripts (St Louis, MO), both unrelated to this study. The other authors declared no conflict of interest.

**Study Highlights**

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

- The CYP2D6 metabolizer phenotype has been shown to influence metoprolol pharmacokinetics in several small studies.

**WHAT QUESTION DID THIS STUDY ADDRESS?**

- This meta-analysis of 11 clinical trials that utilized plasma samples from healthy volunteers after a single oral dose of metoprolol addresses the impact of CYP2D6 metabolizer phenotype on metoprolol pharmacokinetics.

**WHAT THIS STUDY ADDS TO OUR KNOWLEDGE**

- The pooled analysis ($n = 264$) demonstrated a 5.3-fold difference in peak plasma metoprolol concentration, a 13-fold difference in area under the concentration-time curve, a 2.6-fold difference in elimination half-life, and a 15-fold difference in apparent oral clearance between UMs and PMs. Enantiomer-specific analysis revealed genotype-dependent enantio-selective metabolism, with nearly 40% greater R- than S-metoprolol metabolism in UMs and EMs.

**HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS**

- These results could have further implications in a pharmacogenetics-oriented, personalized β-blocker therapy.

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