Relationship between the Concentration of Hydrocodone and its Conversion to Hydromorphone in Chronic Pain Patients Using Urinary Excretion Data

Neven H. Barakat1, Rabia S. Atayee1,2, Brookie M. Best1,3 and Amadeo J. Pesce4,5*

1University of California, San Diego (UCSD), Skaggs School of Pharmacy & Pharmaceutical Sciences, La Jolla, CA, 2UCSD Medical Center, Department of Internal Medicine, San Diego, CA, 3Department of Pediatrics, School of Medicine (UCSD), Rady Children’s Hospital-San Diego, San Diego, CA, 4Millennium Research Institute, San Diego, CA, and 5Department of Pathology and Laboratory Medicine, School of Medicine (UCSD), La Jolla, CA

*Author to whom correspondence should be addressed. Email: apesce@millenniumresearchinstitute.org

Hydrocodone in combination with acetaminophen is commonly used to control moderate pain and is metabolized by cytochrome P4502D6 to form the active metabolite, hydromorphone. The purpose of this study was to determine the metabolic relationship and variability between hydrocodone and its conversion to hydromorphone using urinary excretion data from chronic pain patients. Liquid chromatography–tandem mass spectrometry was used to quantify hydrocodone and hydromorphone concentrations in urine specimens. The first visits of 25,200 subjects who took hydrocodone and had measurable concentrations were included in this study. The geometric mean (95% confidence index) of hydrocodone and hydromorphone urine concentrations were 1.39 (1.37–1.41) mg per gram of creatinine and 0.224 (0.221–0.227) mg per gram of creatinine, respectively. The log of creatinine-corrected hydromorphone versus the log of creatinine-corrected hydrocodone showed a positive relationship (R² = 0.20), with 60-fold variability between subjects. The plot of the log of the metabolic ratio ([hydromorphone] divided by [hydrocodone]) versus the log of creatinine-corrected hydrocodone had a coefficient of determination of R² = 0.42, with 125-fold variability between subjects. Ultra-rapid metabolizers represented 0.6% of the population, whereas 4% were poor metabolizers. Within-subject variability for the excretion of hydrocode- done in urine was 23-fold, whereas between-subject variability was 134-fold. Hydrocodone and hydromorphone urine concentrations showed great variability within and between subjects.

Introduction

Hydrocodone is a semi-synthetic opioid that is structurally related to codeine and is frequently used for the relief of moderate pain. Similar to other opioids, it stimulates the mu-opioid receptor, inhibits the release of transmitters from sensory neurons and alters pain transmission. Although hydrocodone has proven effective in the treatment of pain, it has also been associated with poisonings and deaths, which makes a better understanding of hydrocodone metabolism an important task. In 2008, the American Association of Poison Control Centers’ National Poison Data System (NPDS) reported 26,166 poisoning cases that involved hydrocodone in combination with other drugs and 11,726 poisoning cases that involved hydrocodone alone, with 21 hydrocodone-associated deaths (1). Hydrocodone is currently not available as a single compound. Rather, it is marketed as part of combination products with non-opioids, most commonly acetaminophen.

Hydromorphone being the only pharmacologically active metabolite. Hydromorphone is formed by the O-demethylation of hydrocodone, as catalyzed by cytochrome (CYP) P4502D6 (3). After administration of hydrocodone, 5–6% of the dose is recovered in urine as hydromorphone and conjugated hydromorphone (2) (Figure 1). Hydromorphone has approximately 4–6-fold higher potency than hydrocodone (4), and is itself marketed as Dilaudid for the management of severe pain. When administered subcutaneously, the analgesic potency of hydromorphone is 5–8 times greater than that of morphine (5).

Enzymatic conversion of hydrocodone to hydromorphone by CYP2D6 does not occur in approximately 7% of Caucasians, called poor metabolizers (PM) (6). Patients who are considered PM are distinguishable from extensive metabolizers (EM) by their inability to perform CYP2D6-catalyzed biotransformations at the same rate (5). As a result, the in vivo formation of hydromorphone is profoundly low in PM compared to the rest of the population, who are EM (7). This impaired O-demethylation of hydrocodone to form hydromorphone is also thought to result in phenotypic differences in drug response (5).

This retrospective study was conducted to evaluate the metabolism and variability in metabolism of hydrocodone to hydromorphone. Understanding the conversion of hydrocode- done to hydromorphone within pain patients will help establish a predictive model to help maintain therapeutic and safe pain regimens. Assessing the amount of variability between and within patients in their relative concentrations of hydrocodone and hydromorphone may help explain unexpected toxicities and variability in efficacy.

Methods

Drug concentrations from 160,380 random urine specimens collected as part of routine clinical care from adult patients treated for pain were measured by Millennium Laboratories (San Diego, CA) between March 2008 and February 2010. From this dataset, concentration results from patients with reported use of hydrocodone were included. Those reporting use of hydromorphone in addition to hydrocodone as part of their pain therapy were excluded. All study data were de-identified and Institutional Review Board-exempt status was granted by the University of California, San Diego Human Research Protections Program. The study dataset included a study-specific patient identification number, specimen identification number and liquid chromatography–tandem mass spectrometry (LC–MS-MS) urinary concentration results for hydroco-done and hydromorphone.

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An Agilent 1200 series binary pump SL LC system, well plate sampler and thermostatted column compartment paired with an Agilent Triple Quadrupole Mass Spectrometer and Agilent Mass Hunter software were used for analysis of hydrocodone and hydromorphone. Chromatographic separation was performed using an acetonitrile–formic acid–water gradient running at 0.4 mL/min and a 2.1 × 50 mm², 1.8 μm Zorbox SB C 18 column. Mobile phase A was +0.1 percent formic acid in water, B was 0.1 percent formic acid in acetonitrile, and column temperature was set to 50°C. Specimens were prepared for injection by incubating 25 μL of urine with 50 units of β-glucuronidase Type L-II from Patella vulgata (keyhole limpet) Sigma Product number G 8132 (Sigma-Aldrich Corp, St. Louis, MO) in a 50 μL 0.4M acetate buffer (pH 4.5) for 3 h at 45°C. Five microliters of the solution was injected for each specimen.

All spectra were collected using positive electrospray ionization. The optimized instrumental parameters were as follows: gas temperature, 350°C; drying gas, 12 L/min; nebulizer gas (nitrogen), 35 psi (~24,100 Pa); capillary voltage, 3,000 V; and fragmenter voltage, 60 V. Multiple reaction monitoring (MRM) mode was used for quantitation. Scan time was set to 500 ms. In MRM mode, two transitions were used to identify and quantitate a single compound. A quantitative transition was used to calculate concentration based on the quantifier ion and a second transition was used to ensure accurate identification of the target compound based on the ratio of the qualifier ion to the quantifier ion. The ion criteria were used for the qualitative identification with ±20% of the average ion ratios for calibrators.

HPLC-grade water, acetonitrile, methanol and formic acid were obtained from VWR (Westchester, PA). Hydrocodone and hydromorphone were obtained from Cerilliant Corp. (Round Rock, TX). At the beginning of the analysis, the internal standard solution contained 1,500 ng/mL of deuterated standard and enzyme β-glucuronidase. One hundred microliters of this solution was added to 25 μL of patient’s sample. The final concentration of the internal standard was 1,200 ng/mL.

Quantitative analysis was performed using Agilent Mass Hunter Quantitative Analysis software. A four-point calibration curve was created by using a linear fit and forcing the line to go through the origin. Accepted accuracy for calibrators was ±20 percent of the target value and the coefficient of determination (R²) was required to be greater than or equal to 0.99 as verification of linearity and goodness-of-fit. The lower limit of quantitation for both the hydrocodone and hydromorphone was 50 ng/mL. The upper limit of linearity for both the hydrocodone and hydromorphone assays were 100,000 ng/mL.

Descriptive statistics and graphical analyses were conducted with Microsoft Excel 2007 (Microsoft Corp., Redmond, WA) and OriginPro v8.1 (OriginLab, Northampton, MA). Data were log-transformed, means, standard deviations and confidence intervals were calculated, and the results were back-transformed to determine the geometric means and 95% confidence intervals. Single values for hydrocodone, hydromorphone, and metabolic ratio ([hydromorphone] divided by [hydrocodone]) were also calculated for each subject by log-transforming the data, calculating an average and a standard deviation within a subject, and back-transforming the values.

Subjects with urine creatinine concentrations less than 20 mg/dL were excluded because this indicated highly dilute urine specimens (2, 8). Data from the first visit were used from...
each subject who took hydrocodone but not hydromorphone for pain. Subjects with detectable concentrations of morphine, codeine, and heroin metabolite (6-monoacetylmorphine) were excluded due to interference with hydrocodone metabolism (9). Subjects at or above the lower limit of quantitation (50 ng/mL) for both hydrocodone and hydromorphone were used in the summary quantitative analyses. Subjects with concentrations below the lower limit of quantitation for one analyte, either hydrocodone or hydromorphone, were plotted to determine the percent frequency of the population that are ultra-rapid or poor metabolizers.

Results

Figure 2 is a flow chart of patient selection for the study. Urine specimens from 153,215 subjects had creatinine concentrations ≥20 mg/dL. From this group, 53,728 subjects reportedly taking hydrocodone, and no other medications that would lead to formation of hydromorphone or hydrocodone, were included for further study. 25,200 subjects had a first visit that was analyzed. If a subject had multiple visits, only their first visit was analyzed to prevent skewing the data toward subjects with multiple visits. In addition, a separate analysis to determine within-subject variability included urine specimen results from 273 subjects with five or more visits (1,699 total visits). The excretion observations showed that the range of concentration values was quite large. For that reason, logarithmic representations of the data were used. Figure 3A is a histogram showing the inter-subject population distribution of the urinary concentrations of creatinine-corrected hydrocodone (mg/g cr). The data are plotted logarithmically and approximate a Gaussian distribution. The geometric mean [95% confidence interval (CI)] was 1.39 (1.37–1.41) mg/g cr. The median was 1.59 mg/g cr, with a 25th percentile of 0.658 mg/g cr and a 75th percentile of 3.22 mg/g cr. The arrows show that 95% of the population have a hydrocodone concentration within the range of 0.089–12.2 mg/g cr. These statistics are summarized in Table I.

Figure 3B is a similar histogram showing the inter-subject population distribution of the concentration of creatinine-corrected (mg/g cr) hydromorphone (as a metabolite). The logarithmic plot also approximates a Gaussian distribution. The geometric mean (95% CI) was 0.224 (0.221–0.227) mg/g cr. The median was 0.219 mg/g cr, with a 25th percentile of
0.108 mg/g cr and a 75th percentile of 0.443 mg/g cr. The arrows show that 95% of the population have a creatinine-corrected hydromorphone concentration within the range of 0.035–1.77 mg/g cr. These statistics are also summarized in Table I. These statistics describe the range of values expected of patients prescribed hydrocodone.

The next analysis was performed to establish whether or not the metabolic pathway for conversion of hydrocodone to hydromorphone was saturable. For this analysis, log creatinine-corrected hydrocodone (mg/g cr) was plotted against log creatinine-corrected hydromorphone (mg/g cr; Figure 4A). A positive correlation was observed with a linear regression between hydrocodone and hydromorphone \( (R^2 = 0.203 \text{ and } y = 0.37x - 0.7) \) (95% CI: 0.784, 0.801; \( p \)-value < 0.0001) (A). Plot of log creatinine corrected (mg/g cr) hydrocodone versus log MR, [hydromorphone] divided by [hydrocodone]; a negative relationship is visible between creatinine corrected hydrocodone and the MR \( (R^2 = 0.422, y = -0.63x - 0.7) \) (95% CI: 0.927, 0.945; \( p \)-value < 0.0001) (B).

In an attempt to correct for the lack of hydrocodone dose information, the variance in metabolism and metabolic ratio were calculated from a narrow range of excreted hydrocodone concentrations (excluding the extremes of concentrations to try to capture subjects taking the most common doses). To examine this concept, a slice of the range of values around the median hydrocodone concentration of Figure 4A was used. For the selected hydrocodone concentration range (median log value of 0.201 mg/g cr, range of logged values of 0.101–0.301 mg/g cr), the corresponding hydromorphone concentrations were highly variable but approximated a Gaussian distribution when plotted on a log scale. The variance is the square of the standard deviation (SD). To determine the variance, the range from \(-2\) to \(+2\) SDs was calculated. The variance was 59.7 as calculated by the formula: antilog of 4 times the SD; the SD was 0.444. A similar analysis was performed using the corresponding metabolic ratios for the same range of hydrocodone concentrations. Again, an approximated Gaussian distribution of values was observed. The SD was 0.524 for log MR and the fold variance was 125.

The large population base allowed determination of the percent of ultra-rapid and poor metabolizers. For this analysis, ultra-rapid metabolizers were defined as those patients whose urine excretion pattern contained no hydrocodone in the presence of high concentrations of hydromorphone. Specimens with values of hydrocodone below 50 ng/mL were considered to contain no hydrocodone. A sigmoidal plot (Figure 5A) was

| Table I  |
|-------------------------------|----------------|----------------|----------------|----------------|----------------|
| Intersubject Hydrocodone and Hydromorphone Concentrations and MRs | | | | | |
| | Hydrocodone (mg/g cr)* | Log hydrocodone* | Hydromorphone (mg/g cr)* | Log hydromorphone* | MR | Log MR |
| Geometric mean | 1.39 | 0.143 | 0.224 | -0.649 | 0.161 | -0.793 |
| Standard deviation | 3.44 | 0.536 | 2.78 | 0.444 | 3.34 | 0.524 |
| 95% CI (upper) | 1.41 | 0.150 | 0.227 | -0.644 | 0.164 | -0.786 |
| 95% CI (lower) | 1.37 | 0.137 | 0.221 | -0.655 | 0.159 | -0.799 |
| Median | 1.59 | 0.201 | 0.219 | -0.660 | 0.162 | -0.792 |
| 25th percentile | 0.658 | -0.182 | 0.108 | -0.968 | 0.074 | -1.13 |
| 75th percentile | 3.22 | 0.508 | 0.443 | -0.353 | 0.351 | -0.455 |
| *Creatinine-corrected.
used to estimate the number of patients with no hydrocodone versus increasing concentrations of hydromorphone. The resulting estimation for the prevalence of ultrarapid metabolism was approximately 0.6 ± 0.4% of the population. In contrast, considering patients forming no hydromorphone as poor metabolizers, a similar sigmoidal plot analysis (Figure 5B) revealed an estimate of the prevalence of poor metabolizers of 4.0 ± 3.3%. However, some subjects described as poor metabolizers may include those that ingested their hydrocodone directly before voiding a specimen and thus did not have sufficient time to metabolize hydrocodone to hydromorphone.

Inter-subject variability was examined by comparing variability in concentrations from specimens obtained from the first visit of all subjects. Intra-subject variability was assessed by examining the specimens available from patients with five or more visits to the physician’s office. The degree of variability is expressed as the fold difference between the upper and lower 95% confidence limits of concentrations for both inter-subject and intra-subject populations. For hydrocodone excretion concentrations, inter-subject variability was 134-fold and intra-subject variability was 23-fold (Table II). Using the same analysis for hydromorphone excretion, a 51-fold variability between-subjects and a 27-fold within-subjects variability were observed (Table II).

Table II
<table>
<thead>
<tr>
<th>Intra-subject statistics</th>
<th>Hydrocodone (mg/g cr)*</th>
<th>Log hydrocodone*</th>
<th>Hydromorphone (mg/g cr)*</th>
<th>Log hydromorphone*</th>
<th>MR</th>
<th>Log MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean</td>
<td>1.77</td>
<td>0.249</td>
<td>0.288</td>
<td>–0.572</td>
<td>0.151</td>
<td>–0.821</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>2.21</td>
<td>0.344</td>
<td>2.28</td>
<td>0.358</td>
<td>2.35</td>
<td>0.372</td>
</tr>
<tr>
<td>95% CI (upper)</td>
<td>1.95</td>
<td>0.289</td>
<td>0.295</td>
<td>–0.530</td>
<td>0.167</td>
<td>–0.777</td>
</tr>
<tr>
<td>95% CI (lower)</td>
<td>1.61</td>
<td>0.208</td>
<td>0.243</td>
<td>–0.615</td>
<td>0.136</td>
<td>–0.885</td>
</tr>
<tr>
<td>Median</td>
<td>1.86</td>
<td>0.269</td>
<td>0.267</td>
<td>–0.574</td>
<td>0.156</td>
<td>–0.806</td>
</tr>
<tr>
<td>25th percentile</td>
<td>1.10</td>
<td>0.041</td>
<td>0.151</td>
<td>–0.820</td>
<td>0.088</td>
<td>–1.05</td>
</tr>
<tr>
<td>75th percentile</td>
<td>2.92</td>
<td>0.465</td>
<td>0.408</td>
<td>–0.389</td>
<td>0.266</td>
<td>–0.575</td>
</tr>
</tbody>
</table>

*Creatinine-corrected.

Relationship between the Concentration of Hydrocodone and its Conversion to Hydromorphone in Chronic Pain Patients Using Urinary Excretion Data

The excretion histograms and the tabulated data in Table I and Figures 3A and 3B should give practitioners interpreting urinary excretion data a range of expected values. Tremendous variability was observed in both hydrocodone and hydromorphone urine concentrations.

Discussion

The metabolic ratio [hydromorphone] divided by [hydrocodone] represents the metabolism of hydrocodone for a subject at a point in time. The variability of metabolic ratio between subjects was 115-fold and within subjects was 30-fold. This analysis was also performed using the sum total of both the hydrocodone and hydromorphone. The sum of hydrocodone and hydromorphone was calculated by converting hydromorphone to hydrocodone using molar ratios and adding together. The inter-subject and intra-subject variability of the sum analysis was 75-fold and 18-fold, respectively.

To compare the extent of variability between and within-subjects, we used the SD of MR (Figure 6). The geometric SD of the intersubject group was 3.34 (Table I). For the intra-subject group, the SD of the MR for each individual subject was determined, and those values (one value per subject) were averaged. This resulted in an average of the intra-subject geometric SDs of the MR of 1.94 (Table III). Figure 6 shows that the intra-subject population variability is smaller than the inter-subject variability in hydrocodone metabolism to hydromorphone.

Relationship between hydrocodone and hydromorphone

Our results demonstrate a positive correlation between hydrocodone and hydromorphone concentrations. However, the...
In the third case, the subject excreted 100 mg of hydrocodone, and therefore the MR would be equal to 0.1. In the fourth case, the subject excreted 1 mg of hydrocodone, then for the sake of simplicity we may assume that they also excreted 1 mg of hydromorphone, and therefore the MR would be equal to 1. Let us also assume that the subject excreted 10 mg of hydrocodone and made 1 mg of hydromorphone, in which case the MR will be 0.1. In the third case, the subject excreted 100 mg of hydrocodone and made 1 mg of hydromorphone, and therefore the MR will be 0.01. This shows that the relationship is linear, not a one-to-one relationship between the parent drug and its metabolite. In this case, the MR is decreasing as the concentration of hydrocodone is increased. Therefore, we show that the MR decreases with increasing concentration of hydrocodone, which illustrates saturation. An alternative explanation is that the metabolite has not had time to reach steady state. In other words, patients that took hydrocodone recently before providing a specimen and thus had a high concentration of the parent drug did not have sufficient time for the metabolite to appear in the urine. The variability in the metabolic ratio around the median is large, 125-fold in the total population.

### Relationship between hydrocodone and metabolic ratio
A negative relationship is observed between the hydrocodone concentration and the MR, as in Figure 4B. This demonstrates that the concentration of hydrocodone increases as the MR decreases, indicating saturation of metabolism. The variance in the MR ranges from 113 to 133-fold. The MR variability increases with higher hydrocodone concentrations, where metabolism may be saturated. This is caused by pharmacogenetic variability of CYP2D6, or by differing time intervals since intake of prior doses. The main enzyme responsible for the formation of hydromorphone from hydrocodone is CYP2D6, which has many polymorphisms. Some allelic variants can lead to a complete loss of CYP2D6 activity, as seen most commonly in Caucasian populations. Observations in other ethnic populations reveal reduced function and even hyperfunctional CYP2D6 alleles. The large variance seen in this study may be explained by these polymorphisms, resulting in ultra-rapid metabolizers (UM), EM, intermediate metabolizers (IM), and PM (10) included in the test population (11).

### Ultra-rapid and poor metabolizers
The lower asymptote of the sigmoidal fit (Figures 5A and 5B) allows estimation of the proportion of UMs and PMs. Subjects with detectable hydromorphone and undetectable hydrocodone were used in the estimation of UMs (0.6 ± 0.4% of the population). This observation is consistent with reports that the prevalence of CYP2D6 UMs in the European population is 1–2% (12). Another source of detectable hydromorphone with no hydrocodone may be subjects taking non-reported hydrocodone. Subjects with detectable hydrocodone and undetectable hydromorphone were used in the estimation of PMs (4.0 ± 3.3%). Outliers may be due to deception (adding hydrocodone directly to urine specimens) or variability in the time the specimen was collected after dose intake. The expected percent of PMs for a Caucasian population is approximately 7% (5). Our observation (4%) was less, but is reasonable considering the possible diversity of the test population.

PMs may develop higher concentrations of hydrocodone with chronic use, allowing for tolerance for these high concentrations to develop (8, 13). UMs may form higher concentrations of hydromorphone, which has greater activity on the mu-opioid receptor than hydrocodone, causing toxicity (including death) from high hydromorphone concentrations while hydrocodone concentrations remain low (13, 14). However, Otton and colleagues (5) failed to find a significant difference between hydrocodone concentrations in UMs versus PMs, although a significant difference between the hydromorphone concentration was observed (13, 15). Few studies have used urine data to compare and differentiate between PMs and UMs (16, 17). However, the results of the current study show that it is possible to use urine data to differentiate between PMs and UMs.
The sigmoid plot for EMs includes subjects that have parent drug (hydrocodone) concentrations below the lower limit of quantitation (50 ng/mL), as represented on the y-axis, and concurrent metabolite (hydromorphone) concentrations above the lower limit of quantitation (50 ng/mL), represented on the x-axis. Each point on the graph is the percentage of subjects in this category. The percentage is calculated such that the frequency of subjects with hydromorphone in the absence of hydrocodone (n = 859) is divided by the frequency of subjects in the total population (n = 25,029) at that specific bin size (log hydromorphone concentration). The frequency count of these two populations was done using the same computational control of the bin size, i.e., the same minimum, maximum and number of bin sizes. Therefore, the percentage of subjects below the lower limit of quantitation is divided by the total population at that specific concentration of hydromorphone.

The same method is applied to the PM estimation in the population, except that it includes subjects that have hydrocodone concentrations above the lower limit of quantitation (50 ng/mL), as represented on the x-axis, and hydromorphone concentrations below the lower limit of quantitation (50 ng/mL), represented on the y-axis. The tail of the sigmoid plot is not the extension of the data where hydrocodone was detectable.

**Intra-subject and inter-subject variability**

This study shows that urine drug specimens taken from the same patient at different times have considerable variability. Although inter-subject variability has been primarily attributed to the inter-subject pharmacogenetic differences of the enzyme CYP4502D6, these data indicate that other variables such as dose amount, the time of the last dose, drug-drug interactions, circadian time, and fed or fasted state contribute to the observed variability between subjects.

The level of variation in the inter-subject population was two times greater than the intra-subject population. One explanation of the observed variation between patients is interferences of hydrocodone metabolism by co-medications. These data provide an estimate of the MR expected when hydrocodone is administered. If the MR values fall outside of this range, it is important to discuss with the patient which external factors are responsible.

**Limitations**

The major limitations of this study are that it is retrospective and no data were collected with regard to dose, collection time after last dose, age, gender or ethnicity (18). In addition to the variability in dosing regimens, hydrocodone doses range from 2.5 mg to 10 mg per tablet. Furthermore, hydrocodone is given in combination with acetaminophen (APAP). The dose limit is based on APAP doses and not hydrocodone. Because this medication is prescribed to be taken as needed, further variability may be observed in urine concentrations of both hydrocodone and hydromorphone due to intermittent dosing. Given the range of possible doses and schedules, CYP2D6 variability (5 to 10 fold between subjects) (10), and variability between subjects in disease state, kidney function, liver function and age, the observation of high (59.7-fold) variability in the metabolism of hydrocodone to hydromorphone is expected. This study was also limited by the lack of information on which subjects were UM or PMs and the potential of non-reported hydromorphone use.

**Conclusion**

For practitioners responsible for interpreting urine drug tests, it is helpful to know whether or not hydromorphone detection is expected and, when applicable, its relationship to the observed hydrocodone concentration. This work suggests that the MR of hydromorphone to hydrocodone is a useful marker because it can be compared to the reference ranges identified in this study and unusual findings can be further investigated by the physician. Because this is a large dataset, we have enough power to identify clinically relevant metabolic ranges. The study shows that there is a wide range of observed values as expressed by the MR. This is consistent with the known polymorphic variance of CYP2D6 expression and function.

**References**


