Naltrexone Metabolism and Concomitant Drug Concentrations in Chronic Pain Patients

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Naltrexone is effective in treating opioid dependence by blocking μ, κ and δ opiate receptors. Naltrexone is mainly metabolized to an active metabolite 6β-naltrexol by dihydrodiol dehydrogenase enzymes. Concomitant opioids will not be effective while patients are taking this antagonist. This was a retrospective analysis of urinary excretion data collected from patients being treated with pain between November 2011 and May 2012. Naltrexone, 6β-naltrexol and concomitant opiate concentrations were measured by liquid chromatography–tandem mass spectrometry. Interpatient variability was calculated from first-visit specimens, and intrapatient variability was calculated from patients with two or more visits. Relationships of the metabolic ratio (MR; 6β-naltrexol/naltrexone) with age, gender and urinary pH were also explored. From 88 first-visit patient specimens, the median MR was 3.28 (range 0.73–17.42). The MR was higher in women than men (5.00 vs. 3.14, P < 0.05). The MR showed no association based on age and urinary pH. Eighteen of 88 patients taking oral naltrexone tested positive for concomitant opiate use. Urinary MRs of 6β-naltrexol/naltrexone were highly variable, which may contribute to variability in efficacy, toxicity and patient willingness to take naltrexone as directed. Twenty percent of patients tested positive for opiates and naltrexone, thus showing the importance of monitoring patients taking naltrexone.

Introduction

Prescription drug abuse is a growing problem, and opioids are among the classes of medications that are commonly abused. The National Institute on Drug Abuse has reported that opioid prescriptions dispensed by retail pharmacies in the USA have nearly doubled from 2000 to 2010 (1, 2). Opioids are prescribed to reduce pain but have a high abuse potential. Methadone and buprenorphine have been successful in treating patients with opioid dependence, but their use has been restricted by policies that limit patients’ access to these medications (3). Another option is naltrexone, which is generally well tolerated with no potential for addiction (4). Naltrexone is an opioid antagonist that can treat opioid dependence by blocking μ, κ and δ opioid receptors and prevents the feeling of reward in opioid users (5, 6). Patients should be free of opioids for 7–10 days before starting naltrexone to prevent withdrawal symptoms, and opioid medications should not be used during treatment with naltrexone. The biggest concern, providers have in prescribing naltrexone, is the low rate of patients taking the drug as prescribed, and the high rate of patients relapsing with opioid use (7).

Naltrexone is metabolized through liver cystolic dihydrodiol dehydrogenases into 6β-naltrexol, which is an active metabolite that participates in the pharmacological response (5, 8). The metabolite has a much longer half-life than the parent drug but is less potent in reducing opioid cravings (9, 10). Although the previous studies have reported interpatient variability in the metabolism of naltrexone, the population sizes were quite small (8, 9, 11). Interpatient variability of naltrexone metabolism may contribute to differences in side effects and patient adherence. The retention of patients on naltrexone therapy is low, and methods need to be developed to improve the likelihood of patients taking the medication as directed (7). Detection of naltrexone in the urine and monitoring concentrations is important to ensure that patients are taking the medication and thus reduce the number of relapses to opioid dependence.

Prior studies have analyzed cravings of patients using opioids while on naltrexone therapy, and patients who discontinued naltrexone due to relapse (6, 12). However, data are limited documenting the percentage of patients who may be taking concomitant opioids while on naltrexone therapy, without their prescribers’ knowledge (7). Serious injury, adverse effects and death have been reported in cases of patients who used opioids concomitantly with naltrexone, in an attempt to overcome the opioid blockade (13–15). Adverse effects of naltrexone-activated opioid withdrawal may include delirium, severe vomiting and diarrhea, tachycardia and agitation (13). Some of these patients presenting to the emergency room were unaware that they were taking an opioid antagonist (15). Patients need to fully understand the risks of taking opioids while on naltrexone therapy. One suggested approach to help decrease naltrexone-related toxicities is that patients carry a medical card in case of emergencies, indicating they cannot receive opioids for pain (16).

The previous studies have shown higher concentrations of plasma naltrexone decreased cravings for opioids (12). Ideal plasma levels of naltrexone have been studied (12), but it may be useful to establish expected urinary concentrations of naltrexone and 6β-naltrexol to aid in interpreting urine drug tests for monitoring. The purpose of this analysis was to observe the variability in metabolic ratios (MRs), and the ranges of concentration prescribers can expect in the urine of patients taking naltrexone. The effects of variables such as patient age, sex and urinary pH on metabolism were explored, and prevalence rates of subjects taking concurrent opioids and naltrexone were analyzed.

Experimental

Data collection of urine specimens

This retrospective data analysis included urine specimens collected from routine clinical testing of patients with chronic pain between November 2011 and May 2012. Specimens were...
Quantitating analyte concentrations in urine specimens

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 naltrexone and 6β-naltrexol. 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 Zorbax SB-C18 column. Mobile phase A = +0.1% formic acid in water, B = 0.1% formic acid in acetonitrile and column temperature was set to 50°C. Samples were prepared for injection by incubating 25 µL of urine with 50 U of β-glucuronidase type I-LI from Patella vulgata (keyhole limpet) Sigma Product number G 8132 (Sigma-Aldrich Corp., St. Louis, MO, USA) in 50 µL 0.4 M acetate buffer (pH 4.5) for 3 h at 45°C. Samples were centrifuged for 10 min at 3,000 rpm to remove turbidity. Five microliters of the solution were injected for each sample.

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 quantify a single compound. Data were acquired running the QQQ in MRM mode, using transitions naltrexone-D3: 345.2 → 327, naltrexone: 342.2 → 324, 342.2 → 55, 6β-naltrexol: 344.2 → 308.1 and 6β-naltrexol: 344.2 → 254.1. A quantitative transition was used to calculate concentration based on the qualifier 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. HPLC grade water, acetonitrile, methanol and formic acid were obtained from VWR (Westchester, PA, USA). Naltrexone and 6β-naltrexol were obtained from Cerrilliant Corp. (Round Rock, TX, USA). The deuterated internal standards were diluted to 1,000 ng/mL by adding them to synthetic urine (Microgenics Corp., Fremont, CA, USA). Quantitative analysis was performed using an 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% of the target value, and the coefficient of determination ($R^2$) was required to be ≥0.99 as verification of linearity and goodness of fit. The lower limit of quantitation (LLQ) for both the naltrexone and 6β-naltrexol was 10 ng/mL. The upper limit of linearity for both the naltrexone and 6β-naltrexol assays was 50,000 ng/mL. Based on the analysis of 2427 QC sample runs, for naltrexol tested at concentrations of 13.1 and 341 ng/mL, the coefficients of variation were 14.1 and 9.0%, respectively. For naltrexol tested at concentrations of 14.7 and 363 ng/mL, the coefficients of variation were 10.8 and 9.0%, respectively.

Inclusion criteria and sorting methodology

The sorting schematic employed is illustrated in Figure 1. Naltrexone and 6β-naltrexol concentrations and urine pH and creatinine were measured in 39,286 urine specimens. Medication lists were reported for each patient at the time of specimen collection. Inclusion criteria were: a creatinine concentration of ≥20 mg/dL, measured concentration of naltrexone and 6β-naltrexol above the LLQ of 10 ng/mL and patients taking oral naltrexone. Exclusion criteria were: patients reported taking intramuscular (IM) naltrexone, and specimens below the LLQ of either naltrexone or 6β-naltrexol. Patients who had indicated IM naltrexone on the list of medications were excluded from the analysis because this method of administering naltrexone bypasses first-pass metabolism and reduces metabolite production (17). Patients with self-reported naltrexone or without reported naltrexone were assumed to be taking the oral dosage form. From this, specimens from 88 patients were placed in the interpatient population for single or first visits only. Thirty-seven patients had two or more visits, and these were used to represent the inpatient population.

Study parameters

The MR was calculated as 6β-naltrexol/naltrexone, which was the best estimate of naltrexone metabolism in the absence of dose and time; the specimen was taken after administering the dose. Naltrexone and 6β-naltrexol concentrations were normalized to creatinine concentration to account for body mass and hydration status (18, 19) and log transformed to approximate a Gaussian distribution for the analyses. Intercal patient data were presented as medians and ranges of MR (20). Intrapatient data were reported as a range of fold differences within each individual (largest MR/smallest MR), with a median MR fold difference and ranges between those 37 patients.

Graphical and descriptive statistics

Descriptive statistics and graphical analyses were carried out with Microsoft® Excel 2010 (Microsoft Corp., Redmond, WA, USA) and OriginPro® 8.6 (OriginLab, Northhampton, MA, USA). Ranges of back-transformed urinary concentrations of...
naltrexone were also reported. Fold difference in MR was calculated as dividing highest MR by lowest MR for the inter- and intrapatient populations to describe differences in variability in the populations.

Linear regression analyses were used to determine relationships between naltrexone, 6β-naltrexol and MR with patient sex, age and urine pH. Age was calculated as the date of birth subtracted by date of specimen collection. Twelve patients did not report age. Fifty-seven men and 30 women reported their sex, and their MRs were compared using the Mann–Whitney U test. A P-value of <0.05 was considered to be statistically significant.

In a secondary analysis, specimens from 88 patients taking naltrexone which tested positive for naltrexone and its metabolite were screened for concentrations of heroin metabolite, 6-monoacetylmorphine (6-MAM), morphine, buprenorphine, codeine, hydrocodone, hydromorphone, norhydrocodone, oxycodone, noroxycodone, oxymorphone, fentanyl, methadone, propoxyphene, tramadol and meperidine. The LLQ for 6-MAM and buprenorphine was 10 ng/mL. The LLQ for morphine, codeine, hydrocodone, hydromorphone, norhydrocodone, oxycodone, noroxycodone and meperidine was 50 ng/mL. Fentanyl was 2 ng/mL, and methadone, propoxyphene and tramadol were set at 100 ng/mL. Regression analyses were performed to determine the relationship between morphine and 6β-naltrexol concentrations in the urine.

### Results

Of 39,286 urine specimens with creatinine at or >20 mg/dL, 265 (0.67%) specimens had concentrations of naltrexone and 6β-naltrexol above the LLQ. After filtering for duplicate visits, 88 patients had naltrexone and its metabolite above the LLQ. The MRs and concentrations of naltrexone and its metabolite are presented in Table I.

The median naltrexone concentration was 1.049 mg/g creatinine, and the range was 0.013–25.729 mg/g creatinine. The median 6β-naltrexol concentration was 4.30 mg/g creatinine, and the range was 0.063–45.209 mg/g creatinine. The median MR was 3.277, and the range was 0.728–92.972 (128-fold range). A strong positive correlation between naltrexone and 6β-naltrexol concentrations (Figure 2; \(y = 0.78x + 0.58, \quad R^2 = 0.76\)) was observed.

For the intrapatient population, the median fold difference of MRs was 2.08, ranging from 1.02 to 67.08 (Figure 3). One patient had a much higher average MR than the rest of the population (36 compared with the average MR of 3.79). This patient had three visits, with MRs of 9.40, 42.64 and 57.15 (fold difference 6.08).

Fifty-seven men and 30 women reported gender. The median MR for men was 1.64, and median MR for women was 2.01 (\(P = 0.04\)). No correlation was found between patient age and MR (\(y = 0.0065x + 0.3758, \quad R^2 = 0.04\)) or subject urinary pH and MR (\(y = 0.0063x + 0.6458, \quad R^2 = 0.0002\)).

In the secondary analysis, patients were analyzed for taking concomitant opioids. Of the 88 patients who tested positive for naltrexone, 18 (20%) were positive for a prescription opioid (Figure 4). Ten of these 18 patients tested positive for >1 opioid analyte. Twelve patients tested positive for morphine, four for hydromorphone, three for hydrocodone, four for codeine, three for oxymorphone, three for oxycodone, one for buprenorphine and two for tramadol. Three patients tested positive for the heroin metabolite, 6-MAM. First-visit specimens from 12 patients positive for both naltrexone and morphine showed a negative correlation between urinary morphine concentrations and naltrexone concentrations (\(y = -0.29x - 0.81, \quad R^2 = 0.27\)). A negative correlation (Figure 5: \(y = -0.35x - 0.27, \quad R^2 = 0.37\)) was observed between urinary morphine concentrations and 6β-naltrexol concentrations.

![Figure 2. 6β-Naltrexol vs. naltrexone concentrations. Log creatinine-corrected 6β-naltrexol as a function of log creatinine-corrected naltrexone with a linear regression line. Cr, creatinine.](https://academic.oup.com/jat/article-abstract/38/4/212/2798007)

![Figure 3. Distribution of MR in the intrapatient population. 6β-Naltrexol/naltrexone MR was calculated from 37 patients with two or more visits.](https://academic.oup.com/jat/article-abstract/38/4/212/2798007)

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**Table 1**

<table>
<thead>
<tr>
<th>Naltrexone (mg/g Cr)</th>
<th>6β-Naltrexol (mg/g Cr)</th>
<th>Metabolic ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.049</td>
<td>4.302</td>
</tr>
<tr>
<td>25th percentile</td>
<td>0.246</td>
<td>1.520</td>
</tr>
<tr>
<td>75th percentile</td>
<td>2.492</td>
<td>9.327</td>
</tr>
<tr>
<td>Range</td>
<td>0.013–25.729</td>
<td>0.063–45.209</td>
</tr>
</tbody>
</table>

Cr, creatinine; n = 88 patients, first visits.
between individuals (5). The fold difference of 128 concurs with previous reports of the considerable subject-to-subject variation in the pharmacokinetics of naltrexone (8, 9, 11). As expected from its longer half-life, 6β-naltrexol concentrations were higher than naltrexone concentrations. The previous studies have suggested genetic polymorphisms of metabolism. Some people might be poor metabolizers of naltrexone. Although no genetic tests were conducted in this analysis, the previous studies have suggested genetic polymorphisms contributed to the intersubject variability of 6β-naltrexol, which may affect the likelihood of patients taking their medication as prescribed (8, 25).

The variability between this patient’s three visits was not large (6-fold), which suggests that this was not an error of measurement. One possibility could be that he was a fast metabolizer, which might be seen to a greater extent with a larger sample size.

**Discussion**

**Inter- and intrapatient variability**

Naltrexone urinary concentrations and MRs of the interpatient population reflect the large variability found in the previous studies (Table I). The previous studies also found significant variability in the urinary excretion of 6β-naltrexol (9). The log transformation of data did not approximate a Gaussian distribution, again highlighting the large variability of MR between subjects. Naltrexone oral bioavailability ranges from 5 to 40%, between individuals (5). The fold difference of 128 concurs with previous reports of the considerable subject-to-subject variation in the pharmacokinetics of naltrexone (8, 9, 11). As expected from its longer half-life, 6β-naltrexol concentrations were higher than naltrexone concentrations. The previous studies have suggested that the higher MR or longer duration of metabolism in the body may contribute to prolonged side effects of the medication, including nausea and headache (11). These side effects may result in patients not taking naltrexone as prescribed (11). A comparison of the two populations shows that interpatient variability was much greater than intrapatient variability (128-fold difference vs. median 2.08-fold). One patient in the intrapatient population had much greater MRs than the average. The variability between this patient’s three visits was not large (6-fold), which suggests that this was not an error of measurement. One possibility could be that he was a fast metabolizer, which might be seen to a greater extent with a larger sample size.

**Variations in the metabolism of naltrexone**

A strong positive correlation was observed between log naltrexone and log 6β-naltrexol concentrations (Figure 2) (11). The value of the regression line was somewhat <1:1, which might be explained by: (i) decreased first-pass metabolism of naltrexone (22), (ii) genetic variability in metabolizing enzymes and (iii) gender differences in the metabolism of naltrexone (8). The elimination half-life for naltrexone and 6β-naltrexol vary within subjects and in different studies, but plasma concentrations of the metabolite are always observed as higher than the parent drug (23), which was also observed in this analysis. Naltrexone is well absorbed, but extensively biotransformed by first-pass metabolism, which limits the systemic amount of unchanged drug (24). In one study, however, naltrexone concentrations were found to be abnormally higher than 6β-naltrexol in some patients (23). Higher overall naltrexone exposure (area under the concentration–time curve) without a significant difference in half-life may be due to a decrease in first-pass metabolism. The exact cause of the higher than expected naltrexone was unknown, but the investigators hypothesized that decreased first-pass metabolism was due to drug interactions, or disease states such as hepatitis C. These same possibilities may explain why the slope of the regression line in this analysis was <1.

Pharmacogenetic differences in the polymorphic enzyme dihydriodiol dehydrogenase may play a part in the rate and extent of metabolism. Some people may be poor metabolizers of naltrexone. Although no genetic tests were conducted in this analysis, the previous studies have suggested genetic polymorphisms contributed to the intersubject variability of 6β-naltrexol, which may affect the likelihood of patients taking their medication as prescribed (8, 25).

The median MR for women was statistically greater than the median MR for men (0.7 and 0.5 log, P = 0.041). The previous literature presented conflicting data regarding a gender effect on the pharmacokinetics of naltrexone (17). Gender-related differences in the pharmacokinetics of naltrexone were not well reported in the past, but potential gender differences in pharmacology affecting the κ opioid receptor have been suggested (17, 26). The literature also stated that women achieved higher naltrexone and 6β-naltrexol concentrations than men given the same dose of naltrexone (27). One explanation for the higher MR in women is the possibility of testosterone inhibiting the metabolism of naltrexone. One study showed that testosterone and dihydrotestosterone inhibit 6β-naltrexol formation by as much as 50% but was not thought to be clinically significant; endogenous concentrations of testosterone would have to be much higher to affect metabolism (8). However, this retrospective data analysis showed a statistically higher MR in women than in men, which suggests that testosterone may inhibit the metabolism of naltrexone enough to be statistically relevant.
Detection of concomitant medications

The presence of concomitant opioids in the urine of patients who tested positive for naltrexone was examined. Twenty percent of patients who reported taking naltrexone tested positive for an opioid, which shows many patients are not following therapy as directed.

Of 18 patients who tested positive for naltrexone and opioids, only five patients reported taking naltrexone, suggesting prescribers are unaware of the illicit use of opioids or naltrexone (Figure 4). Only 38 of the 434 patients who reported taking naltrexone actually tested positive for naltrexone. This suggests an adherence rate of <10%. Fifty additional patients tested positive for naltrexone yet did not report it in their medication list. Patients may be taking naltrexone but are also taking opioids in attempt to overcome naltrexone’s antagonistic effects. This is in agreement with a previous study, in which more than half the patients taking naltrexone used illicit opioids on at least one occasion during a 6-month treatment period (28). The half-lives of the concomitantly observed opioids are under 24 h. Patients should be free of opioids for 7–10 days before initiating naltrexone therapy so it is unlikely that prescriptions for the opioids and naltrexone would overlap (29). Opioid use is most likely unknown to the treating prescriber as concomitant use of opioids is contraindicated (5).

The high frequency of urine specimens testing positive for both naltrexone and opioids suggests that more effective patient education and/or closer monitoring are needed. Three patients who tested positive for heroin and naltrexone were from different clinics, which suggest that it was not an isolated issue. The medication list did not show opioids prescribed along with naltrexone. In patients with unreported naltrexone, it is unclear whether they relapsed, or if they were prescribed naltrexone but had an inaccurate medication list. However, patients who reported naltrexone and tested positive for it should not have tested positive for opioids. Patients who reported naltrexone on their medication list but tested negative for naltrexone in their urine sample suggests non-compliance. Thirty-six percent (156 of 434) tested positive for opioids, which indicates relapse. Patients who reported taking naltrexone, suggesting prescribers are unaware of the illicit use of opioids or naltrexone (Figure 4). Only 38 of the 434 patients who reported taking naltrexone actually tested positive for naltrexone. This suggests an adherence rate of <10%. Fifty additional patients tested positive for naltrexone yet did not report it in their medication list. Patients may be taking naltrexone but are also taking opioids in attempt to overcome naltrexone’s antagonistic effects. This is in agreement with a previous study, in which more than half the patients taking naltrexone used illicit opioids on at least one occasion during a 6-month treatment period (28). The half-lives of the concomitantly observed opioids are under 24 h. Patients should be free of opioids for 7–10 days before initiating naltrexone therapy so it is unlikely that prescriptions for the opioids and naltrexone would overlap (29). Opioid use is most likely unknown to the treating prescriber as concomitant use of opioids is contraindicated (5).

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Several cases of misusing naltrexone with serious adverse effects have been documented. Prior reports suggested that heroin addicts may be self-administering naltrexone to try to prevent drug dependence (13). Some purposely try to overcome the blockade by taking more opioids, leading to severe adverse reactions (14). It has also been recognized that naltrexone patients who return to substance misuse are more sensitive to opioids, and opioid overdose is more common. All of these scenarios provide evidence of why monitoring patients taking naltrexone are so important. Patients who take naltrexone should also be warned about the dangerous adverse effects of taking prescription opioids or heroin while still on naltrexone therapy.

As mentioned previously, variable MRs and concentrations of naltrexone and 6β-naltrexol may contribute to the likelihood of a patient staying on their prescribed therapy. In addition, higher concentrations of naltrexone in blood have been associated with lower chance of heroin use (12). A previous study analyzed blood levels of naltrexone with heroin cravings and found a 35% decrease in weekly heroin use with every 1 ng/mL increase in blood naltrexone concentrations. Two nanograms per milliliter of naltrexone are sufficient to completely block the effects of 25-mg intravenous heroin (12). To see if this relationship held using excretion data, an analysis was performed comparing naltrexone and morphine concentrations in urine, and longer half-life 6β-naltrexol concentrations with excreted morphine. Similar to plasma findings, higher naltrexone and 6β-naltrexol urine concentrations correlated with lower urine morphine concentrations (Figure 5).

Limitations

One limitation of this retrospective data analysis was that indicated use of naltrexone was unknown whether it was for alcohol dependence or opioid dependence. However, as the population size was greater than many previous studies, and specimens were taken from patients with chronic pain, it was assumed that the majority of the patients were taking naltrexone for opioid dependence. Another limitation was the lack of dosage information, but the urinary concentrations of naltrexone and its metabolite provides a range of values that can be expected in chronic pain populations.

Conclusion

The high degree of variability in MR between patients and within patients is consistent with previous studies on naltrexone pharmacokinetics. Several reasons were proposed including the decreased first-pass metabolism of naltrexone, possible polymorphisms in dihydrodiol dehydrogenase, as well as possible inhibitors of the enzyme such as testosterone. Effects of confounding factors on MR such as patient age, sex and urinary pH were also analyzed. Women had a higher MR than men, which may be useful for prescribers to be aware of when prescribing naltrexone. The high prevalence of opioids found concomitantly in urine specimens of patients taking naltrexone supports the need for monitoring patients who may be opioid dependent. It is important to make sure that patients are free of opioids 7–10 days before initially being prescribed naltrexone. Urine drug testing should be continued over the course of naltrexone therapy to ensure that they are taking naltrexone as directed and not relapsing back to opioid use.

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