

CASE REPORT

Rifampin Reduces Oral Morphine Absorption: A Case of Transdermal Buprenorphine Selection Based on Morphine Pharmacokinetics

Jeffrey Fudin, Dania Vanesta Fontenelle, and Annette Payne

ABSTRACT

A 51-year-old male was referred to the Stratton Veterans Affairs Medical Center Pain Service after hospital admission for endocarditis with a history of heroin use and chronic low back pain. During his hospital stay he experienced a reduction in his serum morphine level ostensibly as a result of concomitant rifampin administration. We hypothesize that diminished absorption was from rifampin-mediated intestinal P-glycoprotein induction, ultimately decreasing serum free morphine and metabolites. The case became more complex in an attempt to balance managed pain, history of substance abuse, completion of antibiotic therapy, and a reasonable pain regimen upon discharge. Ultimately, the patient was titrated onto a buprenorphine transdermal patch, the initiation of which was based on serum free morphine and an extrapolated oral morphine dose by calculation.

KEYWORDS buprenorphine, interaction, morphine, P-glycoprotein, pseudoaddiction, rifampin, serum analysis

CLINICAL BACKGROUND

RL is a 51-year-old Caucasian male who presented with chronic low back and pelvic pain secondary to a work related accident in 2003. Per the patient's report, he was examined by a physician at a local hospital emergency room after the incident and discharged the same day. He reported that 10 days later he was unable to exit his vehicle due to numbness in his lower extremities. He required evaluation by an emergency response team that resulted in transport to a local emergency room. A magnetic resonance imag-

ing (MRI) revealed compression spinal fractures at L1 and L2, sacral fractures at S1 through S3, with a conus injury. He was admitted, underwent surgical stabilization, and was fitted with a back brace, which he wore for 3 months. Our earliest medical records dated January 6, 2012, indicate that RL's pain was being managed by a physician outside of the Department of Veterans Affairs medical system. RL subsequently established primary care with a physician at the Veterans Affairs Medical Center (VAMC) and was then referred to the VA outpatient pain clinic. Table 1 summarizes the sequential changes made to his pain regimen.

RL had also previously received three consecutive epidural spinal injections that included bupivacaine and triamcinolone, with no significant improvement reported by the patient. During routine pain clinic visits, RL's urine tested positive for cannabinoids on random screen, which were confirmed by gas chromatography–mass spectrometry (GC-MS). He denied cannabinoid use and per his request he was discharged from the pain clinic. He continued pain management with a private physician and, by his report, was maintained on oxycodone/acetaminophen

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TABLE 1. Documented Changes to RF's Pain Regimen Post Accident to 2011

Provider	Regimen	Reported VAS pain score
Non-VA provider	Oxycodone 7.5 mg/APAP 325 mg PO QID	4/10
VA primary care	Oxycodone 5 mg/APAP 325 mg PO q4h + tramadol 100 mg (2 × 50-mg tabs) daily	4/10
VA outpatient pain clinic	Tramadol discontinued Oxycodone 5 mg/APAP 325 mg PO q4h PRN + fentanyl 25 µg/h transdermal (TD) patch q72h with plan to titrate fentanyl TD alone without oxycodone/APAP IR PRN	4/10

5/325 mg four to eight tablets per day, with a pain score of 4/10 on a visual analogue scale (VAS) for pain intensity of 0 to 10, on which 0 represents no pain and 10, pain as bad as the patient can imagine.

In March 2009, RL received a mechanical heart valve secondary to aortic stenosis. He acknowledged use of intravenous heroin and alcohol abuse, which was first documented on July 6, 2011, when he called the VA substance abuse team requesting detoxification from heroin and alcohol. At the time, RL reported using 10 to 12 bags of heroin per day and consuming 15 to 18 beers per day. RL stated that this abuse was an attempt to manage his pain. As part of his substance abuse rehabilitation, RL attended group therapy and individual counseling sessions, but his attendance was marred by repeated absences that he blamed on work and social stressors. His urine was again confirmed to contain cannabinoids, the use of which he denied.

PREADMISSION

On July 10, 2012, RL presented to the emergency room (ER) with complaints of fever peaking at 103.7°F and with nausea and vomiting that started the previous night. He reported using heroin within 24 hours of his presentation to the ER. With knowledge of his mechanical valve and history of heroin abuse, endocarditis was highly suspected. He received single empiric doses of vancomycin 1.5 g intravenously (IV), rifampin 600 mg orally (PO), and gentamicin 80 mg IV. He was given morphine 2 mg IV push secondary to complaints of an 8/10 pain and headache. RL was transferred to the intensive care unit (ICU) where his antibiotic regimen was main-

tained. Oxycodone 10 mg PO every 4 hours as needed (q4h PRN) was initiated for his pain.

Medical records indicate that the patient was not satisfied with the management of his pain, which he rated as 8/10 on the pain intensity VAS. His pain score was a persistent 8/10 and he made repeated threats of leaving against medical advice (AMA) if he could not be made comfortable. During his stay, he received single doses of IV morphine, IV hydromorphone, and/or additional doses of oral oxycodone. This reduced the patient's pain intensity to a 3/10, but it quickly escalated back to 8/10. Threats of leaving the hospital AMA ensued, until 7 days later when the patient left AMA. He returned to the ER a few hours later, on the advice of his girlfriend, at which time he rated his pain as 8/10. He then received IV hydromorphone 2 mg q6h PRN and was admitted to a medical ward where his antibiotic regimen was reinstated.

ADMISSION

A pain team consult was requested on June 19, 2012. RL was met at bedside and the plan for his pain management in light of his heroin abuse was discussed with him in detail. RL maintained that if we were able to keep him comfortable, he would adhere to the prescribed in-house 6-week antibiotic course for treatment of endocarditis. He understood that eventual placement of a central catheter because of poor venous access would preclude his ability to leave the hospital grounds. At this point endocarditis had been confirmed by multiple blood cultures positive for *Staphylococcus aureus* and vegetation observed via echocardiogram. RL's medication regimen at the time of consultation is listed in Table 2.

Intravenous hydromorphone was discontinued and oral morphine sustained-release (SR) 75 mg PO q8h was started. The intention was to use an agent that would provide stable serum opioid levels

TABLE 2. RL's Pharmacotherapeutic Regimen at the Time of Initial Pain Consultation

Drug	Dose and frequency
Oxacillin	2 g, infuse over 30 min q4h IV
Hydromorphone	2 mg/1 mL q4h PRN IV
Nystatin	500,000 units/5 mL PO TID
Gentamicin	100 mg, infuse over 30 min q8h
Warfarin	7.5 mg PO daily
Lactobacillus	1 tab PO BID
Omeprazole	40 mg PO BID
Enoxaparin	80 mg/0.8 mL BID SQ
Rifampin	600 mg PO daily

TABLE 3. Sequential Changes to RL's Pain Regimen by Pain Team

Date	Plan	Patient response
July 19, 2012	Discontinue hydromorphone Initiate morphine SA 75 mg PO q8h No IV opioids under any circumstances, exception: major acute injury within the hospital Clonidine 0.2 mg PO qAM and 0.1 mg PO qPM	3/10
July 24, 2012	Morphine SA 60 mg PO q8h Morphine sulfate 15 mg IR PO q8h PRN	3/10 No BT requested
July 30, 2012	Morphine SA 45 mg 6 AM and 2 PM Morphine SA 60 mg q 10 PM IR coverage provided	3/10 No BT requested

rather than peaks and troughs that could simulate IV heroin use. RL was started on morphine sulfate SR 75 mg PO three times daily (TID). Clonidine 0.2 mg every morning (qAM) and 0.1 mg every night (qPM) was initiated to mitigate against potential withdrawal and to control his elevated blood pressure. On this regimen the patient's pain intensity score fell to 3/10 and his blood pressure normalized. This and subsequent regimen changes are summarized in Table 3.

RL reported having two "bad nights," but he was able to distract himself by taking warm showers and walking. With manageable pain levels, he expressed hopefulness for returning to a productive life free of heroin use.

OBSERVATION OF INTERACTION

After 7 days on the morphine SR regimen: 225 mg daily in divided doses, a serum free morphine level was ordered. The plan was to follow RL in the outpatient pain clinic after discharge from the hospital. By obtaining an initial serum level in-house, RL would serve as his own control, an especially important precaution when treating the dual diagnosis of chronic pain and substance abuse. Using the conversion factor 36.9 (± 15.1) ng/mL of serum free morphine for every 100 mg of morphine SR, the expected serum level would average 83.03 ng/mL, ranging from 67.93 to 98.13 ng/mL.¹

RL's serum free morphine returned as 19 ng/mL, which was far lower than the anticipated level.¹ Using the same conversion formula noted above, we extrapolated the oral morphine dose to which 19 ng/mL

corresponds using a simple proportion:

$$\begin{aligned} 100 \text{ mg PO morphine} / 36.9 \text{ ng/mL} \\ = X \text{ mg PO morphine} / 19 \text{ ng/mL}; \\ X = 51.5 \text{ mg PO morphine} / 24 \text{ hours} \end{aligned}$$

This was rounded down to a 45 mg dose for convenient dosing. Given RL's TID dosing for morphine SR he was essentially receiving morphine SR 15 mg Q8H. This calculated oral dose of 50 mg daily compared with the prescribed 225 mg oral morphine actually administered was approximately 78% less.

DISCUSSION

This case is multifactorial, but the focus of this report is on three major issues: (1) the serum morphine levels fell significantly outside the expected standard deviations; (2) opioid requirements for analgesia purposes may be skewed by the craving for opioids; and (3) it could be acceptable to calculate the morphine dose based on calculated serum levels that correlate to the *theoretical* oral dose instead of the *actual* prescribed dose. In this case, the appropriateness of drug selection versus morphine serum analysis versus prescribed dose were all important factors.

The low serum morphine level was puzzling because the medications were administered by nurses in a controlled environment. There were no drug interactions noted. The metabolic pathways of morphine and rifampin posthepatically do not intersect. Rifampin is a potent liver microsomal enzyme (cytochrome P450 [CYP] 3A4) inducer; its effect being a decrease in serum concentration of 3A4 substrates with corresponding elevations in parent drug metabolites.² Morphine is not a 3A4 substrate, and its major metabolic pathway is glucuronidation by UDP-glucuronosyltransferase 2B7 (UGT 2B7).³ The clinical response to morphine is due largely to the active metabolite morphine-6-glucuronide (M6G).³

Consultation with colleagues in the field revealed multiple observations of reduced serum morphine levels with concomitant rifampin use. However, an initial literature search via the PubMed database with keywords "morphine rifampin interaction" provided very little explanation of this phenomenon. Tertiary references listed the interaction between oral morphine and oral rifampin as moderate, requiring monitoring or alteration of therapy. These drug references cite a study by Fromm and colleagues as evidence for the interaction while noting that the mechanism of the interaction is currently unclear.^{4,5}

Fromm and colleagues explored the loss of analgesic effect of oral morphine with coadministration of oral rifampin.⁶ The study included 10 healthy patients in a randomized, double-blind, placebo-controlled, crossover study. The study drugs utilized were 10 mg of oral morphine and 600 mg of oral rifampin. On day 0, a baseline pain threshold and pain tolerance level was attained via a cold pressor test. This test was repeated in patients who received morphine only, placebo only, and again after patients who received the combination of morphine plus rifampin or placebo plus rifampin. Patients treated with morphine alone reported an increased pain threshold and pain tolerance. In those patients, baseline serum free morphine and metabolite levels were collected. In the morphine-rifampin arm of the study, patients received 10 mg of oral morphine after a 10-day treatment with 600 mg oral rifampin. The result was a decreased clinical response with a corresponding decrease in serum free morphine and metabolite levels.

The stated intention of the Fromm et al. study was to document the interaction, not to identify a mechanism.⁶ However, the authors did suggest possible mechanisms, the first of which was an interaction between morphine and rifampin orally via an unidentified putative pathway. The second mechanism proposed an induction of the established 3A4 metabolism of morphine to nor-morphine, but this is highly unlikely because this pathway accounts for less than 4% of morphine's metabolism and therefore would not account for the difference in clinical response and serum levels observed with coadministration of the two drugs. The third hypothesized mechanism appears to be the most plausible: that rifampin induction of intestinal P-glycoproteins (PGPs) might explain the morphine-rifampin interaction. PGPs are the principal transport proteins involved in the movement of drugs across biological membranes and are present in multiple organs including the gastrointestinal tract, the liver, and the kidneys.⁷ They are efflux pumps that decrease the transfer of substrates across biological barriers. Based on the limited literature on this potential interaction, we presumed that intestinal PGPs could prevent absorption of morphine across the intestinal tract, which potentially decreased serum free morphine and serum metabolites. That corresponds to the clinical observations.

To date, no published studies directly evaluate the interaction mechanism between rifampin and morphine. A study by Kharasch and colleagues explored the effect of intestinal PGP inhibition and its effect on morphine absorption using quinidine 600 mg PO as the study drug.⁸ That study suggests an absorption interaction between morphine and rifampin because

quinidine is analogous to, yet the reverse of, rifampin in terms of the effect on PGPs and cytochrome P450. Quinidine is a potent 3A4 and PGP inhibitor; rifampin is a potent 3A4 and PGP inducer.⁷ We hypothesize, therefore, an opposite response with coadministration of morphine and rifampin: an increase in clinical response and an increase in serum free morphine and metabolites compared with placebo.

To demonstrate this, Kharasch and colleagues administered 30 mg oral morphine and 0.15 mg/kg intravenous morphine on separate occasions with 600 mg oral quinidine.⁸ The morphine was administered 1 hour after quinidine administration. Clinical response was assessed using visual analog pain intensity scores. Peak serum concentrations, time to peak, and area under the curve (AUC) were tabulated from serum free morphine and metabolite concentrations. Increased serum morphine and metabolite levels were observed with oral morphine administered concurrently with oral quinidine. Conversely, there was no significant change noted with intravenous morphine and oral quinidine.

This dichotomous response is not consistent with the suggested theories of enzyme and UDP induction as the major mechanisms for the observed interaction. Were the interactions based on the aforementioned mechanisms, specifically 3A4 enzyme induction, we would have observed parallel responses in metabolite serum levels and clinical effect regardless of the route of administration. Therefore, interaction with oral administration versus intravenous administration of morphine isolates the interaction at the site of absorption, implicating intestinal PGP as the foundation for the interaction.

Greiner et al. investigated the up-regulation of intestinal PGPs by rifampin using digoxin as a substrate in eight healthy volunteers.⁹ Like morphine, digoxin is an intestinal PGP substrate with negligible CYP450 3A4 activity accounting for its metabolism.⁹ Coadministration of 1 mg oral digoxin following a 10-day regimen of 600 mg oral rifampin resulted in outcomes that paralleled the presumed interaction with oral morphine and rifampin: significantly decreased digoxin plasma concentrations, with maximal plasma levels reduced by 58%.⁹ Exploring the significance of the route of administration by comparing the results with IV administered digoxin 1 mg, the authors noted a less pronounced effect on serum digoxin levels with IV administration.⁹ The authors also performed duodenal biopsies before and after rifampin therapy that showed up-regulation of intestinal PGP content 3.5 ± 2.1 -fold following treatment with oral rifampin relative to placebo.⁹ This can be seen in Figure 1. Greiner and colleagues therefore concluded that there was experimental evidence for

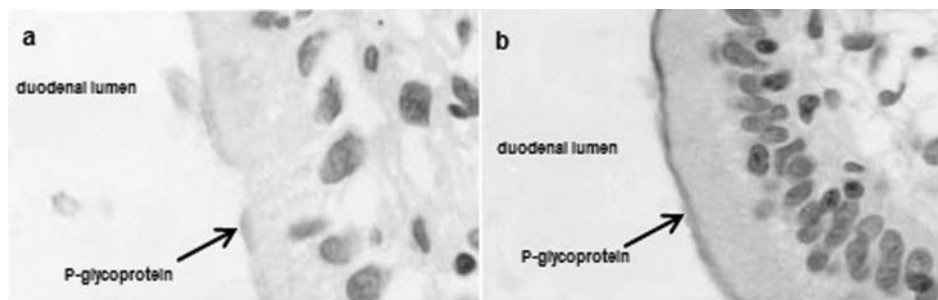


FIGURE 1. (a) Duodenal biopsy (villus tip $\times 40$) immunostained for P-glycoprotein before administration of rifampin. (b) Duodenal biopsy (villus tip $\times 40$) immunostained for P-glycoprotein after 9 days' administration of rifampin (600 mg), obtained from the same volunteer as in a. (Permission to reproduce images by Dr. Michel Eichelbaum.)

the increased expression of intestinal PGPs with oral rifampin.⁹

As noted, this patient had a history of heroin abuse and short-acting prescription opioid noncompliance for pain reduction, which may have contributed to heroin addiction. RL readily admitted to using opioids to “feel better.” It is difficult to assess a patient’s level of pain versus fear/anxiety about withdrawal symptoms and/or craving the opioid.¹⁰ Intermittent use of opioids serves to reinforce pain medication—“seeking” behavior to avoid withdrawal and maintain pain reduction. A dual diagnosis of chronic pain and substance abuse disorder makes it very difficult for clinicians (and patients) to differentiate between pain and opioid craving. Pseudoadiction was described by Weissman and Haddox as an attempt to “delineate the manifestation of distress and medication-seeking behavior of individuals with unrelieved pain.”¹¹ This behavior may be comparable to behavior seen in true addiction. However, the hallmark feature of pseudoadiction is the cessation of aberrant behavior on achieving adequate pain relief.¹²

Given this patient’s history of substance abuse and chronic pain, he would have been a candidate for a buprenorphine transdermal patch trial had his daily dose of oral morphine not exceeded 80 mg per day.¹³ At no time was it presumed that any Food and Drug Administration (FDA)-approved dose of transdermal buprenorphine could or would reduce cravings for a pure agonist such as heroin. But instead buprenorphine was chosen for a once-weekly dosing schedule and the probability that if RL did use heroin, at least some of it would theoretically be blocked by the higher μ -receptor-binding affinity of buprenorphine. To mitigate the onset of withdrawal symptoms in patients who are opioid tolerant, transdermal buprenorphine is contraindicated in patients receiving oral morphine 80 mg per day, or its equivalent, or

higher.¹³ RL by those guidelines was therefore not a candidate for transdermal buprenorphine, even at his lowest prescribed morphine regimen of 150 mg oral morphine daily. However, based on his serum free morphine level, his calculated equivalent dose of morphine was 34 mg + 15.5 mg PO daily¹; based on the calculated equivalent dose of oral morphine, this patient was well within the recommended limits for the buprenorphine transdermal patch.¹³ Without knowledge of the interaction or serum morphine levels, this patient would have required an extended period to titrate his morphine regimen down to an acceptable range for conversion to the buprenorphine transdermal patch.

Beyond this specific patient, interactions between other intestinal PGP inducers and inhibitors may theoretically demonstrate a similar interaction with concomitant administration of morphine or any other PGP substrates.^{7,14} The clinical implication is concern for the ability to attain subtherapeutic serum concentrations, or conversely, supratherapeutic levels of a PGP substrate drug coadministered with either a PGP inducer such as rifampin or a PGP inhibitor such as quinidine, respectively. In addition, consider a patient initiated on oral morphine and oral rifampin, followed by discontinuation of oral rifampin—a very likely scenario. The rapid escalation in serum morphine that could occur with cessation of oral rifampin may place that patient at increased risk for sedation and/or respiratory depression.¹⁵

CONCLUSION

Collectively, this case and the available literature suggest that a potentially important interaction exists between oral morphine and oral rifampin, the effect of which is a significant reduction in the serum

morphine level due to reduced absorption. The interaction is sufficient to influence the course of and response to therapy. Monitoring serum morphine levels can help ensure that patients' needs are met. In this case, the interaction suggests consideration of alternative analgesic pharmacotherapy, specifically the buprenorphine transdermal patch.

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