

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

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## **Clinical Background**

RL is a 51 year old caucasian male diagnosed 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 subsequent to the accident, he was unable to exit his vehicle due to numbness in his lower extremities. He required evaluation by an emergency response team which resulted in transport to a local emergency room. Upon evaluation, an MRI revealed compression fractures to L1 and L2, sacral fractures to S1 through S3 with a conus injury. He was admitted, surgical operations were performed and RL was fitted with a back brace, which he wore for 3 months. Our earliest records dated 1/6/2012 indicate that RL's pain was being managed by a non – VA physician. RL subsequently established primary care with a physician at the VA and was then referred to the VA Outpatient Pain Clinic. Table 1 summarizes the sequential changes made to his pain regimen.

Of note, RL had also previously received three consecutive spinal injections with no significant improvement reported by the patient. During routine Pain Clinic visits, the RL's urine drug screen tested positive for cannabinoids on random screen, which were confirmed by gas chromatography–mass spectrometry (GCMS). He denied cannabinoid use and per his request was discharged from the Pain Clinic. He continued pain management with a private physician and by his report, was maintained on oxycodone 5mg/acetaminophen 325mg, 4-8 tablets per day, with a pain score of 4/10 on a visual analogue scale (VAS) of 0-10.

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 – 12 bags of heroin per day and consuming 15-18 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 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 ER with complaints of fever peaking at 103.7° Fahrenheit and symptoms of nausea/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 1.5g IV; rifampin 600mg PO; and gentamicin 80mg IV. He was given morphine 2mg IV push secondary to complaints of an 8/10 and headache. RL was transferred to the intensive care unit (ICU) where his antibiotic regimen was maintained. Oxycodone 10mg PO Q4H PRN was initiated for his pain.

According to medical records, the patient was not satisfied with the management of his pain which he rated as 8/10 on a VAS of 0-10. 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 dropped the patient's pain score down to a 3/10 but it quickly escalated back to an 8/10; threats of 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 and was given IV hydromorphone 2mg Q6 PRN and 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 oblige to the prescribed in house 6 week antibiotic course for treatment of endocarditis; he understood that eventual placement of a central line 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 tabulated in table 2.

Intravenous hydromorphone was discontinued and oral morphine SR (MS SR) 75mg PO Q8H was started. The intention was to use an agent that would provide stable serum levels of opiates rather than serum peaks and troughs that simulated IV heroin use. RL was started on morphine sulfate SR 75mg PO TID; clonidine 0.2mg QAM and 0.1mg QPM was initiated to mitigate against potential withdrawal and to control his elevated blood pressure. On this regimen the patient's pain score fell to 3 out of 10 and his BP normalized. This and subsequent regimen changes are summarized in Table 3.

RL reported having two "bad nights", but 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 the 7 days of the original MS SR regimen: 225mg daily in divided doses, a serum free morphine level was ordered. The intention was to follow RL in the outpatient Pain Clinic after discharge from the hospital; by obtaining this 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 of 36.9ng/mL (+/- 15.1) of serum free morphine for every 100mg of MS SR, the expected lab report would be an average value of 83.03ng/mL ranging from 67.93 – 98.13 ng/mL.<sup>1</sup> RL's serum free morphine returned as 19ng/mL; far lower the anticipated level.<sup>1</sup> Using the serum morphine value, we extrapolated mathematically to determine the equivalent dose of oral morphine to which 19ng/mL

corresponds. The calculated theoretical oral dose correlated to an oral dose of approximately 50mg daily compared to the 225mg oral morphine prescribed.

## **Discussion**

Important points of this case are multifactorial, but the focus will be on three major issues; the serum morphine levels fell significantly outside the expected standard deviations, opioid requirements for analgesia purposes may be skewed by the craving for opioids, and it could be acceptable to calculate the opioid rotation dose of morphine based on calculated serum level correlates to the *theoretical* oral dose instead of the *actual* prescribed dose. In this particular case, the appropriateness of drug selection vs. morphine serum analysis vs. prescribed dose were all an important factors.

A low serum morphine level was particularly puzzling as the medications were being administered by nurses in a controlled environment. There were no blatant drug interactions noted. The metabolic pathways of morphine and rifampin post-hepatically do not intersect. Rifampin is a potent CYP450 3A4 inducer; its effect being a decrease in serum concentration of 3A4 substrates with corresponding elevations in parent drug metabolites.<sup>2</sup> Morphine is not a 3A4 substrate, and the major metabolic pathway is via glucuronidation by UDP – glucuronosyltransferase 2B7 (UGT 2B7).<sup>3</sup> The clinical response to morphine is achieved via the active metabolites morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G).<sup>3</sup>

Consultation with colleagues in the field revealed multiple observations of reduced serum morphine levels concomitantly used with rifampin in practice; however an initial literature search provided very little insight. Data on this potential drug interaction was almost nonexistent. Fromm and colleagues explored the loss of analgesic effect of oral morphine with co-administration of oral rifampin.<sup>4</sup> The study included 10 healthy patients in a randomized, double blind, placebo controlled, crossover study. The study drugs utilized were 10mg of oral morphine and 600mg of oral rifampin. On day zero, a baseline pain threshold and pain tolerance level was attained via cold pressor tests. This test was repeated in

patients who received morphine only, placebo only, and again after patients that received the combination of morphine plus rifampin or placebo plus rifampin. Patients treated with just morphine recorded an increased pain threshold and pain tolerance. In those patients a baseline serum free morphine and metabolites were collected. In the morphine-rifampin arm of the study, patients received 10mg of oral morphine after a 10 day treatment with 600mg oral rifampin. The result was a decreased clinical response with a corresponding decrease in serum free morphine and metabolites.

The intention of the Fromm study was to document the interaction, but not to identify a mechanism.<sup>4</sup> However the authors do briefly outline a few possible mechanisms, the first proposing an interaction between morphine and rifampin orally via an unidentified putative pathway. The second mechanism offered proposed an induction of the established 3A4 metabolism of morphine to nor-morphine; this is highly unlikely as this pathway accounts for less than 4% of morphine's metabolism, and it therefore would not account for the significant difference in clinical response and serum levels observed with co-administration of the two drugs. Thirdly, the authors hypothesized 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.<sup>9</sup> They are efflux pumps and their effect is to decrease the transfer of substrates across biological barriers. Based on limited literature available on this potential interaction, we too presumed that intestinal PGPs could prevent absorption of morphine across the intestinal tract which potentially decreased serum free morphine and serum metabolites, corresponding to the study observations.

To date there are no studies that directly evaluate the interaction mechanism between rifampin and morphine. There is however a study by Kharasch and colleagues that explores the effect of intestinal PGP inhibition and its effect on morphine absorption using quinidine 600mg PO as the study drug.<sup>5</sup> We propose that the Kharasch study is suggestive evidence for an absorption interaction between morphine and rifampin because quinidine is analogous yet the reverse of rifampin in terms of the effect on P

glycoproteins and cytochrome P450. Quinidine is a potent 3A4 and PGP inhibitor; rifampin is a potent 3A4 and PGP inducer.<sup>10</sup> We hypothesize therefore, the exact opposite response with co-administration of morphine and rifampin; an increase in clinical response and an increase in serum free morphine and metabolites relative to placebo.

To demonstrate this, Kharasch and colleagues administered 30mg oral morphine and 0.15mg/Kg intravenous morphine on separate occasions with 600mg oral quinidine.<sup>5</sup> Morphine was administered one hour after quinidine administration. Clinical response was assessed via VAS scores. Peak serum concentrations, time to peak and area under curve (AUC) were tabulated from serum free morphine and metabolite concentrations. As expected, an increase in serum morphine and metabolites was observed with oral morphine simultaneously administered with oral quinidine. Conversely, there was no significant change noted with intravenous morphine and oral quinidine.

This dichotomous response debunks suggested theories of enzyme and UDP induction as the major mechanism for the observed interaction. Were the interactions based on the aforementioned mechanisms, specifically 3A4 enzyme induction, we undoubtedly 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, hence implicating intestinal PGP as the foundation for the interaction.

Greiner et. al. directly investigated the up-regulation of intestinal PGPs by rifampin using digoxin as a substrate in eight healthy volunteers.<sup>6</sup> Like morphine, digoxin is an intestinal PGP substrate with negligible CYP450 3A4 activity accounting for its metabolism.<sup>6</sup> Co-administration of 1mg oral digoxin following a 10 day regimen of 600mg oral rifampin resulted in outcomes that parallel the presumed interaction with oral morphine and rifampin; significantly decreased digoxin plasma concentrations with maximal plasma levels reduced by 58% .<sup>6</sup> Exploring the significance of the route of administration by comparing the results to IV administered digoxin 1mg, the authors noted a less pronounced effect on

serum digoxin levels with IV administration.<sup>6</sup> In addition, the authors performed duodenal biopsies before and after rifampin therapy that showed up-regulation of intestinal PGP content  $3.5 \pm 2.1$  fold following treatment with oral rifampin relative to placebo.<sup>6</sup> This can be seen in Figure 1. Greiner and colleagues therefore concluded that there was experimental evidence for the increased expression of intestinal PGPs with oral rifampin.<sup>6</sup>

As noted earlier, this patient had a history of heroin abuse and short-acting prescription opiate noncompliance for pain reduction, which eventually served to fuel heroin addiction.- RL readily admitted to using opiates to “feel better.” It is difficult to assess a patient's level of pain vs. fear/anxiety about withdrawal symptoms and/or craving the opiate.<sup>7</sup> Intermittent use of opioids serves to reinforce pain medication “seeking” behavior to avoid withdrawal and pain reduction. A dual diagnosis of chronic pain and substance abuse disorder make it very difficult for clinicians (and patients) to differentiate between pain and opioid craving. The term pseudoaddiction was coined by Doctors Weissman and Haddox in the late eighties.<sup>8</sup> Pseudoaddiction is an attempt to "delineate the manifestation of distress and medication-seeking behavior of individuals with unrelieved pain. Pseudoaddictive behavior may be comparable in form to the behavior of true addiction. However, the hallmark feature of this syndrome, and the characteristic that makes it quite distinct, is the cessation of aberrant behavior on achieving adequate pain relief.<sup>9</sup>

Keen observation and interpretation of this morphine/rifampin interaction was ultimately beneficial for this patient. Given his history of substance abuse and chronic pain, he would otherwise be an excellent candidate for a buprenorphine transdermal patch trial had his daily dose of oral morphine not exceeded 80mg per day.<sup>10</sup> At no point in time was it presumed that any 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 mu-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 80mg per day, or its equivalent.<sup>10</sup>

Based on the dosage intake, RL was not a candidate even at his lowest prescribed morphine regimen of 150mg oral morphine daily. But, based on his serum free morphine, his calculated equivalent dose of morphine was  $34 \text{ mg} \pm 15.5 \text{ mg PO daily}^1$ ; based on the calculated equivalent dose of oral morphine, this patient was well within the recommended limits for the buprenorphine transdermal patch.<sup>10</sup> Without knowledge of the interaction or serum morphine levels, this patient would have required an extended period of time to titrate his morphine regimen down to the 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.<sup>13,14</sup> The clinical implication is concern for the ability to attain subtherapeutic serum concentrations, or conversely, supratherapeutic levels of a PGP substrate drugs co-administered with a PGP inducer like rifampin or a PGP inhibitor like 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.<sup>15</sup>

## **Conclusion**

Collectively, this case study and the available literature suggest that a significant interaction exists between oral morphine and oral rifampin, the effect of which is a significant reduction in serum morphine due to reduced absorption. The interaction is sufficient to influence the course of and response to therapy. Using pharmacokinetic monitoring of serum morphine we can monitor the interaction to ensure that patients pain needs are adequately managed. In this case, the interaction offered more therapeutic options for pain management, specifically the buprenorphine transdermal patch.

## Tables and Figures

<b>Provider</b>	<b>Regimen</b>	<b>Reported VAS Pain Score</b>
Non – VA provider	Oxycodone 7.5mg/APAP 325mg PO QID	4/10
VA Primary Care	Oxycodone 5mg/APAP 325mg PO Q4H + tramadol 100mg (2X50mg tabs) daily	4/10
VA Outpatient Pain Clinic	Tramadol discontinued Oxycodone 5mg/APAP 325mg PO Q4H PRN + fentanyl 25mcg/h transdermal (TD) patch Q72H with plan to titrate fentanyl TD alone without oxycodone/APAP IR PRN	4/10

Table 1: Documented changes to RF's pain regimen post-accident to 2011

<b>Drug</b>	<b>Dose &amp; Frequency</b>
Oxacillin	2 g, Infuse over 30mins Q4H IV
Hydromorphone	2mg/1ml Q4H PRN IV
Nystatin	500000 units/5ml PO TID
Gentamicin	100 mg, Infuse over 30mins Q8H
Warfarin	7.5mg PO daily
Lactobacillus	1 tab PO BID
Omeprazole	40mg PO BID
Enoxaparin	80mg/0.8ml BID SQ
Rifampin	600mg PO daily

Table 2: RL's pharmacotherapeutic regimen at the time of initial pain consultation

<b>Date</b>	<b>Plan</b>	<b>Patient Response</b>
07.19.12	d/c hydromorphone Initiate Morphine SA 75mg PO Q8H No IV opioids under any circumstances, exception: major acute injury within the hospital Clonidine 0.2mg PO QAM and 0.1mg PO QPM	3/10
07.24.12	Morphine SA 60mg PO Q8H. Morphine sulfate 15mg IR PO Q8H PRN	3/10 No BT requested
07.30.12	Morphine SA 45mg 6am and 2pm. Morphine SA 60mg Q10pm IR coverage provided	3/10 No BT requested

Table 3: Sequential changes to RL's pain regimen by pain team

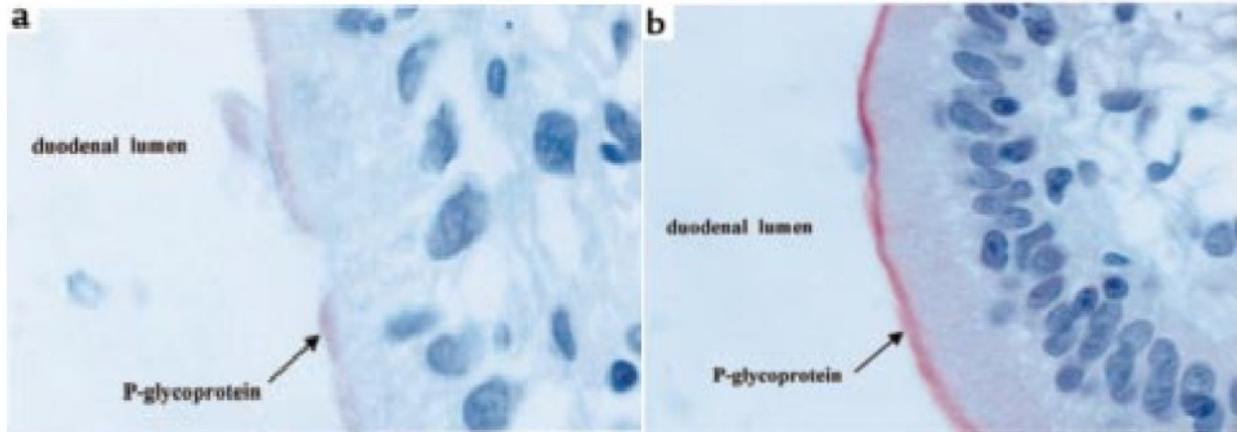


Figure 1: (a) Duodenal biopsy (villus tip X 40) immunostained for P-gp before administration of rifampin. (b) Duodenal biopsy (villus tip X 40) immunostained for P-gp after 9 days administration of rifampin (600mg), obtained from the same volunteer as in a. (*Permission to reproduce images by Dr. Michel Eichelbaum*)

## References

1. Fudin J. Opioid Pharmacokinetics and Expected Metabolites [Internet]. 2011 [cited 2012 Aug 27] Available from: <http://paindr.com/wp-content/uploads/2012/05/Opioid-Serum-Predictability-and-Metabolites.pdf>
2. Pharmacist's Letter [Internet]. Drug Interactions. 2012 [cited 2012 Aug 2012]. Available from: <http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=STUDENT&s=PL&pt=6&fpt=31&dd=260603&pb=PL&searchid=36715122>
3. Baumann TJ, Strickland JM, Herndon CM. Pain Management. In: R.L. Talbert, J.T. DiPiro, G.R. Matzke, L.M. Posey, B.G. Wells, G.C. Yee. Pathophysiology: A Pathophysiologic Approach. 8<sup>th</sup> ed. The McGraw-Hill Companies; 2011: 989 - 1003.
4. Fromm MF, Eckhardt K, Li S, Schänzle G, et. al. Loss of analgesic effect of morphine due to coadministration of rifampin. *Pain*. 1997 Aug;72(1-2):261-7.
5. Kharasch ED, Hoffer C, Whittington D, Sheffels P. Role of P-glycoprotein in the intestinal absorption and clinical effects of morphine. *Clin Pharmacol Ther*. 2003 Dec;74(6):543-54.
6. Greiner B, Eichelbaum M, Fritz P, Kreichgauer HP The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. *J Clin Invest*. 1999 Jul;104(2):147-53.
7. Coluzzi F., Pappagallo M. Opioid therapy for chronic non cancer pain: Practice guidelines for initiation and maintenance of therapy. *Minerva Anestesiologica*. 71(97-8): 425-433, 2005
8. Weissman DE, Haddox JD: Opioid pseudoaddiction – an iatrogenic syndrome. *Pain* 1989, 36(3):363-6.
9. Fudin J, Levasseur DJ, Passik SD, Kirsh KL, Coleman J. Chronic Pain Management with Opioids in Patients with Past or Current Substance Abuse Problems. *Journal of Pharmacy Practice*. 2003, 16;4:291-308.)
10. Butrans: buprenorphine transdermal patch [package insert]. Stamford, CT: Purdue Pharma L.P.; 2010
11. Jasinski, D.R.; Pevnick, J.S.; and Griffith, J.D., 1978. Human pharmacology and abuse potential of the analgesic buprenorphine: A potential agent for treating narcotic addiction. *Archives of General Psychiatry* 35(4):501-516.
12. Cavallari L.H., Lam Y.W. (2011). Chapter 9. Pharmacogenetics. In R.L. Talbert, J.T. DiPiro, G.R. Matzke, L.M. Posey, B.G. Wells, G.C. Yee (Eds), *Pharmacotherapy: A Pathophysiologic Approach*, 8e. Retrieved August 24, 2012 from <http://www.accesspharmacy.com/content.aspx?aID=7966967>.
13. Pharmacist's Letter [Internet]. Cytochrome P450 Interactions. 2012 [cited 2012 Aug 2012]. Available from: [http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=PLPHONLY\\_NDALL\\_LI&s=PL&pt=6&fpt=31&dd=260112&pb=PL&cat=4302](http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDD.aspx?nidchk=1&cs=PLPHONLY_NDALL_LI&s=PL&pt=6&fpt=31&dd=260112&pb=PL&cat=4302)

14. Chang C, Bahadduri PM, Polli JE, et.al. Rapid identification of P-glycoprotein substrates and inhibitors. *Drug Metab Dispos.* 2006 Dec;34(12):1976-84. Epub 2006 Sep 22.
15. Donnelly S, Davis MP, Walsh D, et. al. Morphine in cancer pain management: a practical guide. *Support Care Cancer.* 2002 Jan;10(1):13-35.