COMMENTARY

Potential P-glycoprotein Pharmacokinetic Interaction of Telaprevir With Morphine or Methadone

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ABSTRACT

Telaprevir (TVR) effects on P-glycoprotein and cytochrome P450 (CYP) may significantly elevate serum levels of morphine and methadone. Recent literature points to major interactions when combining TVR with warfarin or rifampin. Opioid interactions are especially dangerous in hepatitis C patients, as coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) occurs in 50–90% of HIV-infected drug users that are prescribed opioids for chronic pain and/or methadone for maintenance. TVR has been shown to significantly inhibit the active transport enzyme pGP and may therefore increase intestinal morphine absorption. TVR also inhibits hepatic CYP3A4 that are responsible for metabolizing methadone. Patients requiring opioid analgesics must be carefully monitored because of potential for elevated opioid levels and overdose risk. Current recommendations minimize potential drug interactions between telaprevir and opioids, especially methadone, based on a single 7-day trial. We outline the various pharmacokinetic mechanisms involved when combining TVR with methadone or morphine and recommend that current data are not sufficiently robust to minimize the potentially significant interaction with opioids, especially methadone. Clinicians must be mindful of these understated interactions, know that the opioid dose may need to be significantly increased or reduced, and use caution during upward titration of opioids affected by these enzyme systems.

KEYWORDS

boceprevir, CYP, cytochrome P450, drug interaction, interaction, methadone, morphine, pGP, P-glycoprotein, pharmacokinetic, telaprevir

INTRODUCTION

A recent commentary by Gatti and Cha, “Apparent Interaction Between Telaprevir (TVR) and Warfarin in a Patient With Chronic Hepatitis C Viral Infection,” likely has wide-reaching implications for patients, pharmacists, and prescribers with respect to opioid dosing and potential risks. Based on the Gatti-Cha observation and a recent case report of significantly reduced serum morphine that implicated rifampin induction of P-glycoprotein (pGP) as the culprit, we caution that opioid dosing needs closer scrutiny in patients receiving telaprevir.

This is especially germane in a population of hepatitis C patients when considering several factors; a common cause of hepatitis C virus (HCV) infection is previous use of dirty needles in substance abuse patients who might now receive methadone maintenance, some have human immunodeficiency virus (HIV) disease as a result, and many of the latter have chronic (neuropathic) pain syndromes commonly caused by antiretroviral therapy and/or the HIV itself. Overall, “coinfection with HIV and HCV is common (50–90%) among HIV-infected injection drug users.”
Moreover, consideration should be given to the high prevalence of HCV mono- and HCV/HIV coinfection among the prison population. In fact, Tan et al. reported in 2008 that the prevalence of chronic hepatitis C in US prisons was at 12–31%.

Since this cohort also has a high incidence of opioid abuse and may be enrolled in hepatitis C treatment and methadone maintenance programs, clinicians should be particularly mindful of these potential dangerous drug interactions.

Another significant public health concern is that a young cohort of intravenous drug users that include nonminority, nonurban, Caucasians ≤ 24 years old has emerged, many of whom began substance abuse with non-prescribed commercially available opioid analgesics. This frequently starts with oral use and progresses to eventual injection of the prescription medication, which is a gateway to heroin use.

Our objectives are to highlight important drug-drug interactions between TVR and commonly prescribed opioids (methadone and morphine) that we suspect are commonly overlooked, often not incorporated into drug interaction databases, and could present significant morbidity or mortality in the HIV- and HCV-infected populations. The mechanisms of these interactions are summarized in Table 1. We also hope to alert medical prescribers and pharmacists of these potentially dangerous interactions and encourage more scrutiny upon drug initiation and dispensing while also inspiring the need for more research.

TVR is a protease inhibitor with a Food and Drug Administration (FDA)-labeled indication for the treatment of chronic hepatitis C in combination with peg-interferon alpha and ribavirin in adult patients with compensated liver disease (including cirrhosis). TVR binds reversibly to nonstructural protein 3 (NS 3) serine protease, inhibiting replication of the HCV as a direct-acting antiviral treatment for hepatitis C.

Critical to this discussion is that the duration of therapy specifically for TVR is no more than 12 weeks. TVR is a major substrate to cytochrome P450 3A4 (CYP3A4) and pGP; it is also an inhibitor of the same enzymes.

TVR has been shown to significantly inhibit intestinal pGP and therefore may increase intestinal absorption of medications such as morphine. This occurs because pGP is an active transport enzyme, specifically an efflux pump that inhibits intestinal absorption. Simply put, by inhibiting the “absorption inhibitor, the transport of morphine across the intestinal boarder increases and serum morphine increases.” Conversely, the interaction between methadone and telaprevir is mediated by cytochrome P450 3A4 isoenzymes (CYP3A4) that are in large part responsible for metabolizing methadone. TVR inhibits CYP3A4 and therefore decreases conversion of methadone into its inactive metabolites. From an infectious disease standpoint, such patients requiring opioid analgesics must be carefully monitored because of theoretical potential for elevated opioid levels and overdose risk.

All of these TVR-treated populations have compensated liver disease and many have cirrhosis, both of which may additionally contribute to the patient’s inherent inability to metabolize methadone and/or morphine.

An interaction between TVR and morphine is of significant concern because the population with the highest incidence of hepatitis C (intravenous [IV] drug users) also has a higher incidence of chronic pain that may necessitate the use of opioids, including morphine and methadone.

Experience tells us that it is also commonly used in patients concomitantly receiving methadone for maintenance and comorbid chronic pain syndromes. Although this commentary focuses only on morphine and methadone, we cannot ignore the complex CYP3A4 interactions frequently seen with antidepressants that also are often used as adjuvant analgesics. There is also evidence to suggest that other opioids, including fentanyl and oxycodone, possess pGP substrate activity, which extends the concern for concomitant treatment of pain and hepatitis C. The prevalence of pGP receptors at the blood-brain barrier also warrants scrutiny due to corresponding changes in absorption and pharmacodynamics at the level of the central nervous system when using this combination of drugs.

**INTERACTION OF TELAPREVIR AND MORPHINE**

TVR is a significant CYP3A4 inhibitor and a pGP inhibitor; morphine is a pGP substrate affected by intestinal absorption. We would therefore expect increased serum morphine levels with coadministration, as indicated above. Inhibition of pGP results in decreased efflux and therefore increased absorption of morphine across the intestinal tract. As the concentration of serum morphine increases, the concentration of metabolites, including morphine 6-glucuronic (M6G), could exhibit proportional increase, as the primary metabolic pathway for it is glucuronidation by UDP-glucuronosyltransferase 2B7 (UGT 2B7). M6G, the active metabolite of morphine, mediates the clinical response, namely, analgesia, as well as side effects such as respiratory depression. M3G is an inactive metabolite, which may contribute to toxicities such as seizures if allowed.
<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Action of metabolism</th>
<th>Telapavir</th>
<th>Morphine&lt;sup&gt;36&lt;/sup&gt;</th>
<th>Methadone</th>
<th>Bocepravir</th>
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</thead>
<tbody>
<tr>
<td>Cytochrome P450</td>
<td>Responsible for metabolism of medication in liver and intestines</td>
<td>3A4 inhibitor and substrate</td>
<td>Substrate: 3A4, 2B6, 2C8, 2C9, 2C19, and 2D6 Primarily 3A4 Substrate and autoinducer 2D6 effected by genetic variability</td>
<td>Substrate 3A4/5</td>
<td></td>
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<tr>
<td>pGP</td>
<td>pGP is an active transport enzyme. Efflux pump that inhibits intestinal absorption of metabolites and metabolites moving across the BBB</td>
<td>Inhibitor and substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Potential inhibitor</td>
</tr>
<tr>
<td>N-demethylation</td>
<td>Removal of methyl group, mediated through cytochrome P450 mechanism</td>
<td></td>
<td></td>
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<tr>
<td>UGT 2B7&lt;sup&gt;33&lt;/sup&gt;</td>
<td>UGT2B7 is a human UGT isoform that catalyzes the conjunction of opioids resulting in D-glucuronides. Binding site of aglycone is located in the N-terminal half of the protein.</td>
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<tr>
<td>OATP&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Genetically polymorphic influx transporter, expressed on the sinusoidal membrane of human hepatocytes and mediates hepatic uptake of many endogenous compounds (opioids) and xenobiotics</td>
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<tr>
<td>ABCB1&lt;sup&gt;24&lt;/sup&gt;</td>
<td>pGP is encoded by the multidrug resistance 1 (ABCB1) gene on chromosome 7p21. This gene is highly polymorphic and a number of variants have been associated with drug response.</td>
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<tr>
<td>Aldoketoreductase (AKR)&lt;sup&gt;31, 35&lt;/sup&gt;</td>
<td>AKRs function as independent metabolic units or as interlinked components of metabolic pathways. These proteins work in collaboration with other carbonyl-metabolizing enzymes such as aldehyde and alcohol dehydrogenases, cytochrome P450s (CYPs), and glutathione S-transferases (GSTs).</td>
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</table>

Metabolized into inactive metabolites

Glucuronidation

Transport capabilities

Variability through resistance

Metabolized to ketone, reduced metabolites (inactive against HCV)
to accumulate.\textsuperscript{14} This interaction could therefore increase “clinical response” to morphine with a simultaneous increase in the dose-dependent side effects such as sedation and/or respiratory depression. Notably, a minor serum level increase or improved clinical response could be difficult to assess in patients who have well-controlled pain. But a significant rise in opioid serum levels could be fatal. It is unlikely that a patient would be able to identify symptoms associated with minor elevated morphine levels, as increased sedation may be written off as fatigue associated with hepatitis C and/or the treatment. This interaction is more concerning in patients who use morphine and other opioids combined with other sedating agents, particularly sedative hypnotics that might promote more significant respiratory depression.\textsuperscript{15}

It is uncertain whether the addition of TVR to such a regimen would increase serum morphine sufficiently to tip the scale into respiratory depression. Controlled pharmacokinetic trials of serum morphine levels in patients prior to and following coadministration of TVR and morphine are unavailable, but could be useful to assess the clinical significance of this proposed interaction. At the time of publication, we were not aware of any controlled studies that implicate TVR to raise serum morphine concentrations, nor are there any case reports to confirm this. Our suspicion is that these reports don’t exist because practitioners and pharmacists are not anticipating the interactions. It is difficult to identify such interactions with discrete agents when considering the potential for confounds due to the polypharmacy common in the relevant patient populations. Nevertheless, Gatti and Cha made an excellent point with warfarin as an example, which could open the floodgates if we start looking. In fact, Taylor et al. exhort that future paradigms for treating HIV/HCV-coinfected persons with direct-acting antivirals (DAAs) should include expedited pharmacokinetic studies to establish important drug-drug interactions with DAAs and antiretrovirals.\textsuperscript{4} Moreover, they acknowledge that DAAs also present a challenge when combined with various opioids. However, upon review of the literature, it is quite clear that comprehensive studies to elucidate various opioid interactions with the DAAs and antiretroviral therapies are sorely lacking.

### INTERACTION OF TELAPREVIR AND METHADONE

The complexity of potential interactions between TVR and morphine pales in comparison to that of methadone. This is because the pharmacokinetics of methadone is far more variable due to polymorphism, multiple CYP enzyme involvement, an extremely long and variable half-life, and large volume of distribution.\textsuperscript{16} After a comprehensive literature search, all mentions of a pharmacokinetic drug interaction between methadone and TVR trail back to one single study (including the package insert of telaprevir), “The Pharmacokinetic Interaction Between Methadone and the Investigational HCV Protease Inhibitor Telaprevir.”\textsuperscript{17} This study originally took place in Belgium (2011). Eighteen methadone maintenance patients receiving once-daily treatment were subsequently placed on TVR 750 mg orally three times daily (PO TID) for 7 days. Three volunteers dropped out of the study, two because they discontinued the TVR, and one who withdrew consent. When methadone was coadministered with TVR, it led to a reduction of both (R)- and (S)-serum methadone when compared with the absence of TVR. The area-under-the-curve (AUC) values after 24 hours were reduced by 29% and 36% in both (R)- and (S)-methadone, respectively. The total minimum concentration ($C_{\text{min}}$) for (R)-methadone was reduced by 31% when it was coadministered with TVR. No changes in the unbound concentration of (R)-methadone were seen, but the free fraction of (R)-methadone was increased by 26%.

The increase in serum methadone and decrease in minimum concentration are expected within the first two doses of a CYP3A4 inhibitor, unlike inducers, which could take weeks.\textsuperscript{18} Also, methadone once-daily administration cannot necessarily be presumed to equate to those patients dosed 3–4 times daily for chronic pain syndromes. And finally, 1 week of TVR may not be sufficient to elucidate what might happen after a full course of TVR for up to 12 weeks.

Breaking the complexity down, methadone is composed of a racemic mixture of (R)- and (S)-methadone. The (R)-methadone component is 8–50 times more potent than the (S)-methadone, demonstrating that (R)-methadone is responsible for most of the action of the medication, including analgesia and side effects such as respiratory depression.\textsuperscript{17,19–21}

Methadone is a mu-opioid agonist with binding affinity at kappa- and delta-opioid receptors.\textsuperscript{19} It also inhibits the reuptake of serotonin and norepinephrine and acts as an antagonist at N-methyl-D-aspartate (NMDA), which supports the theory of methadone to prevent central sensitization and reduce neuropathic pain in patients.\textsuperscript{19}

Methadone is a lipophilic medication, which can be detected in the serum in 15–45 minutes after oral administration. Its oral bioavailability on average is 70–80% with a range of 36–100% and its
peak concentration is obtained at 2,304 hours.\textsuperscript{19,21} Methadone is bound to alpha 1-acid glycoprotein in addition to albumin and globulin but to a smaller degree. Unbound methadone levels vary extensively (up to 4-fold) among patients, which results in profound variability among patients.\textsuperscript{21} The distribution of methadone is extensive throughout the body, including the central nervous system (CNS), gut, kidney, liver, muscle, and lungs.\textsuperscript{22} It is maintained in these tissues and is gradually delivered back to the plasma during the redistribution and elimination phases, resulting in an extremely long half-life. This is why a 7-day trial of TVR and methadone could be grossly inadequate.

Methadone is metabolized extensively and largely through N-demethylation into inactive metabolites, which are eliminated through urine and feces. Metabolism occurs primarily in the liver, with some activity in the gut via the cytochrome 450 mechanism through the enzymes CYP3A4, 2B6, 2C8, 2C9, 2C19, and 2D6 but primarily through 3A4.\textsuperscript{21} This process is considerably influenced by many medications that modify the activity of such enzymes, the result of which can be either an increase or decrease of serum methadone. Furthermore, CYP2D6 metabolism is greatly influenced by genetic variability and methadone can also induce its own metabolism in the liver.\textsuperscript{24}

Enzyme induction can result in either increased (due to a prodrug) or decreased medication exposure contingent with a decreased effect. This can take up to 2–3 weeks to realize its full effect. In contrast, enzyme inhibition is almost instantaneous, as indicated above.\textsuperscript{25}

Although on the one hand methadone is a substrate for hepatic enzyme CYP3A4, it is also a substrate for pGP. Its activity in the intestines and the blood-brain barrier (BBB) has a direct affect on methadone concentration.\textsuperscript{26} So, in theory, by inhibiting the pGP inhibitor, there should be increased serum concentrations and metabolites moving more readily across the BBB. Another way methadone has shown variability is through the resistance of ABCB1 gene on chromosome 7p21. ABCB1 is extremely polymorphic resulting in a varied drug response among patients.\textsuperscript{24,27}

P-glycoprotein is established with the oral bioavailability, brain penetration, and treatment resistance, which are associated with this energy-dependent efflux pump. Alteration of its function has compelling role in drug-drug interactions. Another transporter system, OATP1B1, has distinguishing carrier capability, bidirectionally across the sinusoidal liver membrane.\textsuperscript{28} The exact representation of OATP has not been characterized; therefore, its specific action on substrates and inhibitors is uncertain and requires further scrutiny.\textsuperscript{23}

Methadone has a considerably long elimination half-life, which ranges from 5 to 130 hours (mean 20–30 hours).\textsuperscript{29} This inconstant range is often the consequence of accumulation and toxicity. If an additional medication is taken that either increases or decreases the methadone metabolism, an additional (at least) 4–10 days are needed to achieve steady state. This is capricious at best, depending on interpatient pharmacokinetic and polymorphic unpredictability, since as stated above, the range of methadone half-lives is hugely variable.\textsuperscript{29} There are multiple reasons for variance among individuals taking methadone, including the pharmacodynamic (PD) and pharmacokinetic (PK) parameters of the medication. Pharmacodynamics is influenced by adjuvant medications that can either increase or decrease the therapeutic efficiency or adverse drug reaction. Pharmacokinetic interactions result from concomitant administration of drugs that impact absorption, distribution, metabolism, and/or elimination of methadone established from the competitive nature of the multiple medications on protein binding sites. Moreover, methadone has a 30-fold variability in the liver CYP3A4 and 11-fold in the intestinal CYP3A4 enzymes.\textsuperscript{19,29}

According to the TVR package insert, when referring to methadone, “The concentration of (\textit{R})-methadone was decreased; in addition the concentration of methadone was reduced when it was co-administered with telaprevir.” The insert further states that “No adjustment to methadone dose was needed but clinical monitoring of methadone is recommended during maintenance therapy.”\textsuperscript{30}

After closely analyzing methadone data as they relate to TVR's PK and PD profiles, it is evident that potentially very significant and complex drug interactions occur because of the pGP, CYP3A4, ABCB1, and possibly OAT1B1 and OAT2B1. Perhaps most disconcerting is that the information is based on a single short-term 7-day study in noninfected patients taking once-daily methadone. Since methadone itself is an autoinducer of CYP3A4, which can take 2–3 weeks to cause accumulation, a 1-week trial is insufficient to conclude that “No dose adjustment of methadone is necessary when initiating co-administration of TVR.”\textsuperscript{18}

Since boceprevir is the only protease inhibitor alternative to TVR at the time of this publication, we believe it is important to elucidate any similar concerns. Notwithstanding, the extent to which boceprevir affects pGP and cytochrome 450 morphine and methadone pharmacokinetics remains equally unclear. “Boceprevir is a potential inhibitor of pGP...
CONCLUSION

Protease inhibitors are an invaluable advancement for the treatment chronic hepatitis C infection. Comprehensive studies are needed in the hepatitis C patient population receiving a full-course of TVR to determine its effect on methadone metabolism and to justify the current package insert statement. Clearly, a 7-day trial is not sufficiently robust to minimize the potentially significant interaction with opioids, especially methadone. Perhaps equally important, we cannot ignore that fact that many TVR patients also receive antiretrovirals that could further complicate pharmacokinetic drug interactions.

Considering that methadone prescriptions represent 2% of all prescribed opioids but are attributable to 30% of all opioid deaths, it is entirely possible that significant drug interactions with methadone across many therapeutic classes have largely gone unnoticed. Similar assertions can be made for morphine overdoses, as indicated earlier. As the evidence of pGP impact unravels, we undoubtedly will become more mindful of the potential untreated impacts of pGP. As the evidence of pGP impact unravels, we undoubtedly will become more mindful of the potential for interactions with pGP substrates. But for now, the message is be cognizant of these issues, know that the opioid dose may need to be significantly increased or reduced, and upward titration to therapeutic effect must be slow and cautious.

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REFERENCES


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