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Abstract

In response to the fatal interaction of alcohol with extended-release hydromorphone, the U.S. Food and Drug Administration (FDA) approved a class-wide Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioid analgesics in July 2012. Due to the rising concern of dose-dumping effects, it is important for pharmacists to understand the pharmacokinetic interaction between two of the most commonly prescribed LA opioids (oxycodone and morphine) and alcohol. Clinical trials have looked at the pharmacokinetic profile of these long-acting formulations in conjunction with alcohol, and the results have varied depending on the formulation. For this reason, it is important to know which LA opioids have a serious interaction with alcohol so as to better serve the patient.

Introduction

Pharmacists, in evaluating a patient's response to drug therapy, recognize drug interactions as a cause of toxicity or inefficacy. As most drug interactions are based on pharmacokinetics (PK) or pharmacodynamics (PD), it is important to understand and apply these relationships to daily practice. One such drug relationship exists between alcohol and opioids. Though there have been many studies showing the pharacodynamic relationship between alcohol and opioids, few have examined the pharmacokinetic interactions.[1] With the approval of the REMS for ER and LA opioids, now is a critical time for pharmacists to understand the pharmacokinetics of alcohol and opioids and the harm associated with their concomitant use.[2] These interactions stem from the overlap in metabolism of alcohol and opioids and the altered pharmacokinetics, as is seen in patients with cirrhosis. With an understanding of the pharmacokinetics of individual substances, the interaction can further be examined. Studies of the pharmacokinetics of ER and LA morphine and oxycodone, two of the most commonly used opioids, have been performed.[1,3,4] These studies identified the importance of examining the pharmacokinetics of the drug and determining the influence of various formulations on concentration-time relationships, all in the context of a patient's response to a given dosage form. Once all of these factors have been examined, pharmacists will have the information necessary to educate and monitor their patients.

The Alarm and the FDA Response

According to the 2007 National Survey on Drug Use and Health, one-half of Americans 12 years of age and older report alcohol use.[1] Opioids are also widely used by Americans. While only constituting 4.6 percent of the world's population, Americans consume nearly 80 percent of the world's opioid supply.[5] When each of these substances are used responsibly and correctly, there are few concerns regarding drug interactions and patient safety. The true concern surfaces when these substances are used concomitantly—whether intentionally or not. After a study performed on ER hydromorphone (Palladone®) showed a potentially fatal interaction with alcohol, the FDA requested its removal from the market in 2005.[3,6] While actions, such as black box warnings (BBW) seen in Table 1, have been provided to inform health care providers of the potential toxicity due to the pharmacokinetic interaction between alcohol and opioids, the FDA has only recently approved a more active approach to the issue.[1,2] In July of 2012, the FDA approved its first class-wide REMS for ER and LA opioid analgesics. Introduced in March of 2013, the current REMS features pharmacists as one of the key contributors who will work with both prescribers and patients to ensure correct use of these ER and LA opioids.[2] The platform of patient education regarding the effects of these ER and LA opioids with concomitant use of alcohol is an important one for pharmacists and should not be overlooked. As the number of different ER and LA formulations of opioid analgesics increases, and as altered liver function is recognized in relation to drug metabolism, keeping current with pharmacokinetic research for this issue is imperative for patient care. With a proper understanding of how alcohol affects the pharmacokinetics of a patient's ER or LA opioid analgesic, the pharmacist may better help patients avoid dangerous adverse events and achieve the desired therapeutic outcome.

Alcohol and the Liver

In order to appreciate the interaction between alcohol and LA and ER opioids, the hepatic metabolism of alcohol must be considered. Alcohol's metabolism involves many steps and multiple enzymes. In the main pathway, alcohol is oxidized by alcohol dehydrogenase (ADH) to acetaldehyde, and then further oxidized to acetate by aldehyde dehydrogenase (ALDH) (Figure 1).[7,8] Acetaldehyde can bind to proteins and form adducts. These adducts can impair protein secretion and cause hepatomegaly.[9] The major metabolic point where alcohol and opioids interact is through cytochrome P-450 (CYP) enzymes. In the liver, CYP2E1, 1A2, and 3A4 all contribute to alcohol oxidation.[9] CYP2E1 metabolism in the brain also oxidizes alcohol. The excess oxidation by CYP enzymes in the liver increases the oxygen consumption in the liver. This can cause some areas of the liver to become hypoxic. The metabolism also causes the formation of reactive oxygen species (ROS) in the liver. This oxidative stress along with the hypoxia can cause acute liver damage and hepatitis or cirrhosis with chronic use of alcohol.[9,10]

Table 1. Long-acting Opioid Products and black box warning (BBW) for Alcohol.[14-26]

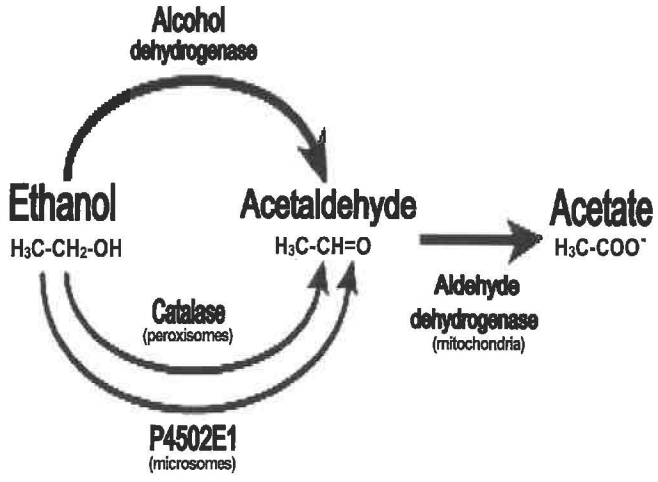
Trade Name	Generic Name	Sponsor	BBW for Alcohol: Yes/No
Avinza	Morphine sulfate extended-release capsules	Pfizer	Yes
Butrans	Buprenorphine transdermal system	Purdue Pharma	No
Dolophine	Methadone hydrochloride tablets	Roxane	No
Duragesic	Fentanyl transdermal system	Janssen Pharmaceuticals	No
**Embeda	Morphine sulfate and naltrexone extended-release capsules	Pfizer	Yes
Exalgo	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt	No
Kadian	Morphine sulfate extended-release capsules	Actavis	No
MS Contin	Morphine sulfate controlled-release tablets	Purdue Pharma	No
Nucynta ER	Tapentadol extended-release oral tablets	Janssen Pharmaceuticals	Yes
Opana ER	Oxymorphone hydrochloride extended-release tablets	Endo Pharmaceuticals	Yes
OxyContin	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma	No
*Palladone	Hydromorphone hydrochloride extended-release capsules	Purdue Pharma	Yes

**No longer being marketed, but is still approved.*
***Not currently available due to a voluntary recall, but is still approved.*

With progression of liver disease, the composition of the body changes, thereby changing the volume of distribution (Vd). Liver disease can also cause metabolic changes. Liver failure with cirrhosis also alters the metabolic enzymes of the liver. More significantly, liver disease affects phase I enzymes, involved in oxidation-reduction reactions, more than phase II enzymes which are involved in conjugation reactions.[10] The phase I enzymes, including CYP enzymes, are more sensitive to hypoxia, which is prevalent in liver disease.

Hepatic metabolism is the primary elimination route for lipophilic drugs. Hepatic clearance is dependent upon hepatic blood flow, plasma protein binding, and intrinsic clearance. The hepatic extraction ratio (Eh) of the drug determines which factors influence clearance most significantly. Clearance of high extraction drugs with an Eh>0.7 are mainly dependent upon liver blood flow whereas low extraction compounds with Eh<0.3 are mainly dependent upon plasma protein binding and intrinsic metabolic clearance.[10] In healthy patients, and in those with mild cirrhosis, morphine is a high extraction compound with an Eh of approximately 0.7, meaning hepatic blood flow will be the main contributor to morphine's clearance. Therefore, when considering patients with chronic liver disease, morphine clearance is not significantly altered until severe cirrhosis has developed.[11] In addition to altering hepatic blood flow, liver disease with cirrhosis also impairs production of plasma proteins albumin and a-acid glycoprotein. As a drug "becomes" a low extraction compound, its clearance switches from being dependent on hepatic blood flow to being dependent on intrinsic clearance and fraction of unbound drug. With clearance decreased and volume of distribution increased, the half-life gets longer.

Figure 1. The Main Oxidative Metabolic Pathway of Alcohol.[7]



Alcohol and CR Oxycodone

To further understand the interaction between opioids and alcohol, it is necessary to understand the kinetics of individual opioids. Each drug in the opioid class has its own set of pharmacokinetic parameter values. Two opioids, oxycodone and morphine, have pharmacokinetics profiles that have been examined extensively.

Controlled-release (CR) oxycodone has become one of the most commonly used CR opioids in the United States, making it crucial to understand its kinetic interaction with alcohol.[12] CR oxycodone is absorbed in a bi-exponential fashion. The initial rapid phase has an absorption half-life of 37 minutes. During this time, 38 percent of the drug is absorbed. The rapid phase is then followed by a slow phase with an absorption half-life of 6.2 hours and duration of action of 12 hours.[12,13] CR oxycodone bioavailability is 60 to 87 percent, and it undergoes first-pass metabolism. Ten percent is metabolized through O-demethylation by CYP2D6 to the minor metabolite, oxymorphone, which is 14 times as potent as oxycodone. Then, N-demethylation produces noroxycodone, a weak analgesic that is the major metabolite of CR oxycodone.[12] Because protein binding is relatively low, hepatic cirrhosis and decreased plasma protein production will not greatly affect Vd.

Recognizing the metabolism of both alcohol and CR oxycodone, one would conclude the interaction could be predicted. Results of recent clinical trials, however, have proven otherwise. For example, Friedmann et al.[4] looked at the new REMOXY (oxycodone) capsule. REMOXY is formulated to have an increased viscosity to prevent crushing and decrease "dose-dumping." As the capsule cannot be crushed, it cannot be dissolved in alcohol to induce a euphoric high from quick dissolution. The study found that there were no significant changes in the pharmacokinetics of the formulation when taken with 4 percent, 20 percent, or 40 percent alcohol acutely. The researchers concluded that, while still not recommended, concomitant use of alcohol and this new controlled-release formulation is safer compared to current formulations of CR oxycodone. This study exemplifies the need to consider a medication's formulation when examining clinically important pharmacokinetics parameters.

Alcohol and ER morphine

In addition to CR oxycodone, ER morphine has been undergoing pharmacokinetic testing to examine its effects when used with alcohol. Similar to CR oxycodone, ER morphine is formulated to have an immediate release component upon contact with GI fluids, followed by a sustained-release component that generally lasts 12 to 24 hours.[3] The bioavailability of oral morphine can increase from 40 percent to 100 percent in patients with severe cirrhosis.[10,11] Furthermore, while CR oxycodone is metabolized by CYP450 enzymes, ER morphine is glucuronidated in the liver to two metabolites, morphine-3-glucuronide (M3G) and to a lesser extent, morphine-6-glucuronide (M6G)

Studies have been performed to evaluate the effects of alcohol combined with ER morphine and its pharmacokinetic profile. When alcohol is used acutely and in reasonable amounts with ER morphine, there is minor concern of increased opioid exposure. One product (Embeda) is a morphine sulfate ER capsule, which possesses a polymer around the beads in the capsule to achieve extended release characteristics. When ingesting 240 mL of 20 percent alcohol (similar to approximately 12 ounces of wine, a pint of beer, or 2.5 glasses of a mixed drink) the rate of absorption and the extent of exposure for morphine did not increase in patients. A change in pharmacokinetics was seen, however, upon concomitant use of morphine extended-release and 240 mL of 40 percent alcohol. This amount of alcohol is equivalent to five 1.5-ounce shots of hard liquor. Although there was no change in bioavailability for morphine, the average maximum concentration (C_{max}) was doubled and the median time to maximum concentration (T_{max}) was decreased from nine hours to four hours. Although this kinetic profile may seem alarming, cumulative morphine exposure while taking Embeda is not similar to that of an immediate-release morphine solution combined with alcohol. This suggests that "dose dumping" is not particularly of concern when mixing Embeda and acute alcohol use.[1] However Embeda still has a BBW for alcohol use. Clinically, all interactions must be taken into account, including pharmacokinetics and pharmacodynamics.

The effect of alcohol on the pharmacokinetics of another ER morphine product, Kadian, has also been studied. Subjects in the experimental groups were either given 100 mg ER morphine with 240 mL of 40 percent alcohol under fasting conditions or ingestion of a high-fat meal. The control received 100 mg of ER-morphine and 240 mL of water under fasting conditions. All three groups had a T_{max} of eight hours, and the area under the curve (AUC) was similar between them as well. Because the mean AUC and C_{max} for each regimen were within 80 percent to 125 percent, no drug interaction was declared. Therefore, no BBW for Kadian and concomitant alcohol consumption currently exists.[3]

The pharmacokinetic interaction of alcohol and opioids is definitely intricate and multifactorial. Influenced by the separate pharmacokinetics of alcohol and opioids, cirrhosis and its effect on hepatic metabolism, and the development of new formulations, the subject can be difficult to understand. Thus it is critical for pharmacists to be aware of these relationships and monitor patients appropriately. Newer CR products like Embeda and Kadian are reducing the risks associated with this pharmacokinetic interaction. The REMS for ER and LA opioids is leading the way by educating pharmacists and physicians of proper prescribing practices. To further advance pharmacist knowledge, continuing education should be offered to pharmacists. With proper prescribing and monitoring, LA and CR opioids can be used effectively in all patients, regardless of their alcohol consumption.

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