FAST FACTS AND CONCEPTS #260
OPIOID USE IN LIVER FAILURE

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Background  Most opioids are at least partially metabolized by the liver, complicating their use in liver failure. This Fast Fact discusses the use of opioids in patients with liver failure (see also Fast Facts #161 about opioid use in renal failure, #176 and #177 about managing ascites and #189 about prognostication in end-stage liver disease). Note: while there are plenty of pharmacokinetic data about opioids & liver failure, all the clinical recommendations below are empiric and not based on clinical outcomes research.

Hepatic Opioid Metabolism  There are two different types of chemical reactions involved in hepatic drug metabolism. The first, oxidation/reduction reactions, occurs through the cytochrome (CYP) P450 enzyme system. The CYP450 enzymes most relevant in palliative medicine include CYP1A2, 2D6, 2C9, 2C19, 3A3 and 3A4; most opioids are metabolized by these enzymes. In hepatic failure, opioid clearance is reduced and drug bioavailability is increased. These changes can be secondary to reduced hepatic blood flow (limiting first-pass metabolism) or decreased CYP450 enzyme levels in these patients. Conjugation and glucuronidation comprise the second group of chemical reactions in the liver. These reactions are less affected in hepatic disease due to glucuronidation enzyme preservation and also because of extrahepatic glucuronidation processes. Glucuronidated opioid metabolites are generally renally excreted. Changes such as decreased serum albumin and ascites can also alter opioid volume of distribution which can lead to either increased or decreased drug concentrations, although there is no practical way to ‘test’ for or predict this apart from close clinical observation.

Morphine  Morphine is metabolized by glucuronidation to two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is an active analgesic that is more potent than morphine, while M3G has no analgesic effect but contributes to neurotoxic side effects such as confusion. Morphine accumulation has been reported in liver disease which can result from decreased plasma clearance and/or increased elimination half-life of the parent drug. In patients with early liver disease, initial lower doses should be used, but at normal dosing intervals. However, as the disease progresses to advanced hepatic failure, longer dosing intervals may be necessary.

Oxycodone  Oxycodone is metabolized to two different metabolites by CYP2D6 and 3A4. However, neither metabolite contributes significantly to analgesia. In advanced liver failure, oxycodone’s maximum concentration increases 40%, and immediate-release oxycodone’s half-life increases to 4.6-24.4 hours (average 14 hours; its usual half-life is ~3.5 hours). Initial oxycodone dosing in patients with severe hepatic failure should be reduced to 30%-50% of the recommended starting dose.

Codeine & Meperidine  Both these drugs should be avoided entirely in patients with liver failure. Codeine is a prodrug that is heptatically converted to morphine by CYP2D6. In patients with liver dysfunction, pain control can be compromised if codeine is not metabolized. Meperidine is metabolized by CYP3A4 to normeperidine and also by hydrolysis. In hepatic disease, meperidine clearance is reduced and its half-life is prolonged. Seizures, a major side effect of meperidine and normeperidine, can occur at reduced doses in patients with hepatic failure (see Fast Fact #71).

Hydromorphone & Hydrocodone  Hydromorphone is glucuronidated to metabolites which have no analgesic properties but can be neurotoxic (see Fast Facts #57, 58, 142). Hydrocodone is a prodrug metabolized by CYP2D6 to hydromorphone and other metabolites, and is only available in combination with non-opioids such as acetaminophen. Hydrocodone dose titrations are limited by the non-opioid component, and overconsumption of acetaminophen-containing products is hepatotoxic. In patients with severe liver disease, initial starting doses of each drug should be reduced to 50% of normal and as the disease progresses, prolonged dosing intervals may also be necessary.

Fentanyl  Fentanyl is primarily metabolized by CYP3A4 and quickly redistributes to muscle and fat upon administration. In single-bolus studies, intravenous fentanyl’s pharmacokinetics were unchanged by
liver failure, however its half-life is prolonged in liver failure with repeated dosing or high dose therapy. Transdermal fentanyl has not been adequately studied in liver failure. Hepatic failure can alter skin permeability and drug absorption; the clinical relevance of this, if any, has not been determined. Some experts suggest fentanyl is a preferred opioid in liver failure (1, 4), although this judgment appears to be entirely empiric.

**Methadone** Methadone is metabolized by CYP3A4, 2D6 and 1A2. Methadone’s clearance is reduced in severe liver disease. Notably, however, hepatitis C infection stimulates CYP3A4 activity and may actually increase methadone clearance, particularly on (before overt liver failure occurs).

**Clinical Management Pearls** As in any clinical setting, the ‘right dose’ of an opioid analgesic medication is that which provides adequate pain relief in conjunction with an acceptable side effect profile. This statement is especially true in end stage liver disease (ESLD). Opioids should not be decreased solely out of concern for hepatic disease (e.g., if a patient with ESLD appears to tolerate and require q3 hour dosing of oxycodone, that dosage should continue). In general, lower doses of most opioids should be initiated in patients with ESLD, and clinicians should be cautious prescribing opioids at ‘regular’ dosing intervals until patients have demonstrated an ability to tolerate them. Patients with deteriorating liver function should be closely monitored for signs of drug accumulation and need for dose reductions, assuming the level of analgesia remains acceptable. Finally, potential drug interactions involving the CYP450 enzyme system must always be considered as there is potential for non-opioid medications to either induce or inhibit the metabolism of any opioid that is a CYP450 enzyme substrate.

**References**


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