The Impact of Liver and Renal Dysfunction on the Pharmacokinetics and Pharmacodynamics of Sedative and Analgesic Drugs in Critically Ill Adult Patients

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KEYWORDS

• Pharmacokinetics • Pharmacodynamics • Critical care • Sedatives • Analgesics • Renal • Hepatic • Dysfunction

KEY POINTS

- Sedative and analgesic drug therapy is often necessary to treat critically ill adult patients.
- Critically ill patients are at high risk for experiencing adverse events from sedative and analgesic drug therapy.
- Renal and hepatic dysfunction, which can occur frequently in critically ill patients, may alter the pharmacokinetics (PK) and pharmacodynamics (PD) of commonly used sedatives and analgesics.
- By anticipating how absorption, bioavailability, distribution, metabolism, and elimination might influence drug disposition for a given pharmacologic agent, a more tailored drug regimen can be designed.
- Frequent monitoring is required to ensure optimal safety and efficacy of sedative and analgesic drugs in critically ill patients, especially in the presence of liver or kidney impairment.

This article is an update of an article previously published in *Critical Care Nursing Clinics of North America*, Volume 17, Issue 3, September 2005.
Authors have no conflicts of interest to disclose.
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Crit Care Nurs Clin N Am 28 (2016) 183–194
http://dx.doi.org/10.1016/j.cnc.2016.02.009 **ccnursing.theclinics.com**
0899-5885/16/$ – see front matter

INTRODUCTION

ICU patients are at heightened risk for experiencing pain, anxiety, or delirium. These syndromes typically occur either as a result of critical illness or as a consequence of ICU care (catheter insertion or adjustment, mechanical ventilation, repositioning, and so forth). Agitated patients are at increased risk of stress-related morbidity, are less likely to tolerate mechanical ventilation, and are more likely to inadvertently remove intravenous catheters or endotracheal tubes. Sedative and analgesic drugs are often used to alleviate and prevent patient discomfort, reduce the risk of self-harm, and improve clinical outcomes.[1–3]

The benefits of these drugs, however, are counterbalanced by their adverse effects. Opioid analgesics are associated with constipation and respiratory depression, whereas dexmedetomidine and propofol are associated with hypotension and bradycardia. Benzodiazepines have been implicated in the development of ICU delirium, and the presence of delirium has been independently associated with prolonged duration of mechanical ventilation, increased length of ICU stays, and greater risk of death.[4,5] To minimize the risk of these adverse events, pharmacologic agents must be carefully selected, monitored, and titrated.[6] The presence of organ dysfunction in critically ill patients can complicate this process.

Hepatic and renal dysfunction is commonly observed in critically ill patients. The incidence of hepatic dysfunction has been shown to range between 11% and 54% among certain critically ill patient populations, whereas the incidence of acute kidney injury (AKI) has been shown to range between 5.4% and 19.2%.[7–9] Kidney and liver injury may also coexist, either acutely or chronically, in a given patient. Among patients with cirrhosis, the incidence of AKI may be as high as 50% to 70%, whereas the incidence of chronic kidney disease (CKD) has been reported as high as 13% and 17%.[10,11] Both the liver and the kidneys play a significant role in the PK of sedative and analgesic drugs. These PK changes, in turn, can affect the dose-response relationship and may lead to toxic effects or adverse events.

The liver is the primary organ responsible for the metabolism of drugs. The kidneys are primarily responsible for the elimination of drugs and their metabolites. Changes in liver or kidney function can have a clinically significant impact on the PK of sedative and analgesic medications that are used in the critical care setting. A drug's PK parameters, such as absorption, distribution, metabolism, and elimination, can be substantially altered as a result of either acute or chronic liver or kidney damage. As a result of these changes, the potency and duration of action for a sedative or analgesic drug dose may be markedly affected.

Unfortunately, most of the available PK data for sedatives and analgesics involve healthy volunteers or noncritically ill patients. Despite this limitation, it is important for clinicians to have a sound understanding of PK and PD principles to design, implement, and evaluate sedative and analgesic drug regimens for critically ill patients. This article provides an evidence-based review on the impact of hepatic and renal dysfunction on the PK and PD of select sedative and analgesic drugs used in the ICU setting. By understanding how PK parameters are affected by liver and kidney dysfunction, it may be possible to reduce the risk of unintended adverse drug events for this vulnerable patient population.[12–14]

The PK parameters for some of the more commonly used sedative and analgesic drugs are shown in **Tables 1** and **2**.

BIOAVAILABILITY

Bioavailability is the percentage of an administered drug dose that enters the systemic circulation. Definitions of this and other common PK terms are listed in **Box 1**. The oral