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Crit Care Nurs Clin N Am 17 (2005) 245 – 250

CRITICAL CARE
NURSING CLINICS
OF NORTH AMERICA

The Effects of Liver and Renal Dysfunction on the Pharmacokinetics of Sedatives and Analgesics in the Critically Ill Patient

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Sedative and analgesic drugs are often used in the ICU to help achieve the best possible level of comfort and safety for critically ill patients. Pain, anxiety, and agitation can complicate therapeutic and diagnostic procedures, increase the risk of patient self-extubation, and make nursing care significantly more difficult [1]. Numerous factors can contribute to the discomfort of critically ill patients, including mechanical ventilation and invasive procedures. In addition to improving patient tolerance of these interventions, sedation and analgesia may improve morbidity by reducing stress-related inflammation and pulmonary complications [2].

Patients in the ICU can display a wide range of organ dysfunctions. Hepatic dysfunction may be seen in up to half of all critically ill patients, and the incidence of acute renal failure in this population may range between 7% and 23% [3,4]. Alterations in hepatic and renal function can significantly alter the pharmacokinetics (PK) of drugs, which may result in adverse outcomes. Patients with renal or hepatic failure, for example, may experience prolonged exposure to sedative agents, resulting in extra days of mechanical ventilation. This, in turn, increases the risk of developing ventilator-associated pneumonia and lung injury, lengthens the course of hospitalization, and raises the costs of patient care. Being familiar with the principles that govern PK in critically ill patients can help minimize unintended consequences of sedative and analgesic drug therapy. This article reviews PK and pharmacodynamic (PD) parameters of sedative and opioid analgesic drugs in critically ill patients with hepatic or renal dysfunction.

The liver

The liver has a wide range of functions. It plays a major role in glucose storage and regulation, and it is responsible for the production of clotting factors, cholesterol, and circulating plasma proteins, such as albumin. In addition, the liver is the primary organ involved in the metabolism of drugs and removal of toxic substances from the systemic circulation. Liver dysfunction can profoundly influence the PK of drugs by altering bioavailability, apparent volume of distribution, and clearance [5–7]. These changes, in turn, can affect the pharmacologic duration and potency of sedative and analgesic drugs. The PK parameters for some common sedatives and opioids, as measured in healthy subjects, are shown in Tables 1 and 2.

Bioavailability

Bioavailability is the amount of administered drug that is available to the systemic circulation. Definitions of this and other common PK terms are listed in

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0899-5885/05/$ – see front matter
doi:10.1016/j.ccell.2005.04.007

Table 1
Pharmacokinetics of sedative agents

Drug	Metabolic substrate	Significant metabolite	E	PB (%)	$t_{1/2}$ (h)	Vd (L/kg)
Lorazepam	Glucuronyltransferase	None	Low	91	12	1.3
Diazepam	CYP 2C19	Desmethyldiazepam Oxazepam	Low	99	19–54	1.1
Midazolam	CYP 3A4	α-Hydroxymidazolam	Intermediate	95	1.8–6.4	1–2.5
Propofol	Glucuronyltransferase	None	High	98	1.5–12.4	60

Abbreviations: E, hepatic extraction ratio; PB, protein binding; $t_{1/2}$ (h), elimination half-life expressed in hours; Vd (L/kg), apparent volume of distribution expressed in liters per kilogram.

Box 1. The oral bioavailability of most drugs is generally less than 100% and can vary widely depending on the molecular characteristics of the drug. Drugs administered orally are absorbed through the lining of the small intestine whereby they enter enterohepatic circulation. Before entering systemic circulation, the drug passes through the liver and is exposed to hepatic metabolism. This process is often referred to as the ''first-pass effect.'' When the liver has a compromised ability to metabolize drugs, the first-pass effect can be significantly diminished. For orally administered drugs that are highly sensitive to first-pass metabolism, this may render a substantial increase in systemic bioavailability. In a study involving seven patients with a history of alcoholic cirrhosis and hepatic encephalopathy, the oral bioavailability of a single dose of morphine was found to be more than twice as high as healthy controls [8]. Similarly, the systemic bioavailability of orally administered midazolam has been shown to be significantly larger in patients with cirrhosis as compared with healthy controls [9]. Most sedatives and analgesics in the ICU, however, are given by the intravenous route. Drugs administered intravenously are not subjected to first-pass metabolism and are 100% bioavailable. Other PK parameters besides bioavailability, however, can be altered in critically ill patients with liver disease.

Distribution

Volume of distribution is a relative term, expressed in liters, that describes the degree to which a drug distributes throughout the body. Drugs that are hydrophilic (water-soluble) or highly protein bound have relatively small volumes of distribution, whereas drugs that are lipophilic (lipid-soluble) or not significantly protein bound have relatively large volumes of distribution. Volume of distribution is directly proportional to half-life, and increases in volume of distribution can result in a prolonged therapeutic effect for certain sedative and analgesic drugs.

Patients with severe chronic liver disease, like alcoholic cirrhosis, often display increases in volume of distribution as a result of decreased circulating plasma proteins. Furthermore, critically ill patients often have reduced albumin because of malnutrition or acute illness [10]. Plasma proteins, such as albumin and α1-acid glycoprotein, serve as the primary source of oncotic pressure within the vascular space. Decreases in oncotic pressure may result in fluid shifting out of the intravascular space, which may increase the volume of distribution of hydrophilic drugs. Low serum albumin has been shown to lead to prolonged sedation with midazolam in critically ill patients with renal failure [11]. This effect was shown to be related to an increase in midazolam's

Table 2
Pharmacokinetics of opioid agents

Drug	Metabolic substrate	Significant metabolite	E	PB (%)	$t_{1/2}$ (h)	Vd (L/kg)
Morphine	Glucuronyltransferase	m-3-Glucuronide m-6-Glucuronide	High	36	1.5–4.5	1–4
Fentanyl	CYP 3A4	None	High	84	3.65	3.2–4
Methadone	CYP 3A4	None	Low	89	23	3.6
Hydromorphone	Glucuronyltransferase	hm-6-Glucuronide	Intermediate	71	2.65	1.22

Abbreviations: E, hepatic extraction ratio; hm-6-glucuronide, hydromorphone-6-glucoronide; m-3-glucoronide, morphine-3-glucoronide; m-6-glucoronide, morphine-6-glucoronide; PB, protein binding; $t_{1/2}$ (h), elimination half-life expressed in hours; Vd (L/kg), apparent volume of distribution expressed in liters per kilogram.

Box 1. Pharmacokinetic terms and definitions

- Absorption: Process by which a drug enters the systemic circulation
- Bioavailability: Fraction of the dose of a drug that reaches the systemic circulation
- Clearance: Volume of fluid (usually blood or plasma) that is cleared of drug per unit time
- Distribution: Movement of drug between body compartments (eg, between blood vessels and peripheral tissues)
- Elimination: Removal of drug from the body through excretion or metabolism
- Extraction ratio: Fraction of the drug presented to an eliminating organ that is cleared after a single pass
- Half-life: Length of time necessary to reduce the concentration of a drug by 50%
- Metabolism: Removal of drug from the body by biotransformation by enzymatic or conjugation reactions
- Pharmacokinetics: Effect of the body on the drug (absorption, distribution, metabolism, elimination)
- Pharmacodynamics: Effect of the drug on the body (dose-response relationship)
- Steady state: Equilibrium condition reached when the rate of administration of a drug equals the rate of elimination
- Volume of distribution: Apparent volume in the body in which the drug is dissolved

volume of distribution with a subsequent reduction in its clearance.

Metabolism and clearance

Liver dysfunction can affect the metabolism of drugs by a variety of mechanisms. Reductions in functional hepatic blood flow, decreases in protein binding, and damage to liver cells can reduce the metabolism and clearance of drugs from the plasma.

Cellular metabolism

The predominant hepatic mechanisms involved in the metabolism of sedatives and analgesics include cytochrome P-450 enzyme reactions (phase I metabolism) and conjugation reactions (phase II metabolism). These processes result in the biotransformation of drugs into water-soluble metabolites that can be eliminated through the kidneys or bile. Metabolites can be inactive, possess some degree of pharmacologic activity, or be toxic. Most active metabolites are generally less potent than their parent compound, but they can result in enhanced or prolonged pharmacologic activity if their elimination is retarded. A description of the metabolic by-products of common ICU sedatives and opioids are listed in Tables 1 and 2.

Clearance and blood flow

Clearance is a term used to describe the volume of fluid that is completely cleared of a substance per unit of time. The clearance of sedative and analgesic drugs from the serum is largely dependent on the extent to which the liver can metabolize these agents. Hepatic clearance is the product of the hepatic extraction ratio and hepatic blood flow. The hepatic extraction ratio is the fraction of drug that is removed from circulation after one pass through the liver. With respect to hepatic clearance, drugs with a high extraction ratio (>70%) are significantly affected by changes in hepatic blood flow and less affected by changes in hepatic function. Conversely, drugs with a low extraction ratio (<30%) are much more sensitive to changes in hepatic function and less sensitive to changes in hepatic blood flow [5–7]. Fentanyl is a synthetic opioid analgesic with a high extraction ratio. The PK of intravenous fentanyl has previously been shown to be unaffected in surgical patients with cirrhosis [12]. The authors attributed this lack of effect to the relatively preserved hepatic blood flow observed in the patients.

Clearance and protein binding

Highly protein-bound drugs exist in a state of equilibrium between unbound and bound drug. Because only the unbound (free) form of the drug is pharmacologically active, decreased plasma proteins can lead to an increase in the amount of drug available at the site of action. Protein binding can have a significant impact on the distribution (discussed previously) and metabolism of sedative and analgesic drugs. The plasma protein binding characteristics of a drug can be classified as either nonrestrictive or restrictive. Drugs that display non-

restrictive protein binding are easily dissociated from their carrier proteins, and are readily available for hepatic metabolism [5]. The extent of protein binding for nonrestrictive drugs does not influence the hepatic extraction ratio. For drugs that display restrictive protein binding, only the free, unbound fraction of the drug is available for hepatic metabolism. A decrease in circulating plasma proteins increases the free-fraction of the drug and increases the hepatic extraction ratio. For restrictive drugs, however, an increased fraction of unbound drug also results in a higher concentration of drug that is available for therapeutic action.

Estimates of liver function

Assessing hepatic function in the critically ill can be challenging. Although creatinine clearance is a generally well-accepted indicator of renal function, there is no hepatic correlate that accurately reflects liver function. To help clinicians objectively assess liver function, a number of scoring systems have been developed. These scoring systems take laboratory data (bilirubin, albumin, prothrombin time), clinical features (ascites, encephalopathy, nutrition status), patient history (alcohol abuse), and patient status (hospitalized or ambulatory) into account to assess objectively the degree of hepatic impairment. Examples of such scoring systems include the Child's Score, Child's Score with Pugh's Modification, and the Model for End Stage Liver Disease Score [13–15]. Although these scoring systems are useful in assessing the severity of liver disease and predicting mortality, they have not been validated as drug dosing tools.

The kidneys

The kidneys are responsible for the elimination of many drugs and their metabolites. There are three major mechanisms involved in the renal clearance of drugs: (1) glomerular filtration, (2) tubular secretion, and (3) reabsorption. Of these, glomerular filtration is primarily responsible for the elimination of most drugs and their metabolites.

Glomerular filtration is a passive process. Water-soluble molecules and drugs of small molecular size are filtered more easily than large or protein-bound drugs. As drugs and metabolites pass through the kidneys, they are removed by glomerular filtration and eliminated through the urine.

Effect of renal pathology on drug clearance

The PK and PD of drugs used in critically ill patients are often difficult to predict because of the dynamic physiologic changes that occur in this patient population. Studies of the effects of renal failure on drug PK in critically ill patients are very limited [16]. Most available data are on healthy populations or in patients with chronic renal failure. It is important for clinicians to have a sound understanding of PK and PD principles and to know how to apply these principles to individualize therapy for a critically ill patient. The following discussion focuses on the effects of renal failure on the distribution, metabolism, and elimination of sedatives and analgesics in critically ill patients.

Distribution

Alterations in protein binding can have a profound affect on a drug's volume of distribution. In a related manner, the accumulation of fluid during renal failure can also have an impact on the extent of drug distribution throughout the body. As fluid accumulates, water-soluble drugs are able to diffuse with excess fluid into the extravascular space. This results in a reduced concentration of drug within the intravascular space that is available for metabolism and elimination, which reduces drug clearance. In a related phenomenon, alterations in fluid status can alter the concentration of drug that is presented to the pharmacologic site of action, resulting in a diminished dose-response relationship. Although changes in fluid status are often difficult to predict in critically ill patients with renal dysfunction, clinicians should be aware that sudden fluid shifts, like what may occur following a hemodialysis session, may impart a significant change in the PK and PD of sedative and analgesic agents.

Metabolism

The kidneys are known to have active drug metabolizing systems, and changes to renal and hepatic drug metabolism have been noted in patients with renal failure [17–20]. The clinical significance of these effects on sedatives and analgesics in critically ill patients with renal disease remains to be determined. Careful drug dosing and monitoring is essential to ensure drug therapy is achieving desired pharmacologic effects without causing adverse events.

Elimination

Determining drug elimination in the critically ill patient population is challenging for many reasons. Most PK studies in renally or hepatically impaired patients are usually performed in stable patients with chronic disease effecting only one organ system. It is difficult to apply these data to unstable, critically ill patients with multiple organ dysfunction. In addition, renal drug clearance in critically ill patients can be influenced by a number of comorbidities, including liver failure, hemodynamic instability, and malnutrition.

Reductions in the glomerular filtration rate leading to renal failure may significantly reduce the elimination of drugs and drug metabolites that are primarily eliminated by filtration. The active metabolites of morphine (morphine-3-glucuronide and morphine-6-glucuronide) and midazolam (glucuronidated α-hydroxymidazolam) have been shown to accumulate in critically ill patients with renal failure [21,22]. When using these medications in this patient population, clinicians should consider using alternative agents or empirically reduce the dose. The glucuronide metabolite of lorazepam has also been shown to accumulate in patients with renal failure, but this is of no clinical significance because the metabolite is neither active nor toxic at high concentrations [23].

Estimates of renal clearance

Assessing renal function in critically ill patients is a challenging but important step in appropriately dosing drugs that are removed by the kidneys. For renally eliminated drugs, the rate of elimination is often directly proportional to the glomerular filtration rate. The creatinine clearance is the most frequently used estimate of glomerular filtration rate, and this value can be measured by collecting 24-hour urine creatinine production or estimated by using calculations based on serum creatinine or other laboratory measures. There are many equations that can be used to estimate creatinine clearance, but the one that is most often used to guide drug dosing is the Cockroft and Gault equation [24–28]. It is important to stress that there are many conditions and situations in critically ill patients that alter the accuracy of any of these methods, including the Cockroft and Gault equation. For example, in renally impaired patients who also have cirrhosis, creatinine-based estimates of renal function have been shown to overestimate glomerular filtration rate to varying degrees [29].

Summary

There are many factors besides organ dysfunction that can alter the PK and PD of drug therapy. In ICU patients with hepatic or renal dysfunction, drug disposition can be influenced by the presence of comorbid conditions, drug interactions, and the use of hemodialysis. To ensure optimal dosing of sedatives and analgesics, and to promote positive therapeutic outcomes, regular and repeated clinical assessments need to be performed [30,31]. There are several bedside assessment tools that are used to assess the adequacy of sedation, including the Richmond Agitation-Sedation Scale, the Sedation-Agitation Scale, the Motor Activity Assessment Scale, and the Ramsey Sedation Scale [31]. The bispectral index, which is a statistically derived variable of the electroencephalogram, is an objective measure of sedation that has undergone limited validity testing in the ICU [32]. Regardless of the sedation scale that is used, it is important that patients in the ICU are monitored regularly. Regular assessment of sedation and pain control minimizes the risks of oversedation and undersedation and reduces the number of unnecessary procedures that are performed to exclude other reasons for unresponsiveness [2,30].

The presence of renal or hepatic dysfunction in the critically ill patient can significantly alter the PK and PD of sedatives and opioid analgesics. By anticipating these changes and routinely assessing the response to therapy, health care providers can offer effective treatment regimens that minimize adverse events.

References

[1] Atkins PM, Mion LC, Mendelson W, et al. Characteristics and outcomes of patients who self-extubate from ventilatory support: a case-control study. Chest 1997; 112:1317–23.
[2] Walder B, Tramer MR. Analgesia and sedation in critically ill patients. Swiss Med Wkly 2004;134:333–46.
[3] Power BM, Forbes AM, van Heerden PV, et al. Pharmacokinetics of drugs used in critically ill adults. Clin Pharmacokinet 1998;34:25–56.
[4] al-Khafaji A, Corwin HL. Acute renal failure and dialysis in the chronically critically ill patient. Clin Chest Med 2001;22:165–74.
[5] Howden CW, Birnie GG, Brodie MJ. Drug metabolism in liver disease. Pharmacol Ther 1989;40:439–74.
[6] Rodighiero V. Effects of liver disease on pharmacokinetics: an update. Clin Pharmacokinet 1999;37: 399–431.
[7] Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics

of opioids in liver disease. Clin Pharmacokinet 1999; 37:17–40.

[8] Hasselstrom J, Eriksson S, Persson A, et al. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. Br J Clin Pharmacol 1990; 29:289–97.

[9] Pentikainen PJ, Valisalmi L, Himberg JJ, et al. Pharmacokinetics of midazolam following intravenous and oral administration in patients with chronic liver disease and in healthy subjects. J Clin Pharmacol 1989;29:272–7.

[10] Marik PE. The treatment of hypoalbuminemia in the critically ill patient. Heart Lung 1993;22:166–70.

[11] Vree TB, Shimoda M, Driessen JJ, et al. Decreased plasma albumin concentration results in increased volume of distribution and decreased elimination of midazolam in intensive care patients. Clin Pharmacol Ther 1989;46:537–44.

[12] Haberer JP, Schoeffler P, Couderc E, et al. Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. Br J Anaesth 1982;54:1267–70.

[13] Child CG. The liver and portal hypertension. Philadelphia: WB Saunders; 1964.

[14] Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–9.

[15] Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70.

[16] Davies G, Kingswood C, Street M. Pharmacokinetics of opioids in renal dysfunction. Clin Pharmacokinet 1996;31:410–22.

[17] Klotz U. Pathophysiological and disease-induced changes in drug distribution volume: pharmacokinetic implications. Clin Pharmacokinet 1976;1:204–18.

[18] Vree TB, Hekster YA, Anderson PG. Contribution of the human kidney to the metabolic clearance of drugs. Ann Pharmacother 1992;26:1421–8.

[19] Gibson TP. Renal disease and drug metabolism: an overview. Am J Kidney Dis 1986;8:7–17.

[20] Anders MW. Metabolism of drugs by the kidney. Kidney Int 1980;18:636–47.

[21] Milne RW, Nation RL, Somogyi AA, et al. The influence of renal function on the renal clearance of morphine and its glucuronide metabolites in intensive-care patients. Br J Clin Pharmacol 1992; 34:53–9.

[22] Bauer TM, Ritz R, Haberthur C, et al. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet 1995;346:145–7.

[23] Morrison G, Chiang ST, Koepke HH, et al. Effect of renal impairment and hemodialysis on lorazepam kinetics. Clin Pharmacol Ther 1984;35:646–52.

[24] Jelliffe RW. Estimation of creatinine clearance when urine cannot be collected. Lancet 1971;1:975–6.

[25] Jelliffe RW. Letter: creatinine clearance: bedside estimate. Ann Intern Med 1973;79:604–5.

[26] Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.

[27] Gaspari F, Ferrari S, Stucchi N, et al. Performance of different prediction equations for estimating renal function in kidney transplantation. Am J Transplant 2004;4:1826–35.

[28] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16: 31–41.

[29] Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. Am J Kidney Dis 2003;41:269–78.

[30] Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119–41.

[31] Watson BD, Kane-Gill SL. Sedation assessment in critically ill adults: 2001–2004 update. Ann Pharmacother 2004;38:1898–906.

[32] Deogaonkar A, Gupta R, Degeorgia M, et al. Bispectral Index monitoring correlates with sedation scales in brain-injured patients. Crit Care Med 2004; 32:2403–6.