

## OPIOIDS AND BENZODIAZEPINES

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The critically ill patient in the intensive care unit (ICU) most certainly is susceptible to anxiety and pain and often is hemodynamically compromised. This article discusses the role of opioids and benzodiazepines in providing anxiolysis, sedation, and analgesia for such a patient. These drugs are effective and therefore are the most commonly used medications to achieve the goal of a calm, comfortable, pain-free patient.

### OPIOIDS

Opioids are the mainstay of analgesics. In addition to providing analgesia, they are also indicated because of their sedative properties when patients demonstrate agitation as a result of pain. Traditionally, opioids have been administered orally, intramuscularly (IM), or intravenously (IV). The latter two modes of administration are the most commonly used in the ICU. In today's ICUs, newer modes of administering opioids are being used with increased frequency. These routes include epidural, intrathecal, and (for completeness, but to a lesser extent), transdermal delivery systems.

Morphine is the opioid to which all other opioids are compared. Morphine and codeine occur as natural substances and are found in raw opium. Chemists have manipulated their structure to produce several

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potent synthetic narcotics (i.e., meperidine, fentanyl, sufentanil, and alfentanil). Figure 1 illustrates several of these drugs' structures.

### Opioid Receptors

Drugs binding with opioid receptors can be divided into three groups: agonists, antagonists, and mixed agonists-antagonists. Table 1 lists several of these drugs and their receptor interactions.

Opioids are exogenous or endogenous substances that bind to opioid receptors and produce a cellular response—an agonist—or inhibition of a response—an antagonist. An understanding of opioid receptors and their response to agonists will help ICU physicians predict the clinical sequelae that their patients may manifest if given an opioid.

The discovery of opioid receptors was first reported in 1973 by several groups of investigators simultaneously.<sup>60, 77, 84</sup> Opioid receptors have been found in both the central nervous system (CNS) and in

**Table 1.** CLASSIFICATION OF OPIOID DRUGS

| Drug  | Receptor Types |       |
|---|----------------|-------|
|   | mu             | kappa |
| Opioid agonist  |                |       |
| Morphine  | Ag             | Ag    |
| Hydromorphone   | Ag             | Ag    |
| Phenylpiperidine analgesics<br>(meperidine, fentanyl and its analogs) | Ag             | Ag    |
| Methadone-congeners   | Ag             | Ag    |
| Opioid agonists-antagonists   |                |       |
| Pentazocine   | Ant            | Ag    |
| Nalbuphine  | Ant            | Ag    |
| Butorphanol   | Ant            | Ag    |
| Buprenorphine   | pAg            |       |
| Opioid antagonists  |                |       |
| Naloxone  | Ant            | Ant   |
| Naltrexone  | Ant            | Ant   |

Ag = agonists; Ant = competitive antagonist; pAg = partial agonists.

Modified from Teepie E Jr: Pharmacology and physiology of narcotics. Crit Care Clinics 6:255, 1990.

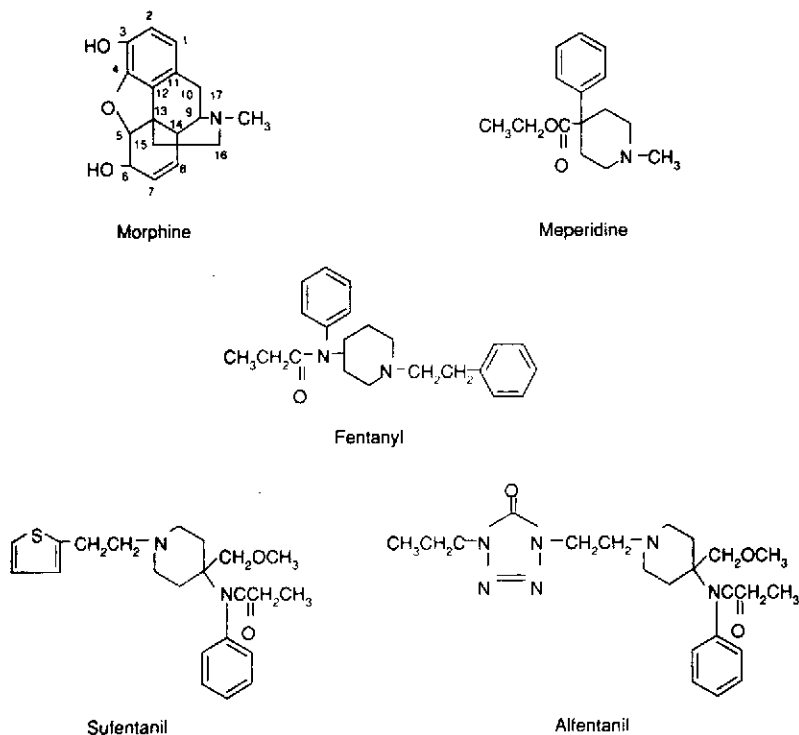
peripheral tissue. In the CNS, they are mainly distributed in the substantia gelatinosa (in the dorsal columns of the spinal cord), limbic system, medial thalamus, and the periaqueductal gray matter.

It is generally agreed that there are three or four classes of opioid receptors with several subclasses. Table 2 lists these receptors and their commonly associated responses evoked by agonists. The mu, kappa, and delta receptors have roles in pain perception. Many no longer consider the sigma receptor to be an opioid receptor<sup>57</sup>; the same is true for a fifth receptor, the epsilon receptor.

The model agonist for the mu receptor is morphine. The clinical effects of stimulating the mu receptor include analgesia and, to a lesser extent, euphoria. These are not necessarily undesirable attributes for acutely ill ICU patients, but there are untoward effects attributable to mu-receptor stimulation. These effects include respiratory depression, depression of gastrointestinal motility, occasionally nausea and emesis, and pruritus. Prolonged use of drugs mediating analgesia via the mu receptor is associated with drug tolerance and dependence that can lead to drug addiction.

Two subtypes of the mu receptor, mu-1 and mu-2, have been identified based on pharmacologic studies. Mu-1 receptors appear to mediate analgesia, whereas activation of mu-2 receptors is associated with respiratory depression, decreased gastrointestinal motility, and so forth. Therefore, the development of a selective mu-1 agonist might have important clinical relevance.

Three subclasses of the kappa receptor have been identified.<sup>57</sup> Kappa-1 receptors mediate analgesia and are localized in the spinal cord. Respiratory depression and other mu-2 receptor attributes are not associated with stimulation of kappa receptors. Furthermore, sedation,



**Figure 1.** Chemical structures of commonly administered opioid agonists. (From Stoelting RK, Miller RD: Basics of Anesthesia, ed 2. New York, Churchill Livingstone, 1989, p 75; with permission.)

**Table 2. OPIOID RECEPTORS AND CLINICAL RESPONSES**

| Receptor | Response                              |
|----------|---------------------------------------|
| Mu       |                                       |
| Mu-1     | Supraspinal analgesia                 |
| Mu-2     | Spinal analgesia                      |
|          | Respiratory depression                |
|          | Inhibition of gastric transit         |
|          | Nausea, vomiting, pruritus            |
|          | Most cardiovascular effects           |
|          | Physical dependence                   |
|          | Euphoria                              |
| Kappa    |                                       |
| Kappa-1  | Spinal analgesia                      |
|          | Diuresis                              |
|          | Sedation                              |
|          | Miosis                                |
|          | Low potential for abuse               |
| Kappa-2  | Pharmacology unknown                  |
| Kappa-3  | Supraspinal analgesia                 |
| Delta    | Modulation of mu-receptor activity    |
|          | Spinal analgesia                      |
| Sigma    | Dysphoria                             |
|          | Hypertonia                            |
|          | No analgesia                          |
|          | Respiratory and vasomotor stimulation |
|          | Mydriasis                             |

Modified from Pasternak GW: Basic pharmacology of opioids. In Bowdle TA (ed): Pharmacologic Basis of Anesthesiology: Basic Science and Practical Applications. New York, Churchill Livingstone, 1994, p 23; and Stoelting RK, Miller RD: Basics of Anesthesia, ed 2. New York, Churchill Livingstone, 1989, p 74; with permission.

not euphoria, is the psychological effect from activating kappa-1 receptors, and there is a reputed lower risk of addiction when this receptor is stimulated repetitively. These desirable attributes might make kappa-agonist drugs ideal for ICU patients, but none have yet been developed for clinical use. The characteristics of kappa-2 receptors have not yet been delineated. Kappa-3 receptors have a high brain density, typically twice that of either mu or delta receptors, thus making kappa receptors the predominate opioid receptor in the brain. Its distribution is similar to that of the mu receptor; there are only some small differences. Kappa-3 analgesia is distinct, localized supraspinally, and is insensitive to the selective mu, delta, and kappa-1 antagonists.

Delta receptors produce analgesia through independent and unique mechanisms. Delta agonists are spinal and supraspinal analgesics. There is evidence for two delta subclasses. The analgesia derived from delta agonists can be reversed by delta antagonists but not by antagonists to mu or kappa-1 receptors.

In summary, analgesia is secondary to activation of a group of receptors by opioids, all of which have a variable affinity for these receptors. The sequelae of receptor activation depends on the opioid used and the specific receptor activated.

## Opioids and Their Routes of Administration

### Drugs

Familiarity with available opioids is essential for comprehensive patient management. Selected drugs and recommended dosages are listed in Table 3. Morphine and meperidine are the most commonly used opioids for pain. Increasingly, fentanyl (50 to 100 times more potent than morphine) is used, especially for epidural administration.

### Patient-Controlled Analgesia (PCA)

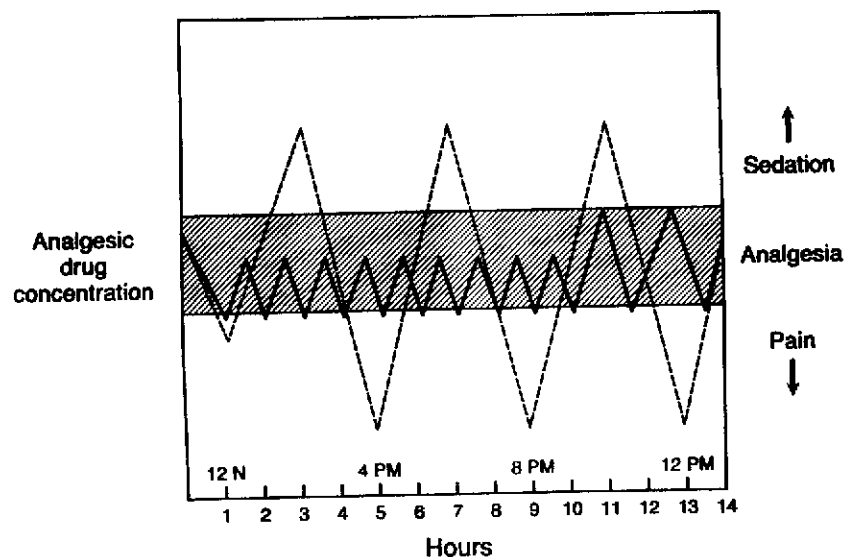
Intravenous and IM routes traditionally have been the mainstays for administering opioids. Patient-controlled analgesia (PCA) with IV opioids is a modification of one of these time-tested techniques. Although first described by Sechzer in 1968,<sup>70</sup> PCA administration of opioid analgesics was under-used until the technology of the delivering devices could be improved. Today, many patients enjoy superior pain control by pushing a button that activates a pump to deliver a preset amount of an opioid. A lockout interval ensures that another dose cannot be delivered unless a prescribed amount of time has elapsed. Additional features include a maximum dose limit in a specific time interval, basal infusion capabilities, and a mechanism to allow priming with a loading bolus of drug. Advantages of PCA include superior pain relief using less medication without an increase in side effects<sup>6</sup>; and the maintenance of drug concentrations that are in an acceptable range (Fig. 2). Less sedation during daytime hours and decreased delay between request for analgesia and relief have been reported, as have improved pulmonary function and fewer pulmonary complications, lower potential for over-

**Table 3. COMMONLY USED OPIOIDS, ROUTES OF ADMINISTRATION, AND DOSING**

| Drug       | Route       | Initial Dose—Bolus (mg) | Dosing Interval | Infusion Rate   | Onset (min) | Duration of Action (h) |
|------------|-------------|-------------------------|-----------------|-----------------|-------------|------------------------|
| Fentanyl   | IV          | 0.05–0.1                | 15–30 min       | 50–100 µg/h     | 1–2         | 0.5–1                  |
|            | Epidural    | 0.08–0.12               |                 | 0.8–1.0 µg/kg/h | 5           | 4–6                    |
| Morphine   | IM          | 2–10                    | 4 h             |                 | 15–30       | 4–5                    |
|            | IV          | 2–10                    | 2–4 h           | 1–4 mg/h        | 2–3         | 4–5                    |
|            | Epidural    | 1–10                    | 8–12 h          | 0.01 µg/kg/h    | 30          | 6–24                   |
| Meperidine | Intrathecal | 0.4–1                   | 12–24 h         | 8 µg/h          | 15–30       | 12–36                  |
|            | IV          | 10–30                   | 2–4 h           | 10–50 mg/h      | 1–2         | 2–4                    |
| Codeine    | IM          | 50–100                  | 4–6 h           |                 | 30–45       | 4–6                    |
|            | PO          | 30–60                   | 4–6 h           |                 | 20–30       | 4–6                    |
|            | IM          | 60                      | 2–3 h           |                 | 15–30       |                        |

IV = intravenously; PO = orally; IM = intramuscularly.

Modified from Compendium of Drug Therapy. Secaucus, NJ, Compendium Publications Group Ltd, 1993, pp 18i and 19iii; and Ziser A, Murray MJ: Postoperative pain. Analgesics make a difference in many ways. Postgrad Med 93(2):179, 1993; with permission.



**Figure 2.** Relationship among dose interval, analgesic drug concentration, and clinical effects in a comparison of patient-controlled analgesia (PCA) system and conventional intramuscular therapy. (From White PF: Use of patient-controlled analgesia for management of acute pain. *JAMA* 259:243-247, Copyright 1988, American Medical Association; with permission.)

dosage when small doses per activation are prescribed, and favorable patient acceptance. A patient must have the strength and comprehension to activate the PCA device, however; these requirements might exclude many ICU patients. Pruritus may be more common with PCA than with IM opioids (but it is significantly less frequent than with epidural or intrathecal administration of an opioid). The costs of PCA are higher than conventional methods because of the special equipment, pharmacy requirements, and training of nursing staff, but these considerations would be the same for other new techniques (e.g., the epidural or intrathecal administration of opioids). Table 4 lists the commonly used drugs for PCAs and their doses.

**Table 4.** PCA OPIOID DOSES

| Drug       | Bolus (mg) (range)    | Lockout (min) (range) | Basal (mg/h) (range) | 4-h Limit (mg) (range) |
|------------|-----------------------|-----------------------|----------------------|------------------------|
| Morphine   | 1-2 (0.4-5.0)         | 6-15 (5-20)           | 0.5 (0.5-2)          | 20 (20-30)             |
| Meperidine | 10-20 (5-30)          | 6-15 (5-20)           | 5 (5-20)             | 100 (80-150)           |
| Fentanyl   | 0.025-0.05 (0.02-0.1) | 6-12 (3-15)           | 0.025-0.05           | 0.3 (0.2-0.4)          |

Modified from DeRuyter M: Patient controlled analgesia. In Faust RJ (ed): *Anesthesiology Review*, ed 2. New York, Churchill Livingstone, 1994, p 298; with permission.

### Epidural/Intrathecal Opioids

Epidural and intrathecal administration of opioids was introduced into clinical practice in 1978 and 1979, respectively.<sup>7, 89</sup> The administration of opioids via epidural and intrathecal routes has become common because these routes provide a safe, effective, and practical approach to providing analgesia.<sup>11</sup> Opioids can be injected through an epidural needle (single injection) or an epidural catheter (bolus or continuous infusion). Meperidine, sufentanil, and alfentanil have been used for epidural analgesia, but these drugs probably offer no advantage over morphine or fentanyl.<sup>27</sup> Compared to patients receiving IM or IV morphine, patients receiving morphine epidurally report superior analgesia, have fewer pulmonary complications, have earlier return of bowel function, and ambulate sooner.<sup>13, 21</sup> Epidural opioids are effective for the pain associated with thoracotomies, intra-abdominal procedures, and genitourinary and lower limb operations. They do not cause sympathetic or motor block or hypotension. Compared to the IV PCA technique, epidural morphine provides more consistent analgesia with a similar incidence of side effects.<sup>34, 65</sup>

The main side effects of epidural narcotics are respiratory depression, pruritus, urinary retention, nausea, and vomiting.<sup>14, 15, 29, 40</sup> Respiratory depression occurs in up to 0.9% of patients and is associated with advanced age, concomitant use of systemic opioids or other CNS depressants, extensive surgery, and higher dosages of opioids.<sup>65</sup> Pruritus can sometimes be relieved by antihistamines or by placing a transdermal scopolamine patch.<sup>42</sup> Urinary retention is more common in males and may require bladder catheterization for relief of symptoms.<sup>15</sup>

Opioids administered intrathecally have essentially the same effects as those administered epidurally. When given intrathecally, the opioid dosage should be decreased appropriately and the dosing interval adjusted accordingly.<sup>54</sup> Long-term infusions of intrathecal opioids are more commonly used for managing patients with cancer pain<sup>75, 88</sup> or in laboring obstetric patients, an unlikely scenario in the ICU. In some countries, bolus dosing of intrathecal opioids is the preferred technique for managing pain in poststernotomy patients.<sup>50</sup> There are disadvantages to either technique. Certainly, the disadvantages associated with an indwelling catheter (i.e., bleeding, infection, paresthesia, tip migration, and so forth) are applicable with either technique. The possibility of a postdural puncture headache is greater with the intrathecal approach, but this may be of less concern in an ICU patient. The most alarming disadvantage of an epidural catheter is the small chance of the catheter tip penetrating the dura and thus delivering a significantly greater amount of agent intrathecally. The advantages of one approach over the other is not clear. With the intrathecal approach, less medication is administered, which may reduce the incidence of side effects. Furthermore, one's confidence in the location of a catheter tip in the intrathecal space is more readily apparent by the presence of cerebrospinal fluid upon aspiration during placement of the catheter, whereas the location

of the catheter tip in the epidural space may be less certain when placing an epidural catheter. Overall, there is not much persuasive evidence to select one technique over the other, but clearly either method of central axis analgesia is favored over other approaches (i.e., IM or IV) for certain patient subgroups (e.g., postthoracotomy patients).

### Pharmacokinetics

An understanding of the pharmacokinetics and the pharmacodynamics of opioids is necessary for an intensivist to use them efficaciously while minimizing their side effects (Table 5).

Morphine is poorly lipid soluble. It is metabolized (primarily by the liver) via conjugation to form water-soluble glucuronides. Two principal metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), are formed. M6G is highly active, approximately four times more potent than morphine, and has a duration of action twice as long.<sup>18</sup> In patients with renal failure, these effects are even greater, as exemplified by reports of altered clearance and plasma concentrations<sup>49</sup> and of prolonged narcosis in such patients.<sup>56</sup> M3G has no analgesic activity and, in fact, may antagonize the analgesic effects of morphine.<sup>79</sup>

Meperidine was the first synthetically derived opioid. It is moderately lipid soluble and is primarily metabolized by the liver to two metabolites. Normeperidine is the predominate and potentially most toxic metabolite. Signs of normeperidine toxicity include CNS excitement, tremor, myoclonus, and grand mal seizures. Normeperidine is generally excreted in the urine; it has an elimination half-life of approximately 15 to 20 hours. Understandably, normeperidine levels accumulate in patients with renal failure because the elimination half-life may be prolonged to longer than 30 to 40 hours.<sup>10</sup> Seizures induced by norme-

peridine do not respond to opioid antagonists (naloxone) and therefore should be treated with anticonvulsants.<sup>17</sup>

Fentanyl, a synthetic opioid, is highly lipid soluble, considerably more potent than morphine, and rapidly and extensively metabolized by the liver to inactive metabolites. It is considered a short-acting opioid. With higher doses or extended administration, its effects are prolonged primarily as a result of a change from a redistribution-limited to a clearance-limited effect.<sup>45</sup>

Opioids are primarily metabolized by the liver and excreted by the kidneys. Disease processes affecting either or both of these systems affect the pharmacokinetics of opioids. Hepatic metabolism can be affected by either reduced blood flow, reduced activity of enzymes, or reduced plasma proteins that affect the bioavailability of these drugs. ICU patients usually have changes in the metabolism of opioids because of altered hepatic function due to sepsis, systemic illness, alcoholic cirrhotic disease, malnutrition, and so forth. Similarly, in patients with renal failure, opioid metabolites often accumulate with associated adverse effects (i.e., prolonged duration of effect).

### Pharmacodynamics

#### Central Nervous System

Analgesia, the primary action of opioids, is a CNS effect, as are many of the adverse sequelae associated with opioids. Sedation, changes in sensorium and temperature regulation, seizures, nausea, and emesis are opioid-mediated CNS effects. These side effects are not specific to opioids, however, and in patients with multiple organ dysfunction syndrome, determining which of these effects are attributable to opioids rather than from other factors may be difficult.

#### Cardiovascular

Overall, heart rate, blood pressure, and systemic vascular resistance remain relatively stable following opioid administration. In fact, a safe, hemodynamic profile is one of the benefits of opioid-mediated analgesia. Opioids such as morphine and meperidine are associated with histamine release, however, which may lead to hypotension. Newer agents, such as fentanyl, do not release histamine and therefore do not have this effect. Peculiar to meperidine is an atropine-like effect that can result in tachycardia. On the opposite side of the spectrum, fentanyl and sufentanil are somewhat "vagotonic" and can result in profound bradycardia, especially when given at higher doses.

#### Respiratory

The primary side effect of opioid administration is respiratory depression. This is a CNS effect and is the result of binding  $\mu$  receptors

Table 5. PHYSIOCHEMICAL AND PHARMACOKINETIC PROPERTIES OF OPIOIDS

|  | Morphine | Meperidine | Fentanyl |
|--|----------|------------|----------|
| Molecular weight                               | 285      | 253        | 336      |
| pKa  | 7.9      | 8.5        | 8.4      |
| % Free base                                    | 23       | 7          | 8.4      |
| % Protein bound                                | 35       | 70         | 84       |
| Lipid solubility                               | Poor     | Moderate   | Highly   |
| Vd <sub>ss</sub> (l/kg)                        | 3.2      | 3.7        | 4.8      |
| Elimination half-life (t <sub>1/2β</sub> ) (h) | 2        | 3-4        | 3.1-3.6  |
| Site of metabolism                             | Liver    | Liver      | Liver    |
| Route of elimination                           | Renal    | Renal      | Renal    |
| Active metabolites                             | Yes      | Yes        | No       |

Modified from Compendium of Drug Therapy. Secaucus, NJ. Compendium Publications Group Ltd, 1993, pp 18i and 19i-ii; and Burns AM, Shelly MP, Park GR: The use of sedative agents in critically ill patients. *Drugs* 43:511, 1992; and Bovill JG: Pharmacokinetics of opioids. In Bowdle TA (ed): *Pharmacologic Basis of Anesthesiology: Basic Science and Practical Applications*. New York, Churchill Livingstone, 1994, p 38; with permission.

in the medullary respiratory center.<sup>17</sup> All opioids clinically used affect respiration to some extent. This effect is due to a blunting of the response to carbon dioxide within the respiratory centers in the brainstem manifested by hypoventilation. Respiratory depression is a concern when using all opioids, especially epidural morphine. Because of morphine's hydrophilicity, it may be more likely to migrate cephalad to the brain stem respiratory centers and induce delayed respiratory depression.<sup>76</sup> This is of special concern in the elderly, who may be more susceptible to this side effect.

### Gastrointestinal

Opioids have direct gastrointestinal effects, including a decreased bowel transit time, which can lead to constipation and ileus. In addition, opioids such as morphine may cause spasm of the sphincter of Oddi and lead to increased pressure within the biliary tract and its sequelae. This may be of particular concern to the patient with pancreatitis, for example. These patients may experience further exacerbation of their pain or worsening or prolonging of their pancreatitis. Morphine's release of histamine is thought to be the initiating factor, thus suggesting that nonhistamine-releasing opioids such as fentanyl may be preferred.<sup>65</sup>

### Clinical Use of Opioids

As suggested earlier, the primary indications and uses for opioids in the ICU setting are for analgesia. It may be more common for an intensivist to use the synergistic effects of both opioids and benzodiazepines (to be discussed), but there are some circumstances that would justify discrete opioid use. Opioids alone may provide sufficient analgesia and sedation for postoperative patients who are admitted to an ICU for a relatively short period (less than 24 hours), primarily for monitoring.

Ideally, patients who had thoracotomies and abdominal procedures benefit from axis administration of opioids, either epidurally or intrathecally, but these modalities are not always available. Another option is the administration of opioids via a PCA device. Dosages and dosing schedules have been presented in Tables 3 and 4. Because of associated discomfort, most critically ill patients, those with sepsis, acute respiratory distress syndrome, or multiple organ dysfunction syndrome, should have either morphine (1-2 mg/hr) or fentanyl (50-100 µg/hr) infused continuously with the dose adjusted to effect.

Another indication for opioids in the ICU setting is to provide analgesia for minor procedures such as central-line placement. Again, morphine or fentanyl titrated by bolus administration to effect is recommended (Table 3). Dosages vary depending on the clinical scenario (i.e., is the patient hemodynamically stable, intubated, etc; has the patient been on other opioids and become somewhat tolerant; or are there

some contraindications or potential drug interactions to note?). All these factors play a role, stressing the need for the physician to have sufficient familiarity with opioids to be able to select and titrate these potent agents to a desired effect.

### Opioid Antagonists

There are multiple opioid antagonists, but only two are clinically useful: naloxone and naltrexone. Naloxone is available for parenteral use, has a short duration of effect, and is active against all available mu-receptor agents. For the patient with suspected drug overdose, it can be given as a 0.4 mg IV bolus, or it can be given IM at the same dosage to the postoperative patient with carbon dioxide retention who may have a relative overdose of an opioid. Often, however, such patients are given IV naloxone, usually 40 µg every 5 minutes to effect. The disadvantage of bolus administration of naloxone is the potential to completely reverse analgesia, resulting in an awake, agitated, tachycardic patient in pain. Rawal et al observed that it was possible to administer naloxone (5 µg/hr) to patients with epidural opioid-induced respiratory depression, with maintenance of analgesia and reversal of carbon dioxide retention.<sup>66</sup>

Animal studies demonstrated that naloxone reverses the sequelae of septic shock,<sup>37, 51</sup> but clinical studies have failed to demonstrate such a benefit.

Naltrexone is an oral opioid antagonist used in drug treatment programs. It probably does not have a unique role in managing patients in an ICU environment.

### BENZODIAZEPINES

Opioids have been known for centuries; on the other hand, chlordi-azepoxide (the first benzodiazepine) was synthesized relatively recently, in 1955. Initially considered inert, it was only during screening compounds for orally active muscle relaxants in 1957 that its hypnotic, sedative, and antistrychnine effects were discovered.<sup>64</sup> By 1960, the Food and Drug Administration (FDA) approved chlordi-azepoxide for use as an oral anxiolytic agent. Diazepam was synthesized in 1959 and approved for use in 1961. Lorazepam was synthesized in 1971; midazolam was synthesized in 1976.

By the early 1960s, the parenteral benzodiazepines were being used in the operating room as induction agents<sup>32</sup> and also for their sedative effects. It is difficult to pinpoint when parenteral benzodiazepines were first used in the ICU. We suspect that the first ICU uses of parenteral benzodiazepines were for procedures such as cardioversion,<sup>55</sup> as an anticonvulsant in status epilepticus,<sup>52</sup> and as a muscle relaxant in tetanus.<sup>21</sup>

One of the earliest reports of the use of an IV benzodiazepine as an anxiolytic in the ICU was by McClish et al in 1968.<sup>46</sup> They administered 2.5 to 5.0 mg of diazepam six times a day, in addition to the usual postoperative analgesia, to a group of mechanically ventilated cardiac surgical patients. Psychiatric complications were decreased from about 33% in the control to under 5% in the benzodiazepine group.

In the general population, benzodiazepines are so widely used because of their anxiolytic and hypnotic properties that they are known as "the opium of the masses."<sup>41</sup> Reflecting the trend, benzodiazepines are now the most commonly used sedative medications in the ICU.<sup>22, 62</sup>

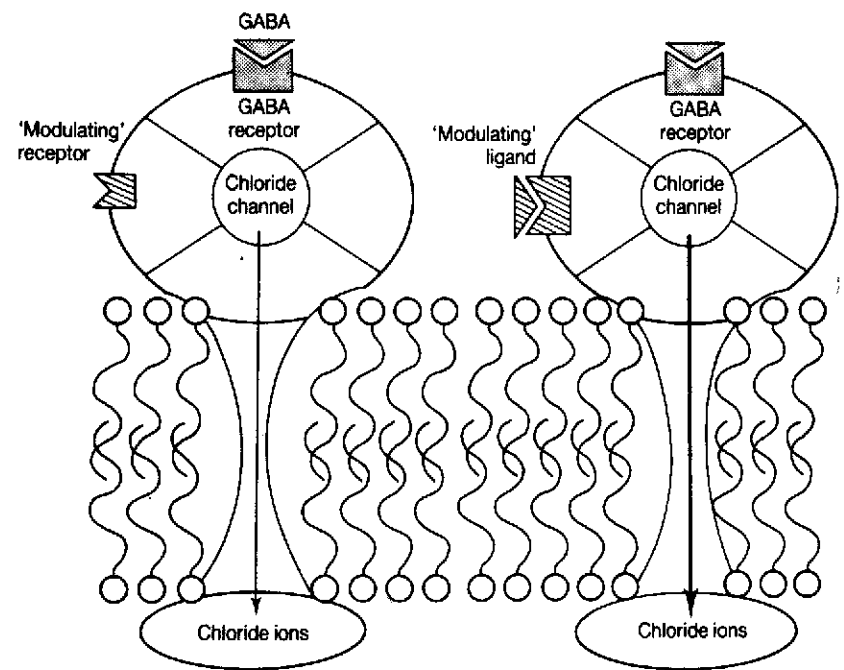
### Benzodiazepine Receptors

Benzodiazepines achieve their effects via binding to and activation of a specific receptor in the CNS within the gamma-aminobutyric acid (GABA) receptor complex. This is a macromolecular complex that includes a high-affinity benzodiazepine receptor, GABA<sub>A</sub> receptor, and chloride channels. Allosteric interaction of central benzodiazepine receptors with GABA<sub>A</sub> receptors and subsequent opening of chloride channels elicit the CNS effects of benzodiazepines (Fig. 3). The GABA receptor complex has other binding sites, permitting the potentiation between benzodiazepines and other agents. No endogenous benzodiazepine ligand has yet been convincingly demonstrated.

### Agonists and Antagonists

Benzodiazepine agonists derived from chlordiazepoxide consist of one 6-membered benzene ring (ring A) fused to a seven-membered 1, 4 diazepine ring (ring B), given the name 1, 4-benzodiazepine. Another six-membered ring (ring C) is attached to the diazepine ring. Position 7 on ring A has the most influence on the structure-activity relationship of the compound. At this site, the presence of heavier halogens and nitro groups increase potency (Fig. 4).

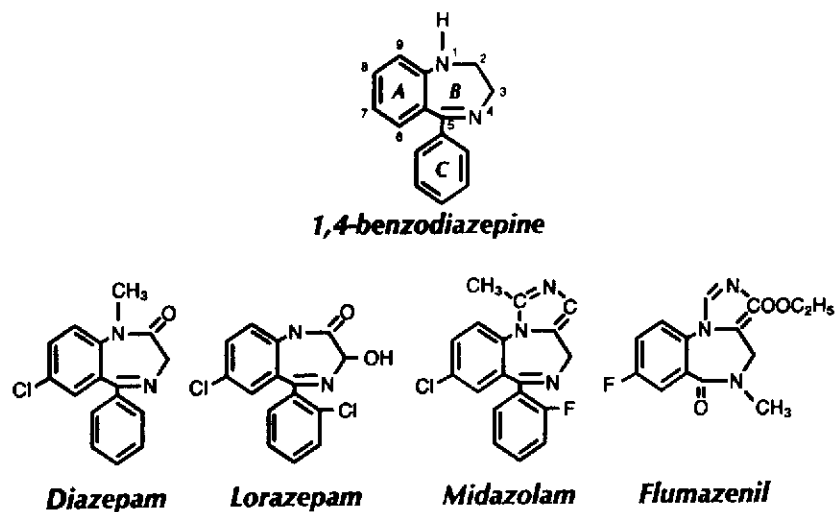
Chlordiazepoxide, diazepam, lorazepam, and midazolam are full benzodiazepine agonists, producing a leftward shift of the GABA dose-response curve in a concentration-dependent manner as a result of the increasing affinity of GABA for its receptor in the presence of increasing concentrations of benzodiazepines. A partial agonist, clonazepam, does not produce a maximal effect on the benzodiazepine receptor even when all receptors are occupied; in addition, it antagonizes the full agonists. Flumazenil retains affinity for the benzodiazepine receptor but has no inherent activity and is therefore a benzodiazepine antagonist.



**Figure 3.** Proposed molecular mechanism for hypnotic action of drugs acting at the GABA<sub>A</sub>-receptor chloride ionophore. After GABA, the inhibitory neurotransmitter binds to its receptor on the GABA<sub>A</sub>-receptor chloride ionophore heteropentamer, and chloride ions flow along the concentration gradient into the cell. The net result of this ionic conductance is to hyperpolarize the neuronal membrane and to make the cell less "excitable." Modulating ligands, such as benzodiazepines, barbiturates, steroid anesthetics, propofol, and etomidate, bind to a separate receptor ("modulating" receptor) on the complex and enhance the GABA-mediated chloride conductance through the membrane (right side). (From Salonen MA, Maze M: Molecular mechanism of action for hypnotic and sedative agents. In Feldman SA, Paton W, Scurr C (eds): *Mechanisms of Drugs in Anaesthesia*, ed 2. London, Hodder & Stoughton Ltd, © 1993, p 205; reproduced by permission of Hodder & Stoughton Ltd.)

### Physicochemical Properties

Whereas the opioids have a range of lipophilicity, the benzodiazepines are small, very lipophilic molecules at physiologic pH. Although chlordiazepoxide is water soluble, it is unstable in water. The suspension of the other benzodiazepines in aqueous solutions is difficult, requiring combinations of organic solvents (glycols, alcohols, benzoates), saline, and water. Midazolam's structure has an imidazole ring that is open at an acidic pH of 3.5, conferring water solubility; at a physiologic pH of 7.4, the ring closes and the molecule becomes more lipophilic.



**Figure 4.** The classic 1,4-benzodiazepine structure as well as the structures of four benzodiazepines used in clinical anesthesia practice. (From McCauley LD, Gee KW, Yamamura HI: Basic pharmacology of benzodiazepines. In Bowdle TA (ed): *Pharmacologic Basis of Anesthesiology: Basic Science and Practical Applications*. New York, Churchill Livingstone, 1994, p 244; and Reves JG, Glass PSA, Lubarsky DA: Nonbarbiturates intravenous anesthetics. In Miller RD (ed): *Anesthesia*, ed 4. New York, Churchill Livingstone, 1994, p 248; with permission.)

## Pharmacokinetics

### Absorption, Onset, and Duration

Following IM administration of lorazepam and midazolam, absorption is rapid and complete. The onset of action for IM lorazepam can take as long as 40 minutes; the duration of action is 12 to 24 hours. IM midazolam's onset is in 5 to 15 minutes; its duration is usually 2 hours (range 1 to 6 hours). The uptake of IM chlordiazepoxide and diazepam is slow and erratic; therefore, they are not recommended for IM use.

The onset of IV midazolam is fast, with a duration of action of approximately 1 to 2 hours. IV lorazepam has a relatively slow onset of action; the time to maximum effect takes approximately 40 minutes, with a longer duration of action.<sup>25</sup>

Table 6 illustrates the IV onset and duration of action data for the parenteral benzodiazepines.

### Distribution

Because of their high lipophilicity, benzodiazepines are widely distributed throughout body tissues and cross the blood-brain barrier and the placenta. Lorazepam is less lipid soluble [octanol:buffer partition

coefficient = 240] than midazolam [475] or diazepam [820] and therefore is less widely distributed.

Compared to midazolam and lorazepam, diazepam, which is 98% protein-bound, displays the highest protein binding, but all benzodiazepines are highly protein bound. Alterations in serum albumin therefore affect free drug concentration and clinical activity. By decreasing serum albumin, malnutrition and liver and renal disease may enhance the effects of benzodiazepines.<sup>87</sup>

Termination of diazepam and midazolam following an IV bolus is primarily as a result of redistribution of the drug from central to peripheral compartments. Lorazepam is less lipophilic and thus has a smaller volume of distribution; therefore, it has a longer duration of action.<sup>3</sup>

### Elimination

The benzodiazepines are similar to the opioids in that they also undergo hepatic metabolism with renal excretion of the metabolites. Diazepam and midazolam undergo hepatic microsomal oxidation, which is influenced by age and the presence of disease and of other drugs. Drugs such as cimetidine, isoniazid, and certain estrogen-containing oral contraceptives inhibit the activity of microsomal enzymes. This in turn inhibits the metabolism of the benzodiazepines. Advanced age and liver disease are known to impair microsomal oxidation of diazepam and midazolam. Because lorazepam undergoes glucuronide conjugation, it is less influenced by these factors.

Elimination half-lives for the parenteral benzodiazepines and their active metabolites are listed in Table 6, but there is a wide range of elimination half-lives reported in the literature. The elimination half-life of midazolam is approximately 2.5 hours following minor surgery, but increases to 5 to 6 hours following major surgery.<sup>35</sup> Even in volunteers or "healthy" patients, prolonged elimination half-lives have been reported.<sup>23</sup>

## Pharmacodynamics

### Central Nervous System

Parenteral benzodiazepines cause a dose-related depression of the CNS. As the dose is increased, individuals experience anxiolysis, conscious sedation, deep sedation, and finally anesthesia.

**Anxiolysis.** All benzodiazepines induce anxiolysis at mildly sedative doses, less than the dose required to produce anterograde amnesia, suggesting that anxiolysis is mediated at lower levels of receptor occupancy.<sup>81</sup>

**Amnesia.** Subhypnotic doses of IV benzodiazepines reliably produce anterograde amnesia.<sup>26, 32</sup> Lorazepam produces longer duration of amnesia than diazepam and midazolam.<sup>47</sup>



Table 6. CURRENTLY AVAILABLE BENZODIAZEPINES, THEIR METABOLITES, AND THEIR DOSAGES

| Drug<br>(Classification)           | Half-Life<br>(hrs) | Major Active Metabolites<br>(t <sub>1/2</sub> -hrs)  | Sedative Doses   |   |                | Duration<br>(hrs) |
|------------------------------------|--------------------|--|--|---|----------------|-------------------|
|                                    |                    |  | Intermittent Bolus<br>Titrated to Effect                       | Continuous Infusion<br>Titrated to Effect | Onset<br>(min) |                   |
| Chlordiazepoxide<br>(Long-acting)  | 5-30               | Demoxepam (14-95)<br>Desmethyldiazepam (18)<br>Desmethyldiazepam (30-200)<br>Oxazepam (3-21) | IV 25-50 mg (70-kg male<br>patient)                            | —   | 1-5            | 0.25-1.0          |
| Diazepam<br>(Long-acting)          | 20-50              | Desmethyldiazepam (30-200)<br>3-Hydroxydiazepam (5-20)<br>Oxazepam (3-21)                    | IV 1-2 mg increments (max<br>0.1-0.2 mg/kg)                    | —   | 1-5            | 0.25-1.0          |
| Lorazepam<br>(Intermediate-acting) | 10-20              | None   | IM 0.05 mg/kg (max 4.0<br>mg)<br>IV 0.05 mg/kg (max 2.0<br>mg) | Up to 0.06 mg/kg/hr                       | 40             | 12-24             |
| Midazolam<br>(Short-acting)        | 1.0-12.3           | 1-Hydroxymethylmidazolam<br>(1.0-1.3)  | IM 0.07 mg/kg<br>IV 0.5-2.0 mg increments<br>(max 0.1 mg/kg)   | Up to 0.25 mg/kg/hr                       | 1-5            | 2*                |

\*See text.

IM = intramuscular; IV = intravenous.

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**Sedation.** IV benzodiazepines produce sedation in a dose-dependent fashion. Increasing age correlates inversely with time to induce unconsciousness.<sup>24</sup> With IV benzodiazepine sedation, there is a disappearance of alpha rhythm and shift to widespread beta activity on the electroencephalogram (EEG).<sup>16, 28</sup> Sufficient quantities of IV midazolam rapidly produce unconsciousness.

**Anticonvulsant.** IV benzodiazepines provide effective therapy for status epilepticus in approximately 80% of patients.<sup>26</sup> As all IV benzodiazepines are efficacious, the choice of an IV benzodiazepine for its anticonvulsive effect is based on pharmacokinetic considerations.

#### Skeletal Muscle Relaxant

Benzodiazepines produce their skeletal-muscle relaxant effect by acting on glycine receptors. The site of action is either in the spinal cord or in supraspinal areas of the CNS.<sup>53, 80</sup>

#### Analgesia

Benzodiazepines do not have an antianalgesic action. If they possess analgesic effects, they are not clinically significant.<sup>78</sup>

#### Cardiovascular

In sedative doses, IV benzodiazepines have proven to be relatively hemodynamically stable. Induction doses of diazepam (0.5 mg/kg) in patients with known coronary artery disease produce no change in heart rate, a mild decrease in blood pressure, a decrease in systemic vascular resistance, and a mild decrease in stroke volume.<sup>68, 69</sup> Similarly, midazolam (0.2 mg/kg) produces a 10% increase in heart rate, a 15% to 25% decrease in blood pressure, no significant change in systemic vascular resistance, and a decrease in stroke work volume.<sup>44, 69</sup>

#### Respiratory

In general, similar to the opioids, IV benzodiazepines depress central respiratory drive. IV benzodiazepines shift the CO<sub>2</sub> response curve to the right<sup>30</sup> and flatten the CO<sub>2</sub> response curve, suggesting a less profound effect on central respiratory drive than the opioids.<sup>91</sup> Sedative doses of IV benzodiazepines can block the ventilatory response to hypoxia.<sup>1</sup>

The effect of benzodiazepines on central respiratory drive depends on the specific benzodiazepine, the dose and route of administration, patient factors, and the presence of other centrally active drugs. The manner in which the central respiratory drive is measured may influence the results. At sedative doses (< 0.1 mg/kg), midazolam decreases tidal volume by approximately 40% with a compensatory increased respiratory rate, usually resulting in no change in the resting minute

ventilation.<sup>31</sup> Smaller doses of midazolam (0.075 mg/kg) do not significantly change the CO<sub>2</sub> response curve in healthy young volunteers.<sup>63</sup> Lorazepam in selective doses of 0.05 mg/kg increases the slope of the CO<sub>2</sub> response curve and shifts it to the left, consistent with an increase in respiratory drive.<sup>58</sup> Initially, there is no change in end-tidal CO<sub>2</sub>; however, 30 minutes after IV lorazepam, the end-tidal CO<sub>2</sub> does increase, probably due to somnolence with a decrease in minute ventilation.

### Clinical Use of Benzodiazepines

Anxiety in the critically ill patient in the ICU ranges from an appropriate behavioral reaction, to an illness, to a pathologic entity manifested by marked agitation. A telephone survey 2 months after ICU discharge of intubated and ventilated patients revealed that 47% of the patients who could remember the experience reported feelings of anxiety or fear during their ICU stay.<sup>8</sup> The true incidence and effect of anxiety and awareness in ICU patients are unknown.

Indeed, we, as intensivists, acknowledge and legitimize anxiety in the ICU only when one of our own has suffered. This is reflected in a recent review of a pediatric intensivist's experience as a critically ill patient in an ICU.<sup>36</sup> Extrapolating from anesthesia, in which intraoperative awareness, although uncommon, can be emotionally devastating, awareness in the ICU and its effects are probably underappreciated. It is our ICU practice to review our long-stay ICU survivors and to evaluate their experience and memory of their ICU stay. Using open-ended questions such as "are you experiencing any dreams," many of the responses have been negative. Responses of note came from a patient feeling that somebody was standing over the right side of her neck and stabbing her with a knife, and from a patient who felt that she had been raped. The first patient had had multiple internal jugular catheter placements; the latter patient had had vaginal bleeding requiring a vaginal examination. Based on these anecdotes and others, we find it surprising that the effects of sedation and of IV benzodiazepines have not been more formally studied in patients in the ICU.

### Sedation

#### Short-Term Sedation

For patients requiring sedation, if there are no contraindications to IM injections, intermittent bolus administration of IM midazolam or lorazepam can be used. Titrating the dose to achieve the desired clinical effect can be difficult with bolus IM injections.

More predictable effects can be achieved with intermittent IV bolus administration of benzodiazepines. Midazolam, with its lack of venous irritability and short half-life, has been thought to be superior to diaze-

pam because of the latter's risk of venous thrombophlebitis and longer elimination half-life. A recent article reviewed 28 trials comparing the recovery from diazepam and midazolam given for sedation in an ICU. No difference was reported in 19 trials, eight reported faster recovery times with diazepam, and only one trial reported a faster recovery time with midazolam.<sup>4</sup> The authors concluded that the elimination half-lives of benzodiazepines do not necessarily correspond with their sedative pharmacodynamic effects, which perhaps correlate better with the drugs' lipophilicity.<sup>33</sup> The concern over venous thrombosis and pain on injection associated with diazepam should be eliminated with the expected release in the United States during 1995 of diazepam formulated in a lipid emulsion.

For short-term sedation, there are no clinically proven pharmacokinetic or pharmacodynamic benefits of one IV benzodiazepine over another. Therefore, the choice of agent relates to familiarity and cost.

#### Long-Term Sedation

Intermittent IV administration of benzodiazepines has frequently been used for long-term sedation (i.e., greater than 24 hours). Theory favors an agent with a long duration of action that does not accumulate.

Although intermittent IV benzodiazepine administration provides adequate long-term sedation, this approach is problematic. With intermittent bolusing, there are peaks and valleys in drug concentration and effect, and the technique is time- and labor-intensive. Accurate and reliable infusion pumps together with IV benzodiazepines having appropriate pharmacokinetic properties allow for safe, continuous, intravenous infusion.

Midazolam's IV pharmacokinetic profile makes it attractive for use as a continuous IV infusion.<sup>2</sup> One study of continuous IV midazolam infusions, however, demonstrated tachyphylaxis and prolonged duration of effect, especially in patients with renal or hepatic failure.<sup>74</sup> One report also demonstrated prolonged sedation after midazolam, which may have been due to impaired hepatic blood flow.<sup>19</sup> A pharmacokinetic study of continuous IV midazolam infusions in critically ill patients found that the volume of distribution was increased causing a prolonged elimination half-life, although the clearance did not change.<sup>43</sup> Another study found a similar prolongation of effect in four out of six critically ill patients as a result of their inability to form the 1-OH metabolite from midazolam.<sup>73</sup>

The problems with continuous IV midazolam infusions have led to a re-evaluation of the use of this drug in the ICU environment. A recent editorial bemoaned the "polypharmacy spiral" and encouraged "back to basics please" regarding sedation for mechanically ventilated patients.<sup>72</sup> Pohlman et al prospectively compared midazolam to lorazepam for continuous IV sedation and found no statistical differences in the time for return to baseline in mental status once the drugs were discontinued.<sup>61</sup>

In summary, although midazolam is the most commonly used benzodiazepine for continuous IV sedation in the ICU, lorazepam is increasingly being used in a similar fashion for the reasons mentioned.

### Treatment of Alcohol Withdrawal

Benzodiazepines are indicated for all phases of alcohol withdrawal. Investigators have shown that symptom-triggered therapy (with chlordi-azepoxide) decreased the duration of treatment and the amount of benzodiazepine administered compared with the traditional fixed schedule therapy.<sup>67</sup> Lorazepam may have certain advantages in alcohol withdrawal because it undergoes glucuronization, which may be of benefit in the elderly and in patients with liver disease. There is no study, however, demonstrating an advantage of one benzodiazepine over another for the treatment of alcohol withdrawal or delirium tremors.<sup>9</sup>

### Drug Interactions

Opioids and benzodiazepines are synergistic, allowing lower doses of both to be given to a patient, maintaining the desired goals while minimizing side effects. The combination of an opioid and a benzodiazepine should be used with caution, however. The addition of IV fentanyl (2 µg/kg) to IV midazolam (0.05 mg/kg) can increase the incidence of hypoxia from 50% to 90% and increase the incidence of apnea from 0% to 50% compared to the fentanyl or midazolam alone.<sup>5</sup> IV diazepam administered immediately prior to high-dose fentanyl for induction of anesthesia causes a significant decrease in mean arterial blood pressure and systemic vascular resistance compared to either agent used alone.<sup>85</sup>

### Other Concerns

Tolerance and dependence are recognized during the use of continuous IV benzodiazepines. Thus, withdrawal reactions can occur following benzodiazepine discontinuation. The time of onset of the withdrawal reaction is related to the elimination half-life of the benzodiazepine. In general, withdrawal is more likely to occur with short-acting than with long-acting benzodiazepines. Because of the potential problem of withdrawal, some advocate a gradual decrease in dose when discontinuing a benzodiazepine.

Because there is potential for abuse with the benzodiazepines, appropriate precautions need to be observed when storing and using them in the ICU.

### Benzodiazepine Antagonist

Flumazenil is the only FDA-approved benzodiazepine antagonist. It is a receptor ligand with high affinity, great specificity, and minimal intrinsic effect. Flumazenil's structure is similar to midazolam except for the substitution of a carbonyl group for a phenyl group. It is water-soluble, allowing its preparation in an aqueous solution.<sup>86</sup>

Intravenous flumazenil's onset is fast. It has a short plasma half-life of about 1 hour. Compared to other benzodiazepines, it has only moderate lipid solubility, and its protein binding is low: 54% to 64%.<sup>39</sup> It undergoes hepatic metabolism and has three metabolites; their significance is still undergoing evaluation. Flumazenil has the highest clearance of all benzodiazepines.

In the absence of an agonist, flumazenil has minimal or no physiologic effect.<sup>12, 90</sup> In the presence of an agonist, flumazenil reverses the activity of benzodiazepine agonists. Low-dose flumazenil reverses the anesthetic, hypnotic, and sedative effects of high-dose benzodiazepine agonists. High-dose flumazenil antagonizes the low-dose effects of benzodiazepines (e.g., anxiolysis, amnesia, and anticonvulsant).

Flumazenil's ability to reverse benzodiazepine-induced respiratory depression is controversial. A recent review of this topic concluded that flumazenil's ability to reverse benzodiazepine-induced respiratory depression is variable and, when present, short lived.<sup>71</sup> Flumazenil has been evaluated for the reversal of short-term sedation and has been found to be effective and safe.<sup>48</sup> Flumazenil was evaluated in a double-blind study of the reversal of midazolam-induced sedation in the ICU.<sup>59</sup> Thirty patients who required mechanical ventilation, sedation, and analgesia with continuous infusions of midazolam and morphine were studied. After 12 to 24 hours, the infusions were stopped and flumazenil or placebo administered. The flumazenil group was less sedated, able to obey commands, weaned from ventilation, and extubated significantly earlier than those receiving placebo. The dose of flumazenil suggested for the reversal of a benzodiazepine effect is an increment of 0.2 mg, repeated every 2 minutes until the desired level of reversal is achieved, to a maximum of 1.0 mg. Owing to its high clearance rate and short half-life, an infusion of 0.5 to 1.0 µg/kg/min of flumazenil has been suggested when a benzodiazepine antagonist is required.

### CONCLUSION

In summary, opioids have been found to be effective agents for analgesia and sedation in the ICU for patients suffering from myriad illnesses. There are a number of drugs and routes of administration that allow one to titrate the drugs to effect while minimizing their side effects. Many patients with pure anxiety or agitation will benefit the most from the administration of a benzodiazepine. These drugs have a

very low risk:benefit ratio and warrant consideration for any critically ill patient in an ICU for whom anxiolysis is a desired goal.

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