# neurocritical care pharmacotherapy

## A CLINICIAN'S MANUAL

*Eelco F.M. Wijdicks*
*Sarah L. Clark*

OXFORD

# Neurocritical Care Pharmacotherapy

# Neurocritical Care Pharmacotherapy

## A Clinician's Manual

**Eelco F. M. Wijdicks, MD, PHD, FACP, FNCS, FANA**

Professor of Neurology, College of Medicine
Chair, Division of Critical Care Neurology
Consultant, Neurosciences Intensive Care Unit
Saint Marys Hospital
Mayo Clinic, Rochester, Minnesota

**Sarah L. Clark, PHARMD, RPH, BCPS**

Assistant Professor of Pharmacy, College of Medicine
Neurosciences Clinical Pharmacist
Senior Manager of Pharmacy, Clinical Practice
Saint Marys Hospital
Mayo Clinic, Rochester, Minnesota

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Oxford University Press is a department of the University of Oxford. It furthers the University's objective of excellence in research, scholarship, and education by publishing worldwide. Oxford is a registered trade mark of Oxford University Press in the UK and certain other countries.

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America.



CIP data is on file at the Library of Congress
ISBN 978–0–19–068474–7



9 8 7 6 5 4 3 2 1
Printed by WebCom, Inc., Canada

To Barbara, Coen and Kathryn, Marilou and Rob (EFMW)

To Byron, Noah, Audrey, and Austin (SLC)

# Contents

# Preface

More than anything else, knowing how to prescribe neurotherapeutics appropriately and effectively is a core requirement for clinicians treating patients with an acute neurologic illness. Once acutely ill neurologic patients are admitted, the number of drugs on their pharmacy profile quickly increases. Most disorders need specific neurotherapeutics, but there are also less neurospecific medications used to treat or prevent complications associated with mechanical ventilation and immobilization. The treatment of the critically ill neurologic patient is unique and involves drugs infrequently used in other intensive care units (ICUs), such as antiepileptic drugs, antifibrinolytics, thrombolytics, osmotic agents, neurostimulants, or acute immunotherapy agents such as intravenous immunoglobulin and plasma exchange. Interactions with drugs are thus also different. Many other drugs used in medical and surgical ICUs are administered, so clinicians must recognize the changes in vital signs and organ function in the acutely ill neurologic patient in order to optimize medication delivery.



Rounds in the neuroscience ICU always involve a spate of questions and queries to pharmacists. Neurointensivists closely consult with critical care–trained pharmacists who, in major medical institutions, are important members of the multidisciplinary neurosciences ICU and emergency department healthcare team. They are available to answer medication-related questions and to provide important clinical drug monitoring for patients.

Electronic monitoring tools have changed the landscape, and today virtually every drug side effect is at the physician's fingertips. Thus, this book must be different; it cannot just provide an endless list of potential complications of drug administration. Here we list the side effects that are clinically relevant——those that would lead a physician to consult the pharmacist. It is far more important when using these drugs to have a practical understanding of their indications, monitoring, and immediate and lingering effects, and most importantly to have a good understanding of the most commonly prescribed drugs. It is better to know a lot about a few drugs.

The book opens by setting the stage: How do these drugs work and what does the body do with the drug in the acutely ill neurologic patient? How are these drugs best used, administered, and monitored in practice? How do we most effectively practice medication reconciliation? Each of the commonly used neurotherapeutics is discussed in great detail to allow for its efficient use and to allow clinicians to recognize drug-related problems. This book provides not only the tools needed to order and monitor the most commonly prescribed neurocritical care drugs, but also vital information about how they are prepared and how this may delay administration and thus affect drug choice. Fluid administration is needed not only for systemic resuscitation but also for "brain resuscitation" and thus is also included.

This book is deliberately constructed differently. A clinician's manual should be eminently readable and should quickly inform the reader. The amount of information in a small book is inherently curtailed but should be presented logically. Thus we decided to use bullet points and quick-glance boxes and graphs rather than more time-consuming narrative text. Each statement was carefully vetted and rewritten multiple times. Pharmacy books are often awash in acronyms; we tried to avoid them. Ultimately, what we want to know is what drug to use and at what dose, what to expect, what complications could occur, and what we should do if it does not work. Yet, this manual cannot provide all the answers on how to move from one drug to the next ("if this drug does not work, try that one") and often the best sequence is unknown.

These simple principles have guided us in writing this manual, and we hope we have found a good number of knowledge nuggets that will inform physicians and pharmacists. We wanted to write something the reader has not read before, and we wanted to avoid presenting facts that are much less relevant to clinicians.

We created graphs of the most commonly used drugs and included four essential pieces of information: order to the patient (how long does it take to get the drug into the patient); starting dose (how much is needed initially); half-life (how long does it work); and clearance (which organ predominantly clears the drug). All drugs with a graph are listed at the end of the book with abbreviations explained.



This book is the product of a fine joint effort. Writing the book together created an unprecedented opportunity to critically look at each other's specialty (including misconceived orthodoxy) and to come up with a body of work we both agree on. It became quickly clear that small books need much more work than large books. We are grateful to our spouses (and children) who unflinchingly supported us while we were going through yet another round of writing and editing. Some credit should go to the loyal dogs at our feet that provided a necessary state of serenity.

We have many others to thank. First and foremost, Lea Dacy edited this unusual book with great care and suggested changes along the way. We are grateful to several of our experienced hospital pharmacists who provided heavy scrutiny and valuable input. (Jan Anderson, Jeffrey Armon Erin Barreto, Caitlin Brown, Gabriel Golfus, Megan Leloux, Scott Nei, Whitney Bergquist, Andrea Nei, Erin Nystrom, Narith Ou, Christina Rivera.) Jim Rownd masterfully created the illustration on the cover. We thank Craig Panner, associate editorial director with Oxford University Press for US Medicine books Neurology and Clinical Neuroscience for suggesting this work and the staff at Newgen KnowledgeWorks Pvt Ltd (Devasena Vedamurthi) for providing all that was needed to smoothly see it through production.

We compiled this small but chock-full manual to serve the needs of any healthcare provider managing patients with acute neurologic disease and to offer the necessary assistance. We hope this book works for you.

EFMW
SLC

# Chapter 1

# Drug Delivery, Monitoring, and Interactions

It is not a question but a certainty—drugs can be used to treat, salvage, and protect the brain; and there is a growing pharmacopeia. In the neurosciences intensive care unit (NICU), the medication profiles of patients can rapidly expand even during a short stay. Orders include daily prescribed medications and as circumstances arise (*pro re nata*).

Generally, once a drug is infused or absorbed and becomes active, major physiologic changes occur. This is conceptualized as pharmacokinetics and pharmacodynamics. *Pharmacokinetics* is the study of the way drugs move through the body; in other words, the absorption, distribution, metabolism, and elimination of drugs. This is often thought of as "what the body does to the drug." *Pharmacodynamics* is the study of the effects of drugs on the body—"what the drug does to the body" (1).



The nature of critical illness is a major factor. The more pertinent issues in neurologic critical care patients are difficulties with routes of administration (e.g., patients with dysphagia), absorption impairment (e.g., ileus caused by barbiturate use), and drug interactions (e.g., complex interactions with new antiepileptic medications). Furthermore, acute brain injury may change the body's response to medications. These changes may be neurology-specific (e.g., disruption to the blood–brain barrier or exaggerated response to drugs in dysautonomia), or more general such as the acute stress-induced sympathetic response affecting the absorption of the drug (e.g., gastric atony).

## Bioavailability of a Drug

Practicing physicians may appreciate some understanding of the typical pathway of an administered drug and the factors that influence it. The main components that determine pharmacokinetics and pharmacodynamics are shown in Box 1.1. These parameters are mostly of interest to pharmacists but have clinical relevance if a drug–drug interaction or unexpected abnormal metabolism requires further explanation.

An orally administered drug is absorbed, distributed, metabolized, and eliminated, and several factors may change it (Fig. 1.1). When drugs are administered intravenously, bioavailability reaches 100%. One can assume that at five times the half-life, the mean plasma concentration of the drug is constant and at a plateau for drugs with zero-order kinetics (i.e., the rate of drug elimination is constant over time). Assuming there is no organ system

**Box 1.1 Pharmacokinetic Parameters**

- **Area under the curve:** plasma drug concentration related to time; the body's exposure to a drug after administration
- **Bioavailability:** portion of the drug reaching the systemic circulation
- **Clearance:** rate at which a drug is removed from the body
- **First-pass effect:** drug concentration that is removed prior to reaching the systemic circulation; refers to the intestinal and hepatic metabolism of drugs
- **Elimination Half-life:** amount of time required for the drug concentration to decrease by 50%
- **Steady state:** time when the drug has reached full therapeutic effect and elimination and intake are at the same rate; typically achieved after four to five half-lives
- **Therapeutic window:** range between effective dosing and the presence of adverse effects

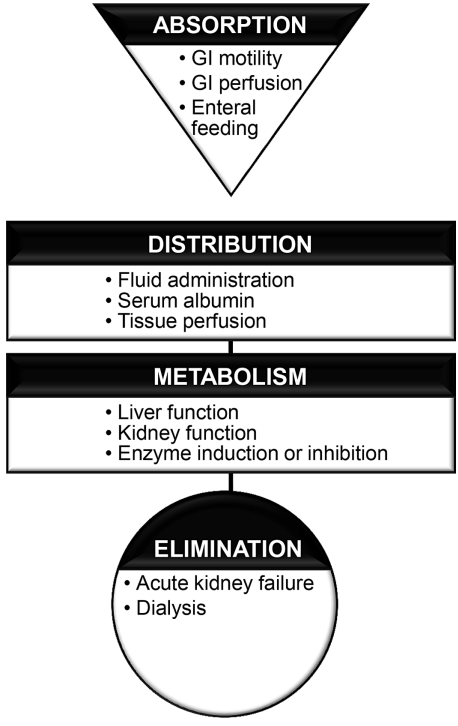



**Figure 1.1** Pathway of a drug and factors that matter (GI = gastrointestinal)

dysfunction, the reverse occurs, with the plasma concentration decreasing to zero in five half-lives. Metabolism in patients with hypothyroidism and hypothermia is reduced, including other factors that can be less precisely assessed are advanced age, morbid obesity, and chronic liver disease. Renal replacement therapy changes the clearance of many antibiotics and also the clearance of certain antiepileptic drugs (Chapter 6) and cardiovascular medications.

Drug absorption is ultimately influenced by the drug's solubility and by gastric motility, gastric perfusion, or enteral feeds (2). Enteral administration is the most common preferred route for drug administration. It is the safest and most convenient route and considered more economical than others. Unfortunately, dysphagia is common after an acute brain injury and precludes the patient's ability to swallow medications. Nasogastric tube placement for enteral nutrition will influence the absorption of drugs (e.g., phenytoin or carbamazepine suspension, nimodipine, carbidopa/levodopa, certain antibiotics). In some instances, enteral administration is not appropriate and intravenous administration is the preferred route (e.g., uncooperative agitated patients, profuse vomiting). However, unfortunately many drugs for neurologic conditions cannot be administered in an intravenous formulation.

A loading dose (intravenously or orally) is advised for drugs when an immediate therapeutic concentration is needed (e.g., antibiotics, antiplatelet agents, anticoagulants, antiepileptic drugs). This approach is used for drugs with longer half-lives, in particular when waiting for a steady state to be achieved would be detrimental to the patient's care. In drugs with a very short half-life (e.g., propofol), where the time to steady state occurs rapidly, a loading dose is not essential.

Once administered, drug distribution follows a two-compartment model: (1) the intravascular volume and rapidly perfused tissues and (2) distribution in other tissues. Lipophilic drugs (e.g., barbiturates) distribute more readily in fat tissues and thus can accumulate in obese patients. Pharmacokinetic changes are common in obese patients and there are differences in dosing. Total body weight is usually used for most sedatives, anticoagulants, and most antimicrobials, but ideal body weight is recommended for other medications (e.g., acyclovir, IV immune globulin) when the patient is overweight. Doses can be modified further in the presence of adverse events (i.e., toxicity) or inadequate clinical response (i.e., underdosing).

Distribution through the blood–brain barrier (BBB) and into the cerebrospinal fluid is restricted (3). Tight junctions between the epithelial cells prohibit many drugs from diffusing through the BBB into the central nervous system. These tight junctions break down with acute brain injury, allowing medications easier access to the central nervous system. This is best exemplified by the use of antibiotics needed to treat bacterial meningitis, which are molecularly too large to penetrate the BBB readily (4). Other factors that improve the ability of a drug to penetrate the BBB include molecular weight (e.g., <400–500 Daltons), drugs that are unionized, and basic molecules with minimal hydrogen bonding. Permeability plays a role in distribution of the drug: Greater lipophilicity is better for penetration into the central nervous system but is also dependent on cerebral blood flow.

Generally, the distribution of a drug is dependent on fluid administration, protein-binding affinity (albumin for acid drugs and glycoprotein alpha for basic drugs), and tissue perfusion. The heart, brain, and kidneys are readily perfused and receive the highest drug concentration after administration. In most patients with acute neurocritical illness, fluid administration remains constant except in patients requiring frequent osmotic diuretics or those who have been resuscitated in a setting of polytrauma. Liver function, renal function, and enzyme induction or inhibition all influence metabolism; these components are generally intact unless a systemic complication intervenes. In some drugs, hepatic clearance is much less sensitive to changes in the hepatic blood flow (e.g., phenytoin). However, the most important factor that influences hepatic function is the use of targeted temperature management, which decreases the metabolic clearance of many drugs including midazolam, fentanyl, phenobarbital, phenytoin, and neuromuscular-junction blockers. The pharmacokinetics in induced hypothermia are substantially changed, often approaching a 10% decrease in drug clearance with any decrease of 1°C—this factor is often underappreciated by clinicians.

Once a drug is distributed and reaches equilibrium between the tissues and the plasma, the unbound or "free" fraction links to the receptor. This implies that the bound (albumin) fraction is inactive, and therefore decreasing the bound fraction increases drug availability. Monitoring free drug levels is especially important when albumin body stores are unknown and with drug interactions between highly protein-bound drugs (e.g., valproic acid, phenytoin, warfarin). Hypoalbuminemia can be seen in elderly or malnourished patients or in patients with prolonged critical illness.

Drug elimination in neurocritical illness changes in patients with acute renal failure or those receiving renal replacement therapy. Glomerular filtration changes in acute kidney injury but mostly after sepsis, prolonged hypotension, and use of vasopressors. Any of these changes can result in altered elimination of antibiotics such as beta-lactams and carbapenems (1). Moreover, acute kidney injury can result with the use of certain antibiotics (e.g., vancomycin, aminoglycosides, beta-lactams).

The glomerular filtration rate (GFR) is an important metric and can be calculated as follows:

$$\text{For males: } C_R CL\,(\text{ml/min}) = \frac{(140 - \text{age})(\text{weight in kg})}{72 \times \text{serum creatinine}}$$

For females: the above result should be multiplied by 0.85.

Most pharmacists would then adjust the dose using the following formula:

Measured GFR/normal GFR × 100 = Dose adjustment in %.

## Drug Administration Routes

Determining the appropriate route (oral, rectal, intravenous, or interosseous) remains a critical question, and some guidelines follow.

### Oral Administration

- Timing of administration: Poor timing may lead to subtherapeutic drug levels and suboptimal clinical response. Antacids markedly reduce absorption because many drugs require low gastric pH for absorption. Food may affect antimicrobials. Other examples are carbidopa/levodopa and high-protein meals (decreased drug absorption) and carbamazepine suspension and nimodipine. Spacing remediates these problems.
- Enteric tube binding: Enteral phenytoin is notorious for binding to tube feedings, and the enteric tube requires frequent flushing. Clogging in tubes can also be solved by flushing with carbonated drinks such as Coca-Cola.
- Sustained/extended-release formulations: Crushing pills prior to administration results in suboptimal disease management or adverse effects. Crushing pills with enteral feeds may alter the absorption of medications, and removal of the pH-protectant coating of the medication results in lower drug concentration. Crushing these pills may also result in supratherapeutic drug concentrations.
- Oral disintegrating tablet: Sublingual mucosa allows for rapid absorption and instant bioavailability. This option could be the solution for patients with poor medication adherence and with dysphagia.
- Liquid formulations (to replace tablets/capsules for ease of administration): Many liquid formulations contain sorbitol, which in high doses can predispose patients to diarrhea, lactic acidosis, and electrolyte abnormalities.
- Pill size may increase the risk of aspiration when a patient experiences dysphagia (5,6).

### Intravenous Administration

- This is the preferred route of administration if a quick effect of the drug is needed
- This is the preferred route of administration when gastrointestinal absorption is inadequate
- There is a greater risk of medication errors and adverse events if medications are not administered appropriately.
  - The use of "smart pumps" with warnings embedded in them (e.g., soft and hard stop warnings) helps prevent medication administration errors.
  - Controlling access to high-risk drugs (keeping them not readily accessible on the nursing unit and requiring a double-check prior to preparing and administering them) is another method to prevent drug administration errors.
- Propylene glycol is a commonly used solvent, found in lorazepam, diazepam, phenobarbital, phenytoin, and barbiturates. Accumulations of propylene glycol have been associated with hypotension, metabolic acidosis, neurotoxicity, and acute renal failure.
- Be aware of particulate matter or crystallization in the bag or tubing when administering drugs intravenously.

*Peripheral Versus Central Intravenous Catheter*

- Catheter line compatibilities and diluent compatibilities: Assistance from a clinical pharmacist is needed if information is not readily available.
- Drug concentration is used to determine the choice of central versus peripheral route and the rate of administration (e.g., Potassium Chloride10 mEq/hr infusion, unless central line and cardiac monitoring, then 20 mEq/hr is allowed).
- Drug osmolarity is used to determine central versus peripheral route (e.g., peripheral infusion with hypertonic saline 3% or more is for emergent use only).
- Recognize high-risk vasopressor agents (e.g., 24-hour norepinephrine drip with peripheral access, 12-hour epinephrine drip with peripheral access).

*Tubing (Choice and Replacement)*

- 0.2-micron in-line filter (e.g., mannitol 20% or greater, parenteral nutrition)
- 1.2-micron in-line filter (e.g., fat emulsion)
- Vented tubing (e.g., nitroglycerin, propofol, tPA, tranexamic acid, acetaminophen)
- Dedicated line (e.g., propofol, fat emulsion, clevidipine, intravenous immune globulin)
- No filter (e.g., propofol, intravenous immune globulin, amphotericin liposome, amphotericin B lipid complex, amphotericin B, nitroglycerin)
- Change every 12 hours: propofol, clevidipine
- Change every 24 hours: fat emulsion
- Change others within 24 to 96 hours or per hospital policy

## Rectal Administration

- Faster onset, higher bioavailability than oral administration
- Typically fewer side effects than oral administration
- Used in patients experiencing vomiting or gastric irritation
- When enteral or injectable routes are inappropriate or unattainable (e.g., actively seizing patients)

## Interosseous Administration

- Bedside drilling in tibia
- For immediate administration of fluids or bicarbonate
- Equivalent to intravenous access in terms of drug delivery
- Transient fluid resuscitation method until intravenous access can be established

## Miscellaneous Routes of Administration

- Intranasal (e.g., midazolam for status epilepticus)
- Intraventricular (e.g., tPA for intraventricular hematoma, antimicrobial agents for ventriculitis)
- Intra-arterial (e.g., verapamil for symptomatic cerebral vasospasm)

## Drug Interactions

It is important to understand how drug interactions could occur in order to prevent or recognize them. Drug interactions, which are to be expected in critically ill patients, are often the result of polypharmacy rather than just from two drugs. Drug interactions can lead to medical complications, the most recognized of which are electrolyte abnormalities, hypotension or hypertension, sedation, and cardiac arrhythmias. With current computer databases and warning programs, clinical pharmacists often identify these drug interactions early and help prevent adverse events or drug interactions.

Drug interactions can be caused by pharmacokinetic interactions (drug A affecting the absorption of drug B) or by pharmacodynamic interactions (drug A having an additive effect with drug B). Additional important principles are (1) additive toxicity (e.g., two nephrotoxic agents); (2) additive effect (e.g., similar mode of action); and (3) multiple drugs, unknown patient history, and unstable patients.

For example, drugs prolonging the clearance of sedatives and analgesic agents are shown in Table 1.1.

Some drugs inhibit the metabolism of benzodiazepines and increase their effects. Calcium channel blockers and cytochrome P450 inhibitors (e.g., erythromycin, fluconazole) all prolong sedation, whereas cytochrome P450 inducers (e.g., phenytoin, carbamazepine) increase the metabolism of midazolam, potentially resulting in inadequate sedation. Barbiturates (e.g., phenobarbital) lead to added respiratory depression when administered concomitantly with midazolam.

Antiepileptic drugs are commonly associated with drug–drug interactions since many of them act upon the cytochrome P450 metabolic pathway, are highly protein-bound, and have a narrow therapeutic index for safety. Many antiepileptic drugs are cytochrome P450 enzyme inducers and decrease the International Normalized Ratio (INR), so higher warfarin doses are needed to achieve a therapeutic target. However, valproate acts as an enzyme inhibitor and increases the INR in patients receiving warfarin. Many antiepileptic drugs decrease the effect of commonly used drugs such as corticosteroids and tricyclic antidepressants because of their inducing effects. The newer second- and third-generation antiepileptic drugs have significantly fewer drug–drug interactions associated with their use and thus have a more

**Table 1.1 Drugs Prolonging Clearance of Sedatives and Analgesic Agents**

| Drug | Interfering Agent |
|---|---|
| Midazolam | Diltiazem, erythromycin, fluconazole, verapamil, conivaptan |
| Lorazepam | Valproic acid |
| Propofol | Lidocaine, valproic acid |
| Morphine | Cimetidine, azithromycin, itraconazole, glycoprotein inhibitors |
| Fentanyl | CYP3A4 inhibitors |
| Diazepam | Cimetidine, erythromycin, fluoxetine, CYP3A4 inhibitors |

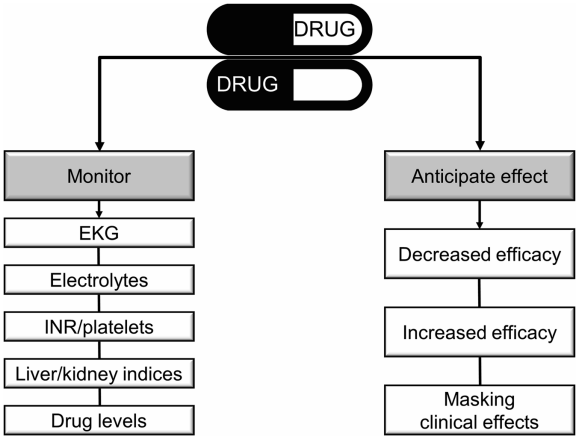



**Figure 1.2** Drug interactions (EKG = electrocardiogram; INR = International Normalized Ratio)



predictable therapeutic response. There is less interaction between the direct oral anticoagulants (e.g., dabigatran, apixaban, rivaroxaban, edoxaban) and antiepileptic medications, but data are limited. A summary of anticipated consequences and monitoring suggestions with drug-drug interactions is shown in Figure 1.2.

## Drug Errors

Errors may occur in all levels of hospital care including unrecognized medication nonadherence (7,8). One major factor is poor healthcare resources (e.g., high patient volumes, high patient acuity). Unfamiliarity with drug product is another common error, especially when there are different doses for different indications. Errors are also commonly associated with failure to adjust a dose in elderly patients and in patients with developing organ failure. Often there are "look-alike—sound-alike" drugs (e.g., tra*mad*ol, traz*od*one), which unknowingly get started and lead to more problems (9–12). Having a clinical pharmacist review medications with the medical team and awareness of the patient's condition is critical to help prevent these kinds of errors. Another important point to remember when using infusions is that most infusions are dosed in mg/kg per hour or mcg/kg per minute—except for dexmedetomidine, which is dosed in mcg/kg per hour.

In the United States each year, there reportedly are 450,000 medication errors and 7,000 deaths due to medication errors, 25% of which are deemed preventable. The intensivist, the clinical pharmacist, and the nurse all have specific roles in ensuring the "five rights" of medication administration: right dose, right patient, right time, right route, and right drug. Steps to ensure safety include medication reconciliation, high-risk drug warnings, bar-coding for medication administration, computerized physician order entry, proactive

medication review by pharmacists, use of smart pumps, and constant vigilance on the part of physicians and the nursing staff. A useful resource is http://www.ismp.org/.

## Pharmacogenomics

Table 1.2 summarizes the potential to find genetic markers for more effective drug dosing and monitoring for adverse effects. It is assumed (and proven in certain circumstances) that underlying genetic factors are associated with variable drug responses (7,13–16). Pharmacogenomics is an emerging field and could have major implications for the drugs used in critically ill neurologic patients (17). Clinical pharmacists will be a reliable source of information for choosing medications and doses, as well as providing the right monitoring, as this field expands.

## Neuropharmacology and Critical Care Pharmacology

Within a short period, neurocritical patients may become a living drug encyclopedia. It remains a major responsibility for the clinician, in conjunction with the ICU pharmacist, to tailor drug administration to the individual patient. Daily rounds must include a conscious effort to review medication lists and to promote drug reconciliation. Some drugs cannot be stopped without consequences (Table 1.3). Drug–drug interactions should be considered, antibiotic drug levels should be ordered regularly, and stop dates are needed to avoid prolonged use. The use of multiple antihypertensive agents is common,

**Table 1.2 Pharmacogenomics**

| Genetic Marker | Relevant in | Most common in |
|---|---|---|
| **CYP2C19 variant** is responsible for the metabolism of 10–15% of drugs in practice. | Phenytoin, diazepam, lorazepam, omeprazole, clopidogrel | Asians |
| **CYP2C9 variant** | Warfarin, phenytoin | Blacks |
| **VKORC1 deficiency** | Warfarin | |
| **CYP2D6 variant** is responsible for the metabolism of about 25% of the drugs in practice. | Many psychoactive and cardiovascular medications | Caucasians |
| **ABCB1 variant** | Antiepileptic drugs | |
| **HLA-B*1502** hypersensitivity reactions (Stevens-Johnson syndrome/toxic epidermal necrolysis) | Carbamazepine, phenytoin | Asians |

**Table 1.3 Problems with Inadvertently Holding Maintenance (Home) Medications**

| Drug Class | Rationale for Holding | Consequences |
|---|---|---|
| Beta-blockers | Permissive hypertension after ischemic stroke | Rebound hypertension, tachycardia |
| Antiepileptic medications | Decreased consciousness | Seizures |
| Diuretics | Permissive hypertension after ischemic stroke | Worsening heart failure |
| Serotonergic medications (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants) | Decreased consciousness, prolonged QT interval on electrocardiogram | Worsening depression, withdrawal (seizures), discontinuation syndrome (nausea/vomiting, sleep disturbances, arrhythmia, psychological symptoms) |
| Baclofen | Decreased consciousness | Withdrawal (hyperpyrexia, muscle rigidity, rhabdomyolysis) |
| Parkinson's medications (e.g., carbidopa/levodopa, amantadine, dopamine agonists) | Dyskinesias, orthostatic hypotension, hallucinations | Acute rigidity and hyperthermia, agitation, delirium |
| Benzodiazepines | Decreased consciousness | Tremors, anxiety, dysphoria, psychosis, seizures |
| Opioids | Decreased consciousness | Dysphoria, nausea/vomiting/diarrhea, muscle aches, pupillary dilation, lacrimation |
| Alpha-agonists (e.g., clonidine) | Decreased consciousness, hypotension | Rebound hypertension (sympathetic overdrive) |

and they should be closely titrated and adjusted. Hypotension can be expected and severe when the recovered patient is mobilized. Antiepileptic drugs are frequently administered prophylactically, and evidence for long-term use is not sufficient. Critical review of all administered drugs helps the patient. Equally important is to regularly calculate creatinine clearance for renally cleared drugs and to make dose adjustments as indicated. Serum creatinine does not reflect clearance and can be normal with abnormal clearance.

## Key Pointers

1. Intravenous drug administration in patients with acute brain injury is often necessary.
2. Nasogastric tube placement for enteral nutrition changes the absorption of drugs.
3. Antiepileptic drugs and sedatives are often associated with drug–drug interactions.

4. Certain drugs require central venous access.
5. Renal and hepatic disease, obesity, advanced age, and hypothermia have an impact on drug effects.

## References


1. Smith, B.S., et al., *Introduction to drug pharmacokinetics in the critically ill patient*. Chest, 2012. **141**: 1327–1336.
2. Roberts, D.J. and Hall, R.I. *Drug absorption, distribution, metabolism and excretion considerations in critically ill adults*. Expert Opin Drug Metab Toxicol, 2013. **9**: 1067–1084.
3. Kasinathan, N., et al., *Strategies for drug delivery to the central nervous system by systemic route*. Drug Deliv, 2015. **22**: 243–257.
4. Kulkarni, A.D., et al., *Brain-blood ratio: implications in brain drug delivery*. Expert Opin Drug Deliv, 2016. **13**: 85–92.
5. Bennett, B., et al., *Medication management in patients with dysphagia: a service evaluation*. Nurs Stand, 2013. **27**: 41–48.
6. Carnaby-Mann, G. and Crary, M. *Pill swallowing by adults with dysphagia*. Arch Otolaryngol Head Neck Surg, 2005. **131**: 970–975.
7. Kelly, J., Wright, D. and Wood, J. *Medicine administration errors in patients with dysphagia in secondary care: a multi-centre observational study*. J Adv Nurs, 2011. **67**: 2615–2627.
8. Kelly, J., Wright, D. and Wood, J. *Medication errors in patients with dysphagia*. Nurs Times, 2012. **108**: 12–14.
9. Floroff, C.K., et al., *Potentially inappropriate medication use is associated with clinical outcomes in critically ill elderly patients with neurological injury*. Neurocrit Care, 2014. **21**: 526–533.
10. Keers, R.N., et al., *Causes of medication administration errors in hospitals: a systematic review of quantitative and qualitative evidence*. Drug Saf, 2013. **36**: 1045–1067.
11. Macdonald, M., *Patient safety: examining the adequacy of the 5 rights of medication administration*. Clin Nurse Spec, 2010. **24**: 196–201.
12. Marengoni, A., et al., *Understanding adverse drug reactions in older adults through drug-drug interactions*. Eur J Intern Med, 2014. **25**: 843–846.
13. Caudle, K.E., et al., *Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing*. Clin Pharmacol Ther, 2014. **96**: 542–548.
14. Chan, A., Pirmohamed, M. and Comabella, M. *Pharmacogenomics in neurology: current state and future steps*. Ann Neurol, 2011. **70**: 684–697.
15. Kasperaviciute, D. and Sisodiya, S.M. *Epilepsy pharmacogenetics*. Pharmacogenomics, 2009. **10**: 817–836.
16. Tate, S.K. and Sisodiya, S.M. *Multidrug resistance in epilepsy: a pharmacogenomic update*. Expert Opin Pharmacother, 2007. **8**: 1441–1449.
17. MacKenzie, M. and Hall, R. *Pharmacogenomics and pharmacogenetics for the intensive care unit: a narrative review*. Can J Anaesth, 2017. **64**: 45–64.

## Chapter 2

# Analgosedation and Neuromuscular Blockers

It is ostensibly a paradox, but many patients with acute brain injury receive sedation (1,2,9). Neurologic examination is rendered virtually impossible, and rapid neuroimaging may be the only option to assess the situation. These scenarios of emergent intubation and use of large amounts of anesthetic drugs are all too common in deteriorating patients with traumatic head injury, status epilepticus, or cerebral hemorrhage. In neurointervention suites, sedation is often used; starting as conscious sedation but then converted to general anesthesia in restless uncommunicative (aphasic) patients (2).

In the general intensive care unit (ICU) population, less or no sedation is associated with a better outcome (3), and daily sedation interruption is beneficial to the patient (4). Similar concerns apply to the use of neuromuscular blockers (NMBs), but now are used sparingly and mostly when there is a hard indication such as inability to ventilate properly in acute lung injury.



## Deciding on Sedation

It remains a clinical judgment, but sedation is unnecessary when patients are not agitated or delirious, tolerate the endotracheal tube, or have a decreased responsiveness as a result of acute brain injury. Not every restless patient requires sedation. In fact, restlessness is often a good sign; transitioning from restlessness to stupor often is not. Indications for sedation are severe agitation resulting in possible harm to the patient, ventilator asynchrony, and poor gas exchange. We think that sedation is overused, for the wrong indications and at doses that are too high. Analgosedation is common in the general ICU but a controversial approach in acute brain injury. Some centers do routinely sedate patients after a severe acute brain injury, others are more reluctant knowing that there are misunderstandings about what sedation can do (Box 2.1). Analgosedation and often paralysis are considered in patients with refractory increased intracranial pressure, in situations that require targeted temperature management (e.g., post-cardiopulmonary resuscitation coma) or when control of extreme agitation is warranted (e.g., autoimmune encephalitis). Once sedated, interruption for a neurologic examination is needed but we have little understanding of what interruption of sedation (wake-up test) 'can do' to the patient physiologically with a damaged brain under pressure (16).

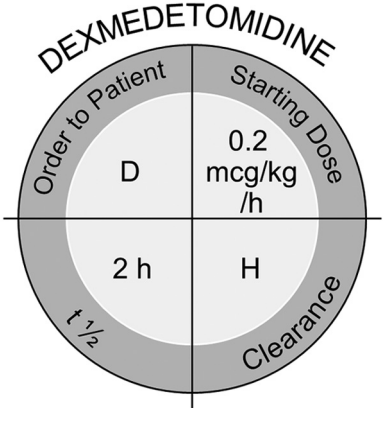
**Box 2.1 Sedation in Critical Neurologic Patients——Hard Truths**

- Sedation does not treat ICP effectively.
- Sedation does not always effectively suppress seizures.
- Sedation does not treat autonomic storming.
- Sedation does not improve cerebral metabolism.
- Sedation does not prevent self-extubation or catheter removal.

## Sedative Drugs

The drugs most commonly used for sedation are propofol and midazolam. Dexmedetomidine is a good alternative and is often also a first choice. In the neurosciences ICU, physicians often switch between dexmedetomidine and propofol. Benzodiazepines are frequently administered in the neurosciences ICU and are used in combination with other sedatives to provide amnesia but are generally discouraged due to alleged increased rates of delirium and longer duration of mechanical ventilation. Sedation can be monitored with nursing scales such as the Richmond Agitation Sedation Scale (RASS), but reliance on these scales likely does not surpass close clinical observation focusing on patient comfort (5). As a rule, light sedation is better than deep sedation. Current consensus calls for a RASS score between 0 and -2.

### Dexmedetomidine IV




***Pharmacologic Characteristics***

- Selective alpha-2 agonist
- Effects are threefold: sedation, analgesia, and anxiolysis
- Peak effect in 15 minutes

- Reduces hypertension and tachycardia (reduces sympathetic drive)
- No significant effect on respiratory drive and can be used in non-ventilated patients
- Can decrease opioid, benzodiazepine, and propofol needs
- Shorter mechanical ventilation and increased patient communication to health care providers compared to propofol and midazolam, when used for sedation (18)

***Dosing and Administration***

- Loading dose: 1 mcg/kg over 10-minute intravenous (IV) infusion
- Continuous infusion: starting at 0.2 up to 0. 7 mcg/kg per hour
- Continuous infusion: up to 1.5 mcg/kg per hour IV allowed for duration of more than 24 hours

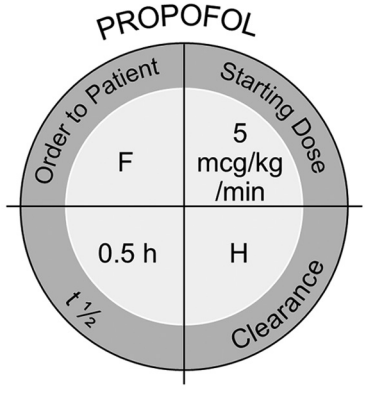
***Monitoring***

- Narrow therapeutic spectrum—side effects common with overshooting

***Side Effects***

- Hypotension when administered as a loading dose or at high infusion rates. Stop infusion—but can be restarted without a bolus and halved infusion rate
- Bradycardia
  - Bradyarrythmias have been associated with cardiac arrest
  - More common in hemodynamically unstable patients, the elderly, and patients with chronic hypertension
  - Discontinue immediately. Do not restart
- Agitation
- Seizures (rare)
- Nausea/vomiting

## Propofol IV



***Pharmacologic Characteristics***

- Pivotal sedative in any ICU
- Onset 10 to 50 seconds; duration 3 to10 minutes
- Preferred sedative because of rapid awakening when stopped (6–8)
- Reduces intracranial pressure only in very high doses and is ill advised for that indication
- Lower mortality in low doses than IV midazolam with earlier ICU discharge and fewer ventilator days

***Dosing and Administration***

- Dosing for procedural sedation: 1 mg/kg IV load, with 0.5 mg/kg IV repeated
- Infusion starting at 5 mcg/kg per minute, up to 80 mcg/kg per minute

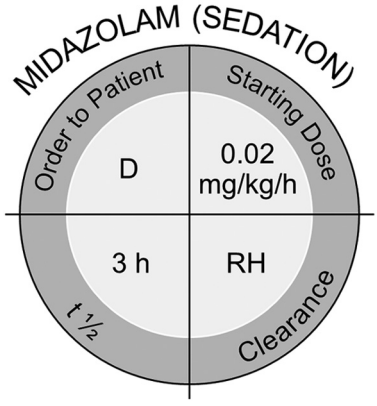
***Monitoring***

- Clearance not significantly altered with renal or hepatic disease, but reduced clearance in critical illness due to decreased hepatic blood flow
- Prior alcohol use disorder may require higher doses
- Provides 1.1 kcal/ml from fat; calories should be counted toward daily nutrition allotments
- Frequent arterial blood gas (metabolic acidosis) and triglyceride levels (rising)—for anticipating propofol related infusion syndrome (These laboratory tests, however, are far from predictive)

***Side Effects***

- Hypotension common (vasodilatory response), especially with bolus administration or in patients with marginal volume status
- Propofol related infusion syndrome (rare)—acute-onset bradycardia or other dysrhythmia, metabolic acidosis, rhabdomyolysis or myoglobinuria, myocardial failure, followed by hypotension and circulatory collapse. Patient may be salvaged by extracorporeal membrane oxygenation (ECMO)
- Propofol related infusion syndrome more common with high doses (>80 mcg/kg per minute for >48 hours), in acute brain and spinal cord injury, in sepsis and with ketogenic diet
- Propofol may be associated with significant neuroexcitation while emerging from the drug with wild, agitated, bizarre behavior mimicking functional behavior, often in young individuals ("propofol frenzy"). Symptoms are self-limiting, may last hours, may repeat but only supportive care is required (17)

## Midazolam IV




***Pharmacologic Characteristics***

- Gamma-aminobutyric acid (GABA)-A agonist
- Short-acting (30–90 seconds), rapid onset (1–2.5 minutes)
- Widely distributed into the cerebrospinal fluid (lipophilic drug)
- Half-life prolonged in cirrhosis, obesity, renal failure and with advanced age
- Extensively metabolized by the liver to active metabolite
- Induces anterograde—not retrograde—amnesia
- Opioid-sparing effect due to modulation of pain response

***Dosing and Administration***

- Bolus dose: 0.01 to 0.05 mg/kg, slow IV push over several minutes
- Starting dose: 0.02 mg/kg per hour and up to 0.1 mg/kg per hour continuous infusion, adjusted up by 25% to 50% to achieve level of sedation

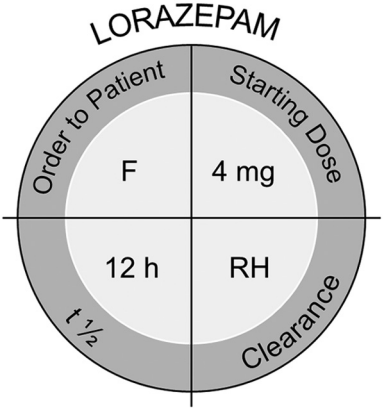
***Monitoring***

- No reliable drug assays
- Active metabolites that accumulate in renal and hepatic dysfunction affect elimination half-life
- Metabolite (1-hydromidazolam glucuronide) has central nervous system depressant effects and can accumulate in renal failure
- Prolonged sedative effects in obese patients or those with reduced albumin levels (i.e., high lipophilicity and protein binding)

***Side Effects***

- Hypotension due to major cardiodepressant effect
- Respiratory depression and respiratory arrest
- Laryngospasm
- Tachyphylaxis (overstimulation of benzodiazepine receptors)

## Lorazepam IV




***Pharmacologic Characteristics***

- GABA-A agonist
- Slower onset than midazolam (2–3 minutes)
- Longer half-life than midazolam (12 hours), prolonged in end-stage renal disease (18 hours)
- Metabolized by hepatic conjugation to inactive metabolite

***Dosing and Administration***

- Continuous infusion: 0.01–0.1 mg/kg per hour (not commonly used)
- Intermittent dosing: 0.02–0.06 mg/kg

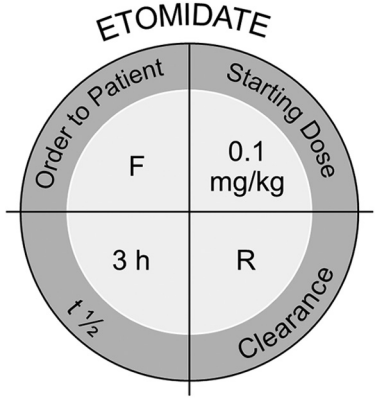
***Monitoring***

- Propylene glycol component in parenteral formulation and higher concentration may lead to toxicity (kidney injury, metabolic acidosis)
- 2 mg/hr = 20 g of propylene glycol (>10 times the WHO-recommended daily intake for 70-kg person)
- Screen for toxicity with doses of 50 mg/day or 1 mg/kg per day lorazepam using serum osmolar gap (toxicity ≥ 12)

***Side Effects***

- Propylene glycol toxicity and higher risk in pregnant patients, patients with renal or hepatic impairment, patients younger than 4 years, and patients receiving treatment with metronidazole. Hemodialysis will remove propylene glycol and correct the hyperosmolar gap.

## Etomidate IV




***Pharmacologic Characteristics***

- Ultra-short-acting non-barbiturate anesthetic agent
- Typically used in short procedures (e.g., endotracheal intubation)
- Preferred in hemodynamically unstable, agitated patients
- Rapid brain penetration and rapid elimination
- Short-term use only
- No known drug–drug interactions
- Produces electroencephalogram burst suppression at high doses
- Onset: 10–20 seconds; duration: 4–10 minutes

***Dosing and Administration***

- Sedation: 0.1–0.2 mg/kg; anesthesia: 0.3 mg/kg over 30 seconds

***Monitoring***

- Risk of toxicity in patients with renal impairment
- Free level increased in patients with hepatic cirrhosis or renal failure (75% protein-bound)
- Cardiac monitoring

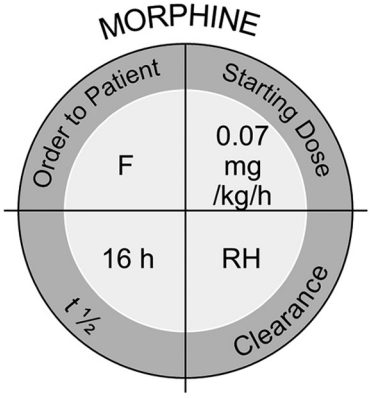
***Side Effects***

- May induce cardiac depression in elderly patients with hypertension, who may need lower doses
- Increased mortality with continuous infusions
- Blocks 11-B hydroxylase (enzyme for adrenal steroid production). A single dose blocks adrenal cortisol production for 6–8 hours, up to 24 hours in elderly or debilitated patients
- Consider corticosteroids in severe stress

## Analgesics

As a rule, opioids are avoided and are prescribed only when pain is obvious or unresponsive to simple analgesics. Opioid use leads to systemic effects such as bradycardia or hypotension. Opioids are used in combination with other sedatives for analgesia and have the potential to reduce the need of hypnotics when used in combination. Most nurses titrate the agent based on the use of arbitrary pain scales (verbal/nonverbal) or physiologic endpoints (Chapter 4). Opioids have significant side effects, most notably sedation, constipation, and vomiting. Dependency on opioids first prescribed in hospital settings (often after neurosurgical procedures) may be greater than appreciated.

### Morphine IV




***Pharmacologic Characteristics***

- Binding to central opioid receptors in sensory pathways
- Onset: 5 minutes for analgesia
- Patients with altered P450 CYP2D6 enzyme activity may have no response to morphine or experience toxicity, depending on their metabolism
- Greater histamine release compared to fentanyl or hydromorphone

***Dosing and Administration***

- Continuous infusion: 0.07–0.5 mg/kg per hour for ventilated patients
- Intermittent dosing: 0.01–0.15 mg/kg every 1–2 hours
- Initiate at lower doses for renal failure; there is a decreased clearance because 90% of drug is renally excreted
- Initiate at lower doses for liver cirrhosis; elimination half-life is prolonged. Increase dosing interval 1.5 to 2 times of normal dosing regimen
- Active metabolite—accumulates several-fold in renal disease (morphine-6-glucuronide)
- Hydrophilic and low volume of distribution, and this leads to higher plasma concentrations

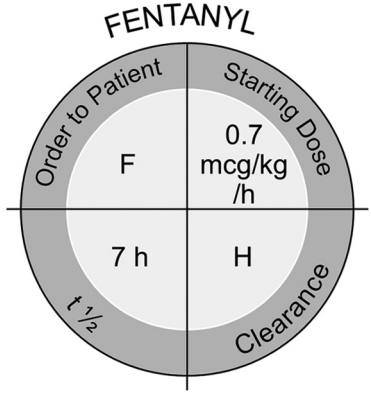
***Monitoring***

- Respiratory drive
- Gastrointestinal function

***Side Effects***

- Marked respiratory depression
- Constipation
- Gastrointestinal intolerance
- Hypotension, urticaria, pruritus, flushing, bronchospasm (from histamine release)
- Serotonin syndrome (Chapter 16) if used together with selective serotonin reuptake inhibitors (SSRIs)
- Adrenal suppression

## Fentanyl IV




***Pharmacologic Characteristics***

- Binding to central mu-opioid receptors in sensory pathways
- Onset: almost immediate; duration: 1–2 hours
- Highly lipophilic thus fast onset (faster than morphine or hydromorphone)
- Comparative study with fentanyl versus propofol showed no difference in ICU length of stay or duration of ventilation, but there was a difference in the need for rescue opioids in those on propofol (10)
- Metabolized by the liver to inactive metabolites
- Half-life is prolonged with continuous infusions

***Dosing and Administration***

- Continuous infusion: 0.7–10 mcg/kg per hour or 25–200 mcg/hr
- Intermittent: 0.35–1.5 mcg/kg every hour for ventilated patients
- Conscious sedation: 0.5–1.5 mg/kg every 3 minutes, repeated if needed
- For mild renal failure, reduce to 75% of dose; severe failure, reduce to 50% of dose
- Hepatic blood flow affects fentanyl disposition

***Monitoring***

- Prolonged duration or effect after repeated doses (tissue accumulation in adipose tissues), especially in obese patients
- Significant accumulation with renal or hepatic disease
- Drug interactions: prolonged sedation/effects when used concomitantly with CYP3A4 inhibitors

***Side Effects***

- Marked respiratory depression
- Histamine release (less than morphine)
- Associated with serotonin syndrome if used with selective serotonin reuptake inhibitors (SSRIs)
- Adrenal suppression

## Remifentanil IV

***Pharmacologic Characteristics***

- mu-receptor opioid agonist
- Rapid onset (1–3 minutes) and peak response (3–5 minutes); duration 3–10 minutes
- 500–1,000 times more potent than morphine

***Dosing and Administration***

- 0.025–2 mcg/kg per minute (when used with propofol or midazolam)
- 0.5–1 mcg/kg boluses every 2–5 minutes as needed
- Dosed based on ideal body weight in obesity

***Monitoring***

- Accumulation with renal failure
- Dialyzable: metabolite is 30% removed by hemodialysis

***Side Effects***

- Marked respiratory depression
- Histamine release (less than morphine)
- Associated with serotonin syndrome if used with selective serotonin reuptake inhibitors (SSRIs)
- Adrenal suppression
- Gastrointestinal intolerance

## Hydromorphone IV

***Pharmacologic Characteristics***

- Binds to central opioid receptors in sensory pathways
- Onset: 5 minutes; duration: 3–4 hours
- Ideal agent for end-stage renal disease

***Dosing and Administration***

- Continuous infusion: 0.5–3 mg/hr
- Intermittent dosing: 0.2–1 mg every 2–3 hours

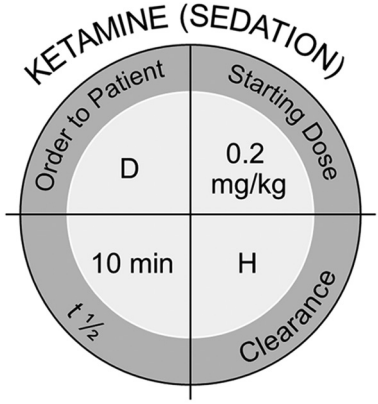
***Monitoring***

- Extensive hepatic metabolism to metabolites with unknown pharmacologic activity

***Side Effects***

- Marked respiratory depression
- Histamine release
- Associated with serotonin syndrome if used with selective serotonin reuptake inhibitors (SSRIs)
- Adrenal suppression

## Ketamine IV




***Pharmacologic Characteristics***

- Noncompetitive NMDA receptor antagonist (excitatory neurotransmitter glutamate)
- Dissociative effect
- Deep analgesia and onset 30 seconds, duration 5–10 minutes
- May increase heart rate and blood pressure (useful in hypotensive patients)
- Contraindicated with myocardial ischemia (increases heart rate and cardiac output)
- Contraindicated in porphyria

***Dosing and Administration***

- Bolus: 0.5 mg/kg
- Profound rapid sedation: 0.2–2 mg/kg IV (maximal 4.5 mg/kg)
- 2 mcg/kg per minute continuous infusion for postoperative opioid-sparing effect

***Monitoring***

- Closely monitor for increased intracranial pressure
- Monitor for hypertension
- Monitor for tachycardia

***Side Effects***

- Hallucinations
- "K-hole" (derealization with visual and auditory hallucinations)
- Emergency reactions
- Risk of laryngospasm

## Neuromuscular Blockers

Neuromuscular blockers (NMBs) are divided into depolarizing (e.g., succinylcholine) and nondepolarizing (e.g., vecuronium, rocuronium, atracurium, cisatracurium, pancuronium) classes (11). Depolarizing NMBs bind to receptors, depolarize the muscle membrane and open the calcium channels. Nondepolarizing NMBs bind to receptors but without channel opening, allowing rapid reversal (Fig. 2.1).

There are few neurologic reasons to use NMBs other than emergent intubation for airway control such as management of mechanical ventilation in patients with severe neurogenic pulmonary edema, targeted temperature management after cardiac resuscitation for prevention of shivering, and in some instances control of refractory intracranial pressure (ICP). There have been varying effects on ICP control with different agents based on systematic review, but administration for more than 12 hours resulted in longer ICU stays, higher occurrence of pneumonia, and a higher proportion of severely disabled survivors (12,13). Ultimately, the clinician must determine the risk/benefit ratio (11,14,15).

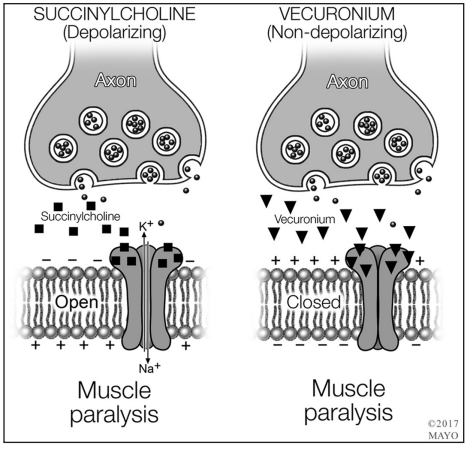



**Figure 2.1** Mechanisms of depolarizing and nondepolarizing NMBs