INTRODUCTION

This chapter is not intended to represent an exhaustive overview of the pharmacologic text on all the drugs used for regional anesthesia but rather to offer a practical review of the minimal information required, especially for continuous peripheral nerve blocks. Readers are referred to pharmacology texts or the extensive list of references at the end of this chapter for complete detailed overviews.

For continuous postoperative pain management, long-acting local anesthetic agents are mostly used. New local anesthetics, such as ropivacaine and levobupivacaine, have a reduced toxic potential compared to bupivacaine. This is important, because using continuous infusions may increase the risk of drug accumulation.

REVIEW OF THE PHARMACOLOGY OF SOME LOCAL ANESTHETIC AGENTS

Ropivacaine is less toxic than bupivacaine at equipotent doses. Several in vitro studies have shown that ropivacaine produces less block in heavily myelinated (motor) fibers and has a faster onset of block in lightly myelinated (sensory) fibers than bupivacaine. This provides a better differential blocking effect than that of bupivacaine.

Levobupivacaine is a new local anesthetic agent that may have a lower cardiotoxicity profile than the racemic mixture bupivacaine. In healthy volunteers, levobupivacaine produced significantly less depression of cardiac output than bupivacaine. Lidocaine, in contrast, has a shorter duration of action and is less toxic than long-acting agents. This makes it a possible alternative for bupivacaine, levobupivacaine, and ropivacaine. However, the denser motor block, the rapid development of tachyphylaxis with levobupivacaine, and the good safety profile of newer drugs make levobupivacaine not the first choice for continuous infusions. An advantage of ropivacaine is that its action stops sooner than that of bupivacaine after discontinuation of an infusion. This information may be useful during continuous blocks in trauma situations, because a blocked limb may mask the pain associated with a compartment syndrome, which should not be masked, since it is an early warning symptom.

Potency

Experimental and clinical evidence suggest that ropivacaine is equipotent to bupivacaine when used in peripheral nerve blockade. Studies have demonstrated that 30 to 40 mL of ropivacaine 0.5% produces a pattern of brachial plexus anesthesia broadly equivalent to that provided by 30 to 40 mL of bupivacaine 0.5%, whether administered via the subclavian perivascular, the axillary, or the interscalene route. In patients undergoing lower arm surgery, McGlade et al. concluded that 30 mL of ropivacaine (0.5%) or bupivacaine (0.5%) is equally effective for
axillary brachial plexus block in terms of the onset time, motor blockade, and overall success rate. However, the duration of residual blockade was significantly longer with bupivacaine (6.8 versus 16 h). Using the same volume of local anesthetic for interscalene block, Klein et al. compared 0.5% and 0.75% ropivacaine and 0.5% bupivacaine in patients undergoing shoulder surgery. They were not able to show any differences in success rate, onset of sensory or motor blocks, or the duration of analgesia among the three groups.

Metabolism and Systemic Toxicity of Local Anesthetic Drugs during Continuous Infusion

With the infusion of local anesthetic agents over a longer period, the accumulation of drugs and their metabolites may be important. In plasma, ropivacaine is mainly bound to alpha-1-acid glycoprotein (AAG), an acute-phase protein that increases gradually postoperatively and may not reach a maximum until the sixth to twelfth postoperative day. This postoperative increase in plasma AAG concentrations enhances the protein binding of ropivacaine and its metabolite, pipecoloxylidine, causing an increasing difference between total and unbound plasma concentrations. In 1989, Tuominen et al. suggested that the rise in AAG probably increases the binding of bupivacaine to plasma proteins, which diminishes the risk of systemic toxicity in spite of a high total drug concentration. During continuous interscalene block, the total plasma concentration of ropivacaine increased slightly but the unbound fraction decreased with time, reflecting an increase in the degree of plasma protein binding.

The use of a large initial interscalene dose of bupivacaine (150 to 200 mg or 30 to 40 mL of 0.5%) followed by a continuous interscalene infusion of bupivacaine of 12.5 to 22.5 mg/h for 24 and 48 h (500 to 800 mg/24 h) is not likely to cause toxic plasma levels. The main reason for this is the unchanged or decreasing plasma concentrations of ropivacaine and its metabolite, pipecoloxylidine, causing an increasing difference between total and unbound plasma concentrations. The enhancement of the protein binding of ropivacaine and ropivacaine 0.6 mg/L. The toxic threshold for levobupivacaine is unknown.

An increase in protein binding of ropivacaine and bupivacaine can result in a decrease in the total plasma clearance. This should have little or no effect on the clearance of the unbound plasma fraction, which mainly depends on the hepatic enzyme capacity. This may explain why unbound plasma concentrations remain relatively stable after 12 to 24 h, in contrast to increasing total concentrations during continuous postoperative epidural infusion of ropivacaine.

Ropivacaine undergoes extensive hepatic metabolism after intravenous administration, with only 1% of the drug appearing unchanged in the urine. As ropivacaine is eliminated with an intermediate to low hepatic extraction ratio, its rate of elimination should depend on the unbound plasma concentration. The major metabolite identified in the urine is 3-OH-ropivacaine, probably conjugated with glucuronic acid. Agents, which inhibit the isoenzyme CYP1A2, affect the pharmacokinetic profile of ropivacaine. Another metabolite of ropivacaine is PPX, which is a minor metabolite after a single dose but a major metabolite during epidural infusion. Epidural infusion of ropivacaine over 72 h caused PPX plasma concentrations approaching that of ropivacaine, while unbound PPX concentrations were approximately eight to nine times higher than unbound ropivacaine concentrations.

In uremic patients, the enhanced absorption of ropivacaine into the circulation after axillary brachial plexus block, the increased binding to AAG, and the reduced urinary excretion of the metabolites led to larger total plasma concentrations of ropivacaine and its main metabolites. Renal function is not important in the elimination of ropivacaine, since its excretion in the urine is minimal. However, renal function is important in the elimination of PPX and 3-OH-ropivacaine. Renal insufficiency may therefore be responsible for accumulation of these compounds. Caution should be exercised when large doses of ropivacaine are administered to patients with impaired renal function during continuous infusion.

Only a small fraction (6%) of intravenously administered bupivacaine is excreted unchanged in the urine of humans. The metabolites of bupivacaine are 4-hydroxybupivacaine (4-OHB) and desbutylbupivacaine (DBB) and are less toxic than bupivacaine. During infusion of 0.25% bupivacaine for continuous interscalene brachial plexus block, there was a slow but significant increase in the plasma concentrations of bupivacaine and of DBB over 12 and 24 h of infusion.
Neurotoxicity and Myotoxicity

Ropivacaine seems to be relatively free of neurotoxicity. Detailed histologic studies in guinea pigs and dogs also indicate that ropivacaine does not cause inflammation in peripheral nerves or the spinal cord. It has been suggested that ropivacaine is significantly less painful on injection than bupivacaine.

There is convincing experimental evidence that skeletal muscle is damaged by exposure to local anesthetic agents. Although this occurs very rarely in the clinical use of these agents, it can be serious when it does occur. Myotoxicity should be suspected when localized muscle dysfunction and tenderness follow anesthetic injection. Biopsy (using procaine for local anesthesia) aids in differential diagnosis, and magnetic resonance spectroscopy might be used to establish the diagnosis noninvasively. Myotoxicity can be clinically relevant after a single injection and more so after repeated administration. This suggests a potential risk of destroying muscle and nerve tissue in patients treated with frequent injections of 0.5% bupivacaine. In animal studies local anesthetic agent myotoxicity is worse after repeated administration of large volumes. Therefore doses that may be safe for single-injection in patients may not be safe for repeat administration.

In pigs, continuous peripheral nerve blockades with the long-acting local anesthetics bupivacaine and ropivacaine, in equipotent concentrations, cause fiber necrosis in skeletal muscle. In comparison with ropivacaine, bupivacaine causes significantly more muscle damage and apoptosis in skeletal muscle cells (see Chap. 32). High concentrations of bupivacaine and the use of epinephrine are associated with increased myotoxicity and should be avoided if injections are to be made into or adjacent to muscle.

Central Nervous System Toxicity

Case reports suggest that plasma concentrations of levobupivacaine or ropivacaine that are toxic to the CNS do not produce cardiotoxic effects. It is therefore important to be aware of CNS toxicity symptoms after injection. These symptoms include numbness of the tongue, metallic taste, light-headedness, visual disturbances, and muscular twitching. More serious signs include convulsions, coma, respiratory arrest, and finally cardiovascular depression.

A wide variety of animal experiments and several double-blind, randomized, controlled volunteer studies have shown that levobupivacaine and ropivacaine are significantly less toxic than bupivacaine. The central neurotoxicity of levobupivacaine is intermediate between that of ropivacaine and bupivacaine when administered at the same dosage and rate, and ropivacaine-induced cardiac arrest appears to be more responsive to treatment than that caused by bupivacaine or levobupivacaine.

Scott et al. demonstrated that ropivacaine caused fewer CNS symptoms and was at least 25% less toxic than bupivacaine in regard to the dose tolerated. The maximum tolerated unbound arterial plasma concentration was twice as high after ropivacaine than after bupivacaine. Muscular twitching occurred more frequently after bupivacaine. The time for all symptoms to disappear was shorter after ropivacaine. Levobupivacaine is also significantly less toxic to the CNS than bupivacaine. Convulsions with levobupivacaine occurred at a higher concentration and were of briefer duration.

Cardiac Toxicity

Ropivacaine appears to be less cardiotoxic than equal concentrations of racemic bupivacaine, probably because of its faster dissociation from cardiac sodium channels, but it seems to be more cardiotoxic than lidocaine. Bupivacaine is more cardiodepressing and arrhythmogenic than either ropivacaine or lidocaine.

Cardiac signs of toxicity such as dysrhythmia, bradycardia, and hypotension occurred at significantly higher doses of ropivacaine than bupivacaine. Bupivacaine increased QRS width in the presence of sinus rhythm compared with placebo and ropivacaine. Bupivacaine reduced both left ventricular systolic and diastolic function compared with placebo, while ropivacaine reduced only systolic function. At doses producing CNS symptoms, cardiovascular changes, such as depression of conduction and diastolic function, were less pronounced with ropivacaine than with bupivacaine.

Reports of cardiovascular toxicity after accidental intravascular administration of ropivacaine are extremely rare. A case report described severe cardiac dysrhythmia, which developed in a patient with an unbound venous plasma ropivacaine concentration of 1.5 mg/L.

Huang et al. compared the cardiovascular effects of intravenous bupivacaine and levobupivacaine, in sheep. Both drugs depressed the myocardium similarly, but myocardial depression was overshadowed by CNS excitation; levobupivacaine was less likely to cause fatal arrhythmias than bupivacaine. Bardsley et al. confirmed the lower cardiotoxicity of levobupivacaine in humans. In particular the negative inotropic effect for levobupivacaine was less than that for bupivacaine.

Stewart et al. compared the cardiotoxicity of ropivacaine and levobupivacaine and found that both produced similar cardiovascular effects when infused intravenously at equal dosages and infusion rates.

Summary

Ropivacaine and bupivacaine are equipotent over a wide range of concentrations when used in peripheral nerve blockade.
Ropivacaine is less cardiotoxic and causes less CNS toxicity than the same concentrations of bupivacaine.

The threshold for CNS toxicity is higher for ropivacaine than for bupivacaine.

Ropivacaine has advantages over bupivacaine in that the former causes CNS toxicity symptoms before cardiotoxic signs and that it has a higher survival rate than the latter after a massive overdose.

The more rapid clearance of ropivacaine, its more predictable duration of blockade, faster block onset, and less pain on injection are advantages that make ropivacaine the preferred long-acting local anesthetic.

**Local Anesthetic Adjuvants**

**Epinephrine**

Epinephrine shortens the onset time of nerve block, causes the block to be denser, increases its duration, and decreases local anesthetic blood concentrations by causing vasoconstriction and relative ischemia to the nerve.\(^{96,99}\) Because of this ischemia, epinephrine is a possible risk factor for the development of peripheral nerve injury,\(^{100}\) and we do not recommend its routine use. It may be handy as a marker of intravascular injection and it may reduce the toxic potential and increase the duration of action of short-acting and fast-absorbed drugs such as mepivacaine and lidocaine. Good nerve block techniques (see later) will shorten block onset time, higher concentrations of relatively safe drugs will improve the “density” of a block if that is required, and continuous peripheral block will increase the duration of the block in a controllable manner.

**Clonidine**

Extrapolating the concept of “balanced analgesia” introduced by Kehlet,\(^ {101}\) some authors advocate adding clonidine\(^ {102,103}\) and/or opioids\(^ {103}\) to the continuous peripheral nerve block solution. Clonidine prolongs duration of action of local anesthetic agents after single injection brachial plexus block.\(^ {104}\) This may also be true for continuous peripheral nerve block, although the logic of extending the duration of action of the drugs used during a continuous nerve block escapes the present authors.

Three mechanisms of action of clonidine can be proposed. Although it is disputed, clonidine may cause local vasoconstriction, thus prolonging local anesthetic action by decreasing the systemic absorption.\(^ {105,106}\) Second, clonidine may have local anesthetic activity.\(^ {107}\) Finally, clonidine could have a potentiating effect on local anesthetics. However, the most common adverse effect of clonidine (orthostatic hypotension) places the patient at risk of falling and injury. Furthermore, the possibility of low oxyhemoglobin levels that may occur in patients who receive clonidine may limit its use in outpatients.\(^ {108}\) A recent study failed to demonstrate better postoperative analgesia when 1 µg/mL of clonidine was added to ropivacaine (0.2%) for continuous femoral nerve block\(^ {109}\) or in continuous infraclavicular perineural infusion.\(^ {110}\) The addition of even 2 µg/mL of clonidine to an interscalene perineural ropivacaine infusion does not provide a clinically relevant improvement in breakthrough pain intensity, local anesthetic consumption, opioid requirements, sleep quality, or satisfaction score.\(^ {111}\)

**Opioids**

In a systematic review\(^ {112}\) and a metanalysis by Picard et al.,\(^ {113}\) it was concluded that there is no evidence for a clinically significant beneficial effect of added opioids during peripheral nerve blocks. The use of opioids does not seem to be warranted. In all trials, however, large doses of high-concentration local anesthetic agents were used. This may have masked the augmentative effect of the opioids.\(^ {114}\) Regional anesthesia with local anesthetic agents produces excellent analgesia with very few side effects compared to intravenous or subcutaneous opioids. Adding opioids to the local anesthetic agents may largely cause a loss of this advantage.

► **INFUSION PUMPS**

A pump that can provide a basal infusion as well as patient-controlled boluses is ideal for patient controlled regional anesthesia (PCRA). In this way, anesthesia can be tailored to provide a minimal basal rate to lengthen the duration of infusion maximally,\(^ {115}\) while breakthrough pain can be treated or prevented with boluses before physical therapy. Moreover, PCRA offers adequate analgesia with a lower consumption of local anesthetic agent as was proven in numerous trials.

For ambulant PCRA, battery-powered electronic and nonelectronic disposable pumps are available. The ideal infusion pump should be disposable, electronic, refillable, completely and easily programmable with both basal and bolus capabilities, and reprogrammable. The pump should be lightweight, allow monitoring of medication delivery through a digital readout screen, and come with a carrying case for ambulant patients. The pump that seems to answer these requirements is the PainPump2 BlockAid (Stryker Instruments, Kalamazoo, MI).

**Nonelectronic Disposable Pumps**

These pumps are classified into elastomeric-, spring-, or vacuum-powered. An elastomeric pump is a device with...
a distensible bulb inside a protective bulb, a filling port, delivery tubing, and a filter. It does not require special care or reprogramming; it is also simple to use, disposable, and potentially cheaper. Recent studies showed that there are fewer technical problems and greater patient and nurse satisfaction with these pumps. Because of the freedom of movement, they have also been used in children. However, these pumps have limitations. There is no way to detect whether and how much local anesthetic is delivered or how much is left in the reservoir. Since there is no high-pressure alarm, detecting and correcting an occlusion in the catheter is difficult. When a pump with a low working pressure is used, the catheter can become occluded (25 percent in Iskandar’s study). Furthermore, the rate of drug delivery cannot be adjusted to the patient’s needs. Ilfeld et al. investigated the accuracy of pump delivery in six PCRA-pumps (spring-, elastomeric-, and electronically powered) and found that both elastomeric- and spring-powered pumps infused at higher than expected rates initially, with infusion volume decreasing over the duration of the infusion period. Increased ambient temperature increased the infusion rates by 5 to 10 percent in certain pumps. Low air pressure led to a decreased infusion rate in some pumps. Therefore atmospheric pressure changes—as, for example, in airplanes—has some effect on fluid delivery.

**Electrical Pumps**

There are a few nonelectrical disposable pumps available that provide continuous infusion and patient-controlled boluses, but only electronic pumps provide the desired profile. In principle, patients, who are often very weak, cannot provide the energy that is needed to inject the patient-controlled bolus. This situation prevents nonelectrical pumps from being ideal. However, most electronic pumps are complex and have to be reprogrammed in case of a too dense or insufficient block. Moreover, these pumps are usually nondisposable and expensive. They can get lost, particularly in an ambulatory setting, with financial hardship for the patient. This problem has been addressed by providing the patient with a self-addressed prepaid envelope to mail the pump back. Ilfeld et al. described the use of small, lightweight, reprogrammable pumps for which the programming instructions can be telephonically explained to the patient. This system allows a progressive decrease in the patient’s basal infusion rate as the pain gets less, which not only decreases the risk of local anesthetic toxicity but also allows a longer period of infusion without the need to refill the pump.

Refer to the recent review article by Ilfeld et al. regarding continuous peripheral nerve blocks at home for more details concerning drugs and infusion pumps.

For needles and catheter systems, see Chap. 20.

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