Legal Briefs

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The nature of supervision

Key words: Captain of the ship, standard of care, supervision.

In some states, nurse anesthetists must be supervised or directed by a physician. Even in states where there is no statute requiring nurse anesthetists to be supervised, hospitals or other institutions may require it. "Supervision," despite its frequent appearance remains one of the least understood concepts in nurse anesthetist practice. Its genesis is traced to the historical development of nurse anesthetist practice. A few months ago, yet another court rejected arbitrary constraints concerning supervision and followed the reality of practice in upholding a jury determination that a surgeon was not liable for the improper supervision of a nurse anesthetist.

In recent years, enemies of nurse anesthesia have attempted to increase responsibilities associated with supervision. The dispute about the nature of supervision has nothing to do with patient care. No study has ever shown that anesthesia administered by an anesthesiologist or administered by a nurse anesthetist supervised by an anesthesiologist is any safer or otherwise "better" than anesthesia administered by a nurse anesthetist working alone. Nonetheless, both the American Association of Nurse Anesthetists (AANA) and the American Society of Anesthesiologists (ASA) have much different positions on supervision. The AANA has stated that *"Supervision or direction refers to a variety of different practice settings within a continuum. While all satisfy the legal requirement, practice settings take into account the education, experience and capabilities of the nurse anesthetist, the rules and guidelines of the institution in which anesthesia is to be provided, and the needs and desires of the patient, nurse anesthetist, physician, dentist, podiatrist or other health care professional."*[1]

ASA's position

The ASA's position is set forth in its "Guidelines for the Ethical Practice of Anesthesiology."[2] Anesthesiologists working with nurse anesthetists are expected by ASA, to carry out the following responsibilities:

a. Preanesthetic evaluation of the patient.
b. Prescription of the anesthesia plan.
c. Personal participation in the most demanding procedures in this plan, especially those of induction and emergence.
d. Following the course of anesthesia administration at frequent intervals.
e. Remaining physically available for the immediate diagnosis and treatment of emergencies.
f. Providing indicated postanesthesia care.

The ASA standards look remarkably like the Tax Equity and Fiscal Responsibility Act (TEFRA) standards which were adopted in 1982 to determine when a CRNA was "medically directed." Although it may appear that TEFRA supports the ASA position, such a conclusion would be incor-

rect. The TEFRA requirements are for reimbursement purposes only and, even then, only if the anesthesiologist is to be reimbursed at the same rate as if the anesthesiologist had personally performed the procedure. The Health Care Financing Administration (HCFA) will reimburse anesthesia services provided by a nurse anesthetist whether or not the nurse anesthetist is medically directed by an anesthesiologist and whether or not the supervising anesthesiologist performs the TEFRA conditions.

While the words may be the same, there is a vast difference between a level of supervision which entitles an anesthesiologist to be paid as if he or she administered the service himself or herself and a level of supervision needed to satisfy certain state licensing requirements that there be physician involvement when anesthesia is administered. Nonetheless, ASA has attempted to maintain that "ethical anesthesia" requires that an anesthesiologist evaluate the patient, be present for induction, and perform the remainder of the steps outlined above.

Standards adopted by JCAHO

The Joint Commission on the Accreditation of Health Care Organizations (JCAHO) has adopted standards for supervising anesthesia care which are quite different from the ASA's requirements. JCAHO standards require that anesthesia care for each patient is provided directly by a licensed independent practitioner or by an individual who is "directed or supervised" by a licensed independent practitioner. A JCAHO publication explains: *"The standards do not require that a supervising, licensed independent practitioner (for example, surgeon or obstetrician) have privileges to administer anesthesia, but the practitioner must be capable of reviewing the results of the preanesthesia evaluation, of determining that the patient is an appropriate candidate to undergo the planned anesthesia* (SA.1.5.2), *and of determining that the patient can be discharged* (SA.1.5.6)."[3]

Some history

Nor does history support the ASA's restrictive position. What was meant by "supervision" when nurse anesthetist statutes were originally enacted? Even in the early days of anesthesia, nurse anesthetists, being bright and capable, rapidly became more adept at anesthesia than the physicians "supervising" them. Consider three nurse anesthetists (these examples are derived from Virginia Thatcher's book, *History of Anesthesia with Emphasis on the Nurse Specialist,* and the historic notion of supervision. Thatcher found the first group of nurse anesthetists to be Catholic sisters and she reported an interview with a Sister Secundina Mindrup, CRNA, who had developed a timing device for administering a mixture of ether and chloroform depending on how much relaxation was required: "a decade of prayers on her rosary and it was time to give a little more."[4] Is it likely that the physician "supervising" Sister Secundina would have told her to give anesthesia by timing it with her prayers?

Alice Magaw, the famous nurse anesthetist at the Mayo Clinic, devised her own method of administering open-drop chloroform and ether anesthesia superior to virtually anything that was being used at the time. Physicians came to Mayo to learn *her* methods. It is obvious that the physicians who admired her work could have added little to her methods or safety through "supervision." Finally, George Crile, MD, wrote that Agatha Hodgins had learned to skillfully adjust dosages based on her experience and experimentation with anesthetic agents.

Thus, historically, those who supervised nurse anesthetists acknowledged that nurse anesthetists were more knowledgeable, got better results, and had better techniques than the "supervisors." It was not necessary that Dr. Crile be able to administer anesthesia to "supervise" Agatha Hodgins, CRNA. Being the bright and dynamic woman that she was, it was obvious that after a relatively short period of time of specialization Agatha Hodgins would clearly know more about anesthesia than Dr. Crile. Yet, under the statutes then being adopted, it was understood that Dr. Crile was "supervising" Agatha Hodgins. ASA's requirements for medical direction were never what licensing laws contemplated by "supervision." Physicians provided some medical input but they were not expected to control the anesthetic process.

In contemporary times, the dispute between AANA and ASA has raged for many years. Since the issue involves the meaning of "supervision" in laws and statutes, it can be assumed that the courts would be involved. However, it has been difficult to find cases in which a court reviews these issues. Licensing and regulatory bodies permit healthcare wide latitude. Since the practice of nurse anesthetists working directly with surgeons is so well accepted, regulatory procedures involving supervision of nurse anesthetists rarely come to court. Similarly, issues of supervision seldom arise in malpractice cases. Nurse anesthetists are expected to administer anesthesia with the same quality and results as anesthesiologists. Thus, most anesthesia malpractice cases are decided on the basis of the standard of care rather than the level of supervision. A surgeon's liability is usually based on

whether the surgeon controlled or had the right to control the procedure which gave rise to the negligence. Cases based on a claim that the surgeon failed to carry out some obligation to supervise are rare. Consequently, it is "news" that the Mississippi Supreme Court recently had an opportunity to discuss supervision in a decision upholding a jury verdict in favor of a surgeon working with a nurse anesthetist.

Starcher v Byrne

In *Starcher v Byrne,* 687 So. 2d 737 (Mississippi, 1997), a patient was admitted to a hospital to correct a ventral hernia. Anesthesia was administered by a CRNA employed by an anesthesiologist. As the CRNA began induction, the surgeon received an emergency page. He went into the hallway outside the operating room, but, in compliance with hospital policy, remained within the operating suite to answer the page while the CRNA induced the patient. The nurse anesthetist had trouble inducing the patient. When the surgeon returned, he and the nurse anesthetist determined that the patient was suffering from a bronchospasm. Based on their diagnosis, the operating team conducted emergency treatment. Due to the patient's condition, her heart rate began to fall rapidly. The surgeon successfully administered cardiopulmonary resuscitation to the patient and she was stabilized. However, as a result of her inability to breathe and the failure of her heart to adequately pump blood to all regions of her body, specifically her brain, for several minutes, the patient suffered brain damage resulting in decreased intellectual and physical capacity. The patient remained comatose for several days following the incident.

The plaintiffs (the patient and her husband) brought suit against the surgeon contending that he was negligent because he was not present in the operating room at the induction of anesthesia by the nurse anesthetist. They contended that the standards of practice for nurse anesthetists required that a CRNA work under the direction of and in the physical presence of a licensed physician. Because the nurse anesthetist's employer, the anesthesiologist, was not in the operating room or even at the hospital, the plaintiffs claimed that the surgeon was in charge of the operating room. Therefore, his failure to be present at the induction of anesthesia constituted a breach of the standard of care. At trial, the jury returned a verdict in favor of the surgeon. The plaintiffs appealed, claiming that the jury's verdict was contrary to the weight of the evidence and that the surgeon's absence from the operating room should mean that he was liable because he failed to properly supervise the nurse anesthetist.

Mississippi does not have a statute on nurse anesthesia practice. The Mississippi Board of Nursing requires that nurse practitioners, which includes nurse anesthetists in Mississippi, practice in a collaborative/consultative relationship with a licensed physician or dentist. Interestingly, the Mississippi Supreme Court never mentioned licensing requirements in its decision. Instead, the case was decided based on practice standards and legal doctrines concerning tort liability. The Supreme Court of Mississippi upheld the jury verdict and dismissed the appeal. Basically, the Supreme Court held that the standard of care did not require the supervising physician to be in the operating room while anesthesia was being induced.

Judge disagrees with decision

The decision in the *Starcher* case was not unanimous. One of the judges did not agree with the majority and wrote his own opinion. His dissent is interesting because it gives us a hint of what the arguments were on the other side. Those arguments are quite familiar to nurse anesthetists.

The dissenting judge quoted a well-known legal work: *"In most states, surgeons may be found liable for the failure to supervise a nurse anesthetist or vicariously liable for a nurse anesthetist's negligence.* 8 Am.Jur. Proof of Facts 2d, Surgeon's Failure to Exercise Supervision and Control over Anesthetist § 1,6 (1976). *Such liability is usually predicated upon the captain of the ship doctrine... That the surgeon is captain of the ship does not expose him to unfettered liability for the acts of all personnel in the operating room. Rather, at least one court has found that the 'vital test' is whether the surgeon has the right to control the employee. Harris v Miller,* 103 N.C.App. 312, 322, 407 S.E.2d 556, 562 (1991). *In...* [this case]*..., the issue of whether* [the surgeon] *had the right to control* [the nurse anesthetist] *was a proper matter for the jury to consider."*

Unlike the dissenting judge, the majority of the Mississippi Supreme Court was willing to analyze the relationship of the defendants and not rely on labels, as the dissent urged. The statement quoted by the dissent from *Proof of Facts* has caused a number of problems for nurse anesthetists. Someone probably *assumed* that surgeons "may be found liable for the failure to supervise a nurse anesthetist" because of a number of legal doctrines which once prevailed, such as "captain of the ship." These doctrines are now outmoded and seldom followed. Even when they were followed, the statement gives an inaccurate picture. It is unclear how it came to

be published or who purported to count the cases. There have been any number of decisions in which surgeons were **not** held liable for the negligence of nurse anesthetists. (In fact, in the *Starcher* case, there is no suggestion or evidence in the report of the case that the nurse anesthetist was negligent.)

The majority of justices of the Mississippi Supreme Court analyzed the relationship between surgeon and nurse anesthetist and concluded that there was sufficient evidence to uphold the jury's verdict. At trial, testimony had showed that the surgeon had little, if any, say over and was not expected to inject himself into the anesthesia process. There was testimony which the court said the jury could have believed that the surgeon could not tell the nurse anesthetist what to do. Nor could the surgeon expect the nurse anesthetist to obey the surgeon's commands if the nurse anesthetist thought that the surgeon was wrong. Moreover, the court found that it was common practice for a CRNA to perform the anesthesia for surgical procedures, in the absence of an anesthesiologist, so long as a physician was available in case of an emergency.

The plaintiffs had claimed that the standard of practice required that a nurse anesthetist work under the direction of and in the physical presence of a licensed physician. The Mississippi Supreme Court said there two reasons why the plaintiff's argument must fail. First, the standards of practice apply to CRNAs, not physicians. The plaintiffs failed to present any evidence that the standards apply to physicians. Second, with the exception of the plaintiffs' expert witness, no doctor called by either side stated that a physician must be physically present in the operating room at the induction of anesthesia. Every other doctor called unequivocally stated that the common practice was only that the surgeon be in the operating suite. It was the general consensus of all doctors who testified, except for the plaintiffs' expert, that the operating physician had a tendency to get in the way more than anything else when he or she was in the operating room at the induction of anesthesia. Further, the head of a neighboring hospital testified that it was their hospital policy that the operating physician be within the operating suite, not in the operating room at the induction of anesthesia.

The plaintiffs had made a number of claims concerning "captain of the ship" and "borrowed servants" which the court dismissed because the nurse anesthetist was an employee of the anesthesiologist. What made the case of interest was the court's holding on supervision. The court rejected artificial rules and looked to the reality of practice in its holding: *"There was adequate evidence that the CRNA could administer anesthesia where neither a surgeon nor an anesthesiologist is present in the operating room, that Mississippi CRNAs are licensed to do so, and that this was a fairly common practice."*

REFERENCES

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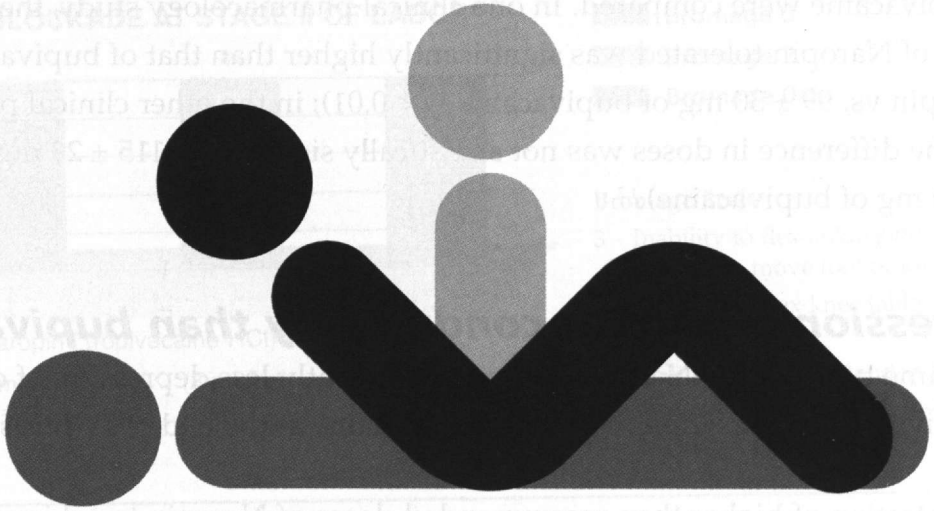

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Dose tolerability

- In two clinical pharmacology studies, equal infusion rates of Naropin™ (ropivacaine HCl) and bupivacaine were compared. In one clinical pharmacology study, the mean maximum IV dose of Naropin tolerated was significantly higher than that of bupivacaine (124 ± 38 mg of Naropin vs. 99 ± 30 mg of bupivacaine, $p < 0.01$); in the other clinical pharmacology study, the difference in doses was not statistically significant (115 ± 29 mg of Naropin vs. 103 ± 30 mg of bupivacaine).[1,2]

Less depression of cardiac conductivity than bupivacaine

- In the same two studies, Naropin caused significantly less depression of cardiac conductivity (less QRS widening) than bupivacaine at the end of IV infusion.*[1,2]

- Administration of higher than recommended doses of Naropin to achieve greater motor blockade or increased duration of sensory blockade may negate the advantages of Naropin's favorable cardiovascular depression profile in the event that an inadvertent intravascular injection occurs. Naropin should be administered in incremental doses.

For obstetrical anesthesia, eg, cesarean section, the 5.0 mg/mL (0.5%) Naropin solution in doses up to 150 mg is recommended. As with all local anesthetics, Naropin should be administered in incremental doses.

Reactions to Naropin are characteristic of those associated with other amide-type local anesthetics. Most adverse events reported in clinical trials were mild and transient, and may reflect the surgical procedures, patient characteristics (including disease) and/or medications administered. Adverse events reported with an incidence >5% were hypotension, fetal bradycardia, nausea, bradycardia, vomiting, paresthesia, and back pain.

Solutions of Naropin should not be used for the production of obstetrical paracervical block anesthesia, retrobulbar block or spinal anesthesia (subarachnoid block) due to insufficient data to support such use. Intravenous regional anesthesia (Bier block) should not be performed due to lack of clinical experience and the risk of attaining toxic blood levels of Naropin. For further information, please see attached brief summary of prescribing information.

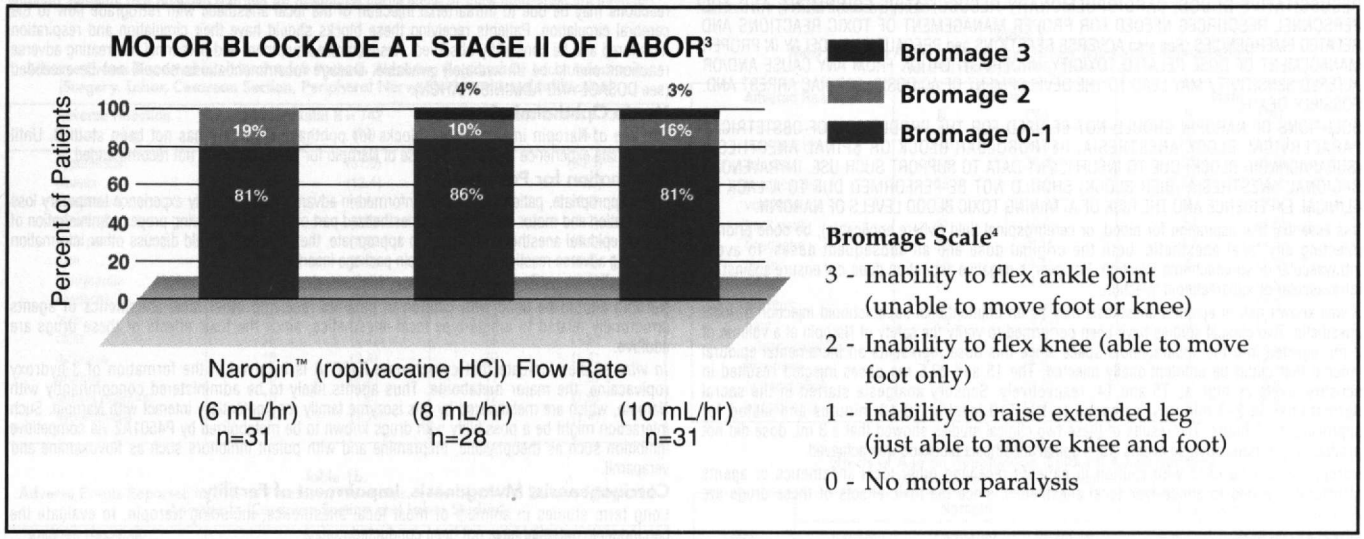
*Not an indicated use of Naropin. Please see a brief summary of prescribing information on the following pages.

REFERENCES: **1.** Scott DB, et al. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg*. 1989;69:563-569. **2.** Knudsen K, et al. Presented at the XIV annual ESRA congress, Prague, September 13-16, 1995. **3.** Data on file. Report No. 802 550-LC-0294-01. **4.** Bromage PR. *Epidural Analgesia*. Philadelphia: WB Saunders Company. 1978;144. **5.** Data on file. Report No. 802 550-LC-0283. **6.** Niesel HC, et al. Comparative study of epidural anesthesia in orthopedic surgery. *Anaesthesist*. 1993;42:605-611.

control

of motor blockade

Limited motor blockade with 2.0 mg/mL (0.2%)[3]



Fewer instrumental deliveries with Naropin than bupivacaine

- In a prospective meta-analysis of six double-blind studies, there were significantly fewer instrumental deliveries in mothers receiving Naropin as compared with bupivacaine ($p = 0.004$).[5]

Reliable management of acute pain

- Analgesia during labor was judged as "good" or "excellent" by 87% of patients with 2.0 mg/mL (0.2%) at 6 to 10 mL/h.[3]

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- Incidence of complete analgesia and complete muscle relaxation similar to bupivacaine 0.75%.[6]

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Naropin is contraindicated in patients with a known hypersensitivity to Naropin or to any local anesthetic agent of the amide type.

WARNINGS

FOR CESAREAN SECTION, THE 5 MG/ML (0.5%) NAROPIN SOLUTION IN DOSES UP TO 150 MG IS RECOMMENDED. AS WITH ALL LOCAL ANESTHETICS, NAROPIN SHOULD BE ADMINISTERED IN INCREMENTAL DOSES. SINCE NAROPIN SHOULD NOT BE INJECTED RAPIDLY IN LARGE DOSES, IT IS NOT RECOMMENDED FOR EMERGENCY SITUATIONS, WHERE A FAST ONSET OF SURGICAL ANESTHESIA IS NECESSARY. HISTORICALLY, PREGNANT PATIENTS WERE REPORTED TO HAVE A HIGH RISK FOR CARDIAC ARRHYTHMIAS, CARDIAC/CIRCULATORY ARREST AND DEATH WHEN BUPIVACAINE WAS INADVERTENTLY RAPIDLY INJECTED INTRAVENOUSLY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN THE DIAGNOSIS AND MANAGEMENT OF DOSE RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE **IMMEDIATE (WITHOUT DELAY)** AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (See also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

SOLUTIONS OF NAROPIN SHOULD NOT BE USED FOR THE PRODUCTION OF OBSTETRICAL PARACERVICAL BLOCK ANESTHESIA, RETROBULBAR BLOCK OR SPINAL ANESTHESIA (SUBARACHNOID BLOCK) DUE TO INSUFFICIENT DATA TO SUPPORT SUCH USE. INTRAVENOUS REGIONAL ANESTHESIA (BIER BLOCK) SHOULD NOT BE PERFORMED DUE TO A LACK OF CLINICAL EXPERIENCE AND THE RISK OF ATTAINING TOXIC BLOOD LEVELS OF NAROPIN.

It is essential that aspiration for blood, or cerebrospinal fluid (where applicable), be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does *not* ensure against an intravascular or subarachnoid injection.

A well-known risk of epidural anesthesia may be an unintentional subarachnoid injection of local anesthetic. Two clinical studies have been performed to verify the safety of Naropin at a volume of 3 mL injected into the subarachnoid space since this dose represents an incremental epidural volume that could be unintentionally injected. The 15 and 22.5 mg doses injected resulted in sensory levels as high as T5 and T4, respectively. Sensory analgesia started in the sacral dermatomes in 2-3 minutes, extended to the T10 level in 10-13 minutes and lasted for approximately 2 hours. The results of these two clinical studies showed that a 3 mL dose did not produce any serious adverse events when spinal anesthesia blockade was achieved.

Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

PRECAUTIONS

General

The safe and effective use of local anesthetics depends on proper dosage, correct technique, adequate precautions and readiness for emergencies.

Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (see WARNINGS and ADVERSE REACTIONS). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Injections should be made slowly and incrementally, with frequent aspirations before and during the injection to avoid intravascular injection. When a continuous catheter technique is used, syringe aspirations should also be performed before and during each supplemental injection. During the administration of epidural anesthesia, it is recommended that a test dose of a local anesthetic with a fast onset be administered initially and that the patient be monitored for central nervous system and cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. When clinical conditions permit, consideration should be given to employing local anesthetic solutions which contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Administration of higher than recommended doses of Naropin to achieve greater motor blockade or increased duration of sensory blockade may negate the advantages of Naropin's favorable cardiovascular depression profile in the event that an inadvertent intravascular injection occurs.

Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient. Debilitated, elderly patients, and acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. Local anesthetics should also be used with caution in patients with hypotension, hypovolemia or heart block.

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Because amide-type local anesthetics such as Naropin are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for malignant hyperthermia. Amide-type local anesthetics are not known to trigger this reaction. However, since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available.

Epidural Anesthesia

During epidural administration, Naropin should be administered in incremental doses of 3 to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given. When clinical conditions permit, the test dose should contain epinephrine (10 to 15 μg have been suggested) to serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart should be continuously monitored for a heart rate increase. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a rise in systolic blood pressure. A test dose of a short-acting amide anesthetic such as 30 to 40 mg of lidocaine is recommended to detect an unintentional intrathecal administration. This will be manifested within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

Use in Head and Neck Area

Small doses of local anesthetics injected into the head and neck area may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intraarterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see DOSAGE AND ADMINISTRATION).

Use in Ophthalmic Surgery

The use of Naropin in retrobulbar blocks for ophthalmic surgery has not been studied. Until appropriate experience is gained, the use of Naropin for such surgery is not recommended.

Information for Patients

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity in the anesthetized part of the body following proper administration of lumbar epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the Naropin package insert.

Clinically Significant Drug-Drug Interactions

Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

In vitro studies indicate that cytochrome P4501A is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. Thus agents likely to be administered concomitantly with Naropin, which are metabolized by this isozyme family may potentially interact with Naropin. Such interaction might be a possibility with drugs known to be metabolized by P4501A2 via competitive inhibition such as theophylline, imipramine and with potent inhibitors such as fluvoxamine and verapamil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals of most local anesthetics, including Naropin, to evaluate the carcinogenic potential have not been conducted.

Weak mutagenic activity was seen in the mouse lymphoma test. Mutagenicity was not noted in the other assays, demonstrating that the weak signs of *in vitro* activity in the mouse lymphoma test were not manifest under diverse *in vivo* conditions.

Studies performed with ropivacaine in rats did not demonstrate an effect on fertility or general reproductive performance over two generations.

Pregnancy Category B

Teratogenicity studies in rats and rabbits did not show evidence of any adverse effects on organogenesis or early fetal development in rats or rabbits. The doses used were approximately equal to 5 and 2.5 times, respectively, the maximum recommended human dose (250 mg) based on body weight. There were no treatment related effects on late fetal development, parturition, lactation, neonatal viability or growth of the offspring in 2 perinatal and postnatal studies in rats, at dose levels up to approximately 5 times the maximum recommended human dose based on body weight. In another study with a higher dose, 23 mg/kg, an increased pup loss was seen during the first 3 days postpartum, which was considered secondary to impaired maternal care due to maternal toxicity.

There are no adequate and well-controlled studies in pregnant women of the effects of Naropin on the developing fetus. Naropin should be used during pregnancy only if clearly needed. This does not preclude the use of Naropin after fetal organogenesis is completed or for obstetrical anesthesia or analgesia. (See Labor and Delivery).

Labor and Delivery

Local anesthetics, including Naropin, rapidly cross the placenta, and when used for epidural block can cause varying degrees of maternal, fetal and neonatal toxicity (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS). The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia with Naropin for obstetrical pain relief. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural anesthesia has been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Spontaneous vertex delivery occurred more frequently in patients receiving Naropin than in those receiving bupivacaine.

Nursing Mothers

Some local anesthetic drugs are excreted in human milk and caution should be exercised when they are administered to a nursing woman. The excretion of ropivacaine or its metabolites in human milk has not been studied. Based on the milk/plasma concentration ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the mother. Assuming that the milk/plasma concentration in humans is of the same order, the total Naropin dose to which the baby is exposed by breast feeding is far lower than by exposure in utero in pregnant women at term (see PRECAUTIONS).

Pediatric Use

No special studies were conducted in pediatrics. Until further experience is gained in children younger than 12 years, administration of Naropin in this age group is not recommended.

ADVERSE REACTIONS

Reactions to Naropin are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs may be associated with

excessive plasma levels, which may be due to overdosage, unintentional intravascular injection or slow metabolic degradation.

The reported adverse events are derived from controlled clinical trials in the U.S. and other countries. The reference drug was usually bupivacaine. The studies were conducted using a variety of premedications, sedatives, and surgical procedures of varying length. Most adverse events reported were mild and transient, and may reflect the surgical procedures, patient characteristics (including disease) and/or medications administered.

Of the 3558 patients enrolled in the clinical trials, 2404 were exposed to Naropin. Each patient was counted once for each type of adverse event.

Incidence >5%

hypotension, fetal bradycardia, nausea, bradycardia, vomiting, paresthesia, back pain

Incidence 1-5%

fever, headache, pain, postoperative complications, urinary retention, dizziness, pruritus, rigors, anemia, hypertension, tachycardia, anxiety, oliguria, hypoesthesia, chest pain, fetal disorders including tachycardia and fetal distress, and neonatal disorders including jaundice, tachypnea, fever, respiratory disorder and vomiting

A comparison has been made between Naropin and bupivacaine for events with a frequency of 1% or greater. Tables 1a and 1b show adverse events (number and percentage) in patients exposed to *similar doses* in double-blind controlled clinical trials. In the trials, Naropin was administered as an epidural anesthetic/analgesic for surgery, labor, or cesarean section. In addition, patients that received Naropin for peripheral nerve block or local infiltration are included.

Table 1a.
Adverse Events Reported in ≥1% of Adult Patients Receiving Regional Or Local Anesthesia (Surgery, Labor, Cesarean Section, Peripheral Nerve Block and Local Infiltration)

Adverse Reaction	Naropin total N = 742		Bupivacaine total N = 737	
	N	(%)	N	(%)
hypotension	237	(31.9)	225	(30.5)
nausea	92	(12.4)	96	(13.0)
paresthesia	51	(6.9)	44	(6.0)
vomiting	48	(6.5)	38	(5.2)
back pain	36	(4.9)	47	(6.4)
pain	39	(5.3)	40	(5.4)
bradycardia	32	(4.3)	38	(5.2)
headache	23	(3.1)	26	(3.5)
fever	25	(3.4)	20	(2.7)
chills	16	(2.2)	14	(1.9)
dizziness	18	(2.4)	10	(1.4)
pruritus	16	(2.2)	11	(1.5)
urinary retention	10	(1.3)	12	(1.6)
hypoesthesia	8	(1.1)	10	(1.4)

Table 1b.
Adverse Events Reported in ≥1% of Fetuses or Neonates of Mothers Who Received Regional Anesthesia (Cesarean Section and Labor Studies)

Adverse Reaction	Naropin total N = 337		Bupivacaine total N = 317	
	N	(%)	N	(%)
fetal bradycardia	58	(17.2)	53	(16.7)
neonatal jaundice	12	(3.6)	12	(3.8)
neonatal tachypnea	8	(2.4)	11	(3.5)
fetal tachycardia	7	(2.1)	8	(2.5)
neonatal fever	6	(1.8)	8	(2.5)
fetal distress	4	(1.2)	8	(2.5)
neonatal respiratory distress	5	(1.5)	4	(1.3)
neonatal vomiting	5	(1.5)	1	(0.3)

Incidence <1%

The following list includes all adverse and intercurrent events which were recorded in more than one patient, but occurred at an overall rate of less than one percent, and were considered clinically relevant.

Application Site Reactions - injection site pain

Cardiovascular System - vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities

Female Reproductive - poor progression of labor, uterine atony

Gastrointestinal System - fecal incontinence, tenesmus

General and Other Disorders - hypothermia, malaise, asthenia, accident and/or injury

Hearing and Vestibular - tinnitus, hearing abnormalities

Heart Rate and Rhythm - extrasystoles, non-specific arrhythmias, atrial fibrillation

Liver and Biliary System - jaundice

Metabolic Disorders - hypokalemia, hypomagnesemia

Musculoskeletal System - myalgia, cramps

Myo/Endo/Pericardium - ST segment changes, myocardial infarction

Nervous System - tremor, Horner's syndrome, paresis, dyskinesia, neuropathy, vertigo, coma, convulsion, hypokinesia, hypotonia, ptosis, stupor

Psychiatric Disorders - agitation, confusion, somnolence, nervousness, amnesia, hallucination, emotional lability, insomnia, nightmares

Respiratory System - dyspnea, bronchospasm, coughing

Skin Disorders - rash, urticaria

Urinary System Disorders - urinary incontinence, urinary tract infection, micturition disorder

Vascular - deep vein thrombosis, phlebitis, pulmonary embolism

Vision - vision abnormalities

For the indication epidural anesthesia for surgery, the 15 most common adverse events were compared between different concentrations of Naropin and bupivacaine. Table 2 is based on data from trials in the U.S. and other countries where Naropin was administered as an epidural anesthetic for surgery.

Table 2. Common Events (Epidural Administration)

Adverse Reaction	Naropin						Bupivacaine			
	5 mg/mL total N=256		7.5 mg/mL total N=297		10 mg/mL total N=207		5 mg/mL total N=236		7.5 mg/mL total N=174	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
hypotension	99	(38.7)	146	(49.2)	113	(54.6)	91	(38.6)	89	(51.1)
nausea	34	(13.3)	68	(22.9)			41	(17.4)	36	(20.7)
bradycardia	29	(11.3)	58	(19.5)	40	(19.3)	32	(13.6)	25	(14.4)
back pain	18	(7.0)	23	(7.7)	34	(16.4)	21	(8.9)	23	(13.2)
vomiting	18	(7.0)	33	(11.1)	23	(11.1)	19	(8.1)	14	(8.0)
headache	12	(4.7)	20	(6.7)	16	(7.7)	13	(5.5)	9	(5.2)
fever	8	(3.1)	5	(1.7)	18	(8.7)	11	(4.7)		
chills	6	(2.3)	7	(2.4)	6	(2.9)	4	(1.7)	3	(1.7)
urinary retention	5	(2.0)	8	(2.7)	10	(4.8)	10	(4.2)		
paresthesia	5	(2.0)	10	(3.4)	5	(2.4)	7	(3.0)		
pruritus			14	(4.7)	3	(1.4)			7	(4.0)

Using data from the same studies, the number (%) of patients experiencing hypotension is displayed by patient age, drug and concentration in Table 4. In Table 3, the adverse events for Naropin are broken down by gender.

Table 3.
Most Common Adverse Events by Gender (Epidural Administration)
Total N: Females = 405, Males = 355

Adverse Reaction	Female		Male	
	N	(%)	N	(%)
hypotension	220	(54.3)	138	(38.9)
nausea	119	(29.4)	23	(6.5)
bradycardia	65	(16.0)	56	(15.8)
vomiting	59	(14.6)	8	(2.3)
back pain	41	(10.1)	23	(6.5)
headache	33	(8.1)	17	(4.8)
chills	18	(4.4)	5	(1.4)
fever	16	(4.0)	3	(0.8)
pruritus	16	(4.0)	1	(0.3)
pain	12	(3.0)	4	(1.1)
urinary retention	11	(2.7)	7	(2.0)
dizziness	9	(2.2)	4	(1.1)
hypoesthesia	8	(2.0)	2	(0.6)
paresthesia	8	(2.0)	10	(2.8)

Table 4.
Effects of Age on Hypotension (Epidural Administration)
Total N: Naropin = 760, bupivacaine = 410

AGE	Naropin						Bupivacaine			
	5 mg/mL		7.5 mg/mL		10 mg/mL		5 mg/mL		7.5 mg/mL	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<65	68	(32.2)	99	(43.2)	87	(51.5)	64	(33.5)	73	(48.3)
≥65	31	(68.9)	47	(69.1)	26	(68.4)	27	(60.0)	16	(69.6)

Systemic Reactions

The most commonly encountered acute adverse experiences that demand immediate countermeasures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total or High Spinal"). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Factors influencing plasma protein binding, such as acidosis, systemic diseases that alter protein production or competition with other drugs for protein binding sites, may diminish individual tolerance.

Central Nervous System Reactions

These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils.

The incidence of convulsions associated with the use of local anesthetics varies with the route of administration and the total dose administered. In a survey of studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1 percent of local anesthetic administrations.

Cardiovascular System Reactions

High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

Allergic Reactions

Allergic type reactions are rare and may occur as a result of sensitivity to the local anesthetic (see WARNINGS). These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Neurologic Reactions

The incidence of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose and concentration of local anesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the drug.

During lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and the physiological and physical effects of a dural puncture. These observations may include spinal block of varying magnitude (including high or total spinal block), hypotension secondary to spinal block, urinary retention, loss of bladder and bowel control (fecal and urinary incontinence), and loss of perineal sensation and sexual function. Signs and symptoms of subarachnoid block typically start within 2-3 minutes of injection. Doses of 15 and 22.5 mg of Naropin resulted in sensory levels as high as T5 and T4, respectively. Sensory analgesia started in the sacral dermatomes in 2-3 minutes and extended to the T10 level in 10-13 minutes and lasted for approximately 2 hours. Other neurological effects following unintentional subarachnoid administration during epidural anesthesia may include persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control, all of which may have slow, incomplete or no recovery. Headache, septic meningitis, meningismus, slowing of labor, increased incidence of forceps delivery, or cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid have been reported (see DOSAGE AND ADMINISTRATION discussion of Lumbar Epidural Block). A high spinal is characterized by paralysis of the arms, loss of consciousness, respiratory paralysis and bradycardia.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid or intravascular injection of local anesthetic solution. (See ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS.)

Management of Local Anesthetic Emergencies

The practitioner should be familiar with standard contemporary textbooks that address the management of local anesthetic emergencies. No specific information is available on the treatment of overdosage with Naropin; treatment should be symptomatic and supportive. Therapy with Naropin should be discontinued.

The first consideration is prevention, best accomplished by incremental injection of Naropin, careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection and during continuous infusion. At the first sign of change, oxygen should be administered.

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine or epinephrine to enhance myocardial contractile force).

The mean dosages of ropivacaine producing seizures, after intravenous infusion in dogs, nonpregnant and pregnant sheep were 4.9, 6.1 and 5.9 mg/kg, respectively. These doses were associated with peak arterial total plasma concentrations of 11.4, 4.3 and 5.0 μg/mL, respectively. In rats, the LD_{50} is 9.9 and 12 mg/kg by the intravenous route for males and females respectively.

In human volunteers given intravenous Naropin, the mean maximum tolerated total and free arterial plasma concentrations were 4.3 and 0.6 μg/mL respectively, at which time moderate CNS symptoms (muscle twitching) were noted.

Clinical data from patients experiencing local anesthetic induced convulsions demonstrated rapid development of hypoxia, hypercarbia and acidosis within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated, endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask.

The supine position is dangerous in pregnant women at term because of aorta-caval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels should be accomplished. Resuscitation of obstetrical patients may take longer than resuscitation of non-pregnant patients and closed-chest cardiac compression may be ineffective. Rapid delivery of the fetus may improve the response to resuscitative efforts.

DOSAGE AND ADMINISTRATION

The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered.

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention although regional anesthesia is frequently indicated in these patients. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly.

Use an adequate test dose (3-5 mL of a short acting local anesthetic solution containing epinephrine) prior to induction of complete block. This test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter. Allow adequate time for onset of anesthesia following administration of each test dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered. For specific techniques and procedures, refer to standard contemporary textbooks.

Dosage Recommendations

	Conc. mg/mL(%)	Volume mL	Dose mg	Onset min	Duration hours
SURGICAL ANESTHESIA					
Lumbar Epidural Administration	5.0 (0.5%)	15-30	75-150	15-30	2-4
	7.5 (0.75%)	15-25	113-188	10-20	3-5
Surgery	10.0 (1.0%)	15-20	150-200	10-20	4-6
Lumbar Epidural Administration Cesarean Section	5.0 (0.5%)	20-30	100-150	15-25	2-4
Thoracic Epidural Administration To establish block for postoperative pain relief	5.0 (0.5%)	5-15	25-75	10-20	n/a[1]
Major Nerve Block (e.g. brachial plexus block)	5.0 (0.5%)	35-50	175-250	15-30	5-8
Field Block (e.g.minor nerve blocks and infiltration)	5.0 (0.5%)	1-40	5-200	1-15	2-6
LABOR PAIN MANAGEMENT					
Lumbar Epidural Administration					
Initial Dose	2.0 (0.2%)	10-20	20-40	10-15	0.5-1.5
Continuous infusion[2]	2.0 (0.2%)	6-14 mL/h	12-28 mg/h	n/a[1]	n/a[1]
Incremental injections (top-up)[2]	2.0 (0.2%)	10-15 mL/h	20-30 mg/h	n/a[1]	n/a[1]
POSTOPERATIVE PAIN MANAGEMENT					
Lumbar Epidural Administration Continuous infusion[3]	2.0 (0.2%)	6-10 mL/h	12-20 mg/h	n/a[1]	n/a[1]
Thoracic Epidural Administration Continuous infusion[3]	2.0 (0.2%)	4-8 mL/h	8-16 mg/h	n/a[1]	n/a[1]
Infiltration	2.0 (0.2%)	1-100	2-200	1-5	2-6
(e.g. minor nerve block)	5.0 (0.5%)	1-40	5-200	1-5	2-6

1 = Not Applicable

2 = Median dose of 21 mg per hour was administered by continuous infusion or by incremental injections (top-ups) over a median delivery time of 5.5 hours.

3 = Cumulative doses up to 770 mg of Naropin over 24 hours for postoperative pain management have been well tolerated in adults.

The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures reflect the expected average dose range needed. For other local anesthetic techniques standard current textbooks should be consulted.

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Experience to date indicates that a cumulative dose of up to 770 mg Naropin administered over 24 hours is well tolerated in adults when used for postoperative pain management.

For treatment of postoperative pain, the following technique can be recommended: If regional anesthesia was not used intraoperatively, then an epidural block with Naropin is induced via an epidural catheter. Analgesia is maintained with an infusion of Naropin, 2 mg/mL (0.2%). Clinical studies have demonstrated that infusion rates of 6-10 mL (12-20 mg), per hour provide adequate analgesia with only slight and nonprogressive motor block in cases of moderate to severe postoperative pain. If patients require additional pain relief, higher infusion rates of up to 14 mL (28 mg) per hour may be used. With this technique a significant reduction in the need for opioids was demonstrated. Clinical experience supports the use of Naropin epidural infusions for up to 24 hours.

HOW SUPPLIED

Naropin™ Astra E-Z Off® Single Dose Vials:		
7.5 mg/mL	10 mL	NDC 0186-0867-41
10.0 mg/mL	10 mL	NDC 0186-0868-41
Naropin™ Single Dose Vials:		
2.0 mg/mL	20 mL	NDC 0186-0859-51
5.0 mg/mL	30 mL	NDC 0186-0863-61
7.5 mg/mL	20 mL	NDC 0186-0867-51
10.0 mg/mL	20 mL	NDC 0186-0868-51
Naropin™ Single Dose Ampules:		
2.0 mg/mL	20 mL	NDC 0186-0859-52
5.0 mg/mL	30 mL	NDC 0186-0863-62
7.5 mg/mL	20 mL	NDC 0186-0867-52
10.0 mg/mL	20 mL	NDC 0186-0868-52
Naropin™ Single Dose Infusion Bottles:		
2.0 mg/mL	100 mL	NDC 0186-0859-81
2.0 mg/mL	200 mL	NDC 0186-0859-91
Naropin™ Sterile-Pak® Single Dose Vials:		
2.0 mg/mL	20 mL	Product Code 0859-59
5.0 mg/mL	30 mL	Product Code 0863-69
7.5 mg/mL	20 mL	Product Code 0867-59
10.0 mg/mL	20 mL	Product Code 0868-59

The solubility of ropivacaine is limited at pH above 6. Thus care must be taken as precipitation may occur if Naropin is mixed with alkaline solutions.

Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection since they have been related to incidents of swelling and edema.

When chemical disinfection of the container surface is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. It is recommended that chemical disinfection be accomplished by wiping the ampule or vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use. When a container is required to have a sterile outside, a Sterile-Pak should be chosen. Glass containers may, as an alternative, be autoclaved once. Stability has been demonstrated using a targeted F_0 of 7 minutes at 121°C.

Solutions should be stored at controlled room temperature 20° – 25°C (68° – 77°F) [see USP].

These products are intended for single use and are free from preservatives. Any solution remaining from an opened container should be discarded promptly. In addition, continuous infusion bottles should not be left in place for more than 24 hours.

Caution: Federal law prohibits dispensing without prescription.