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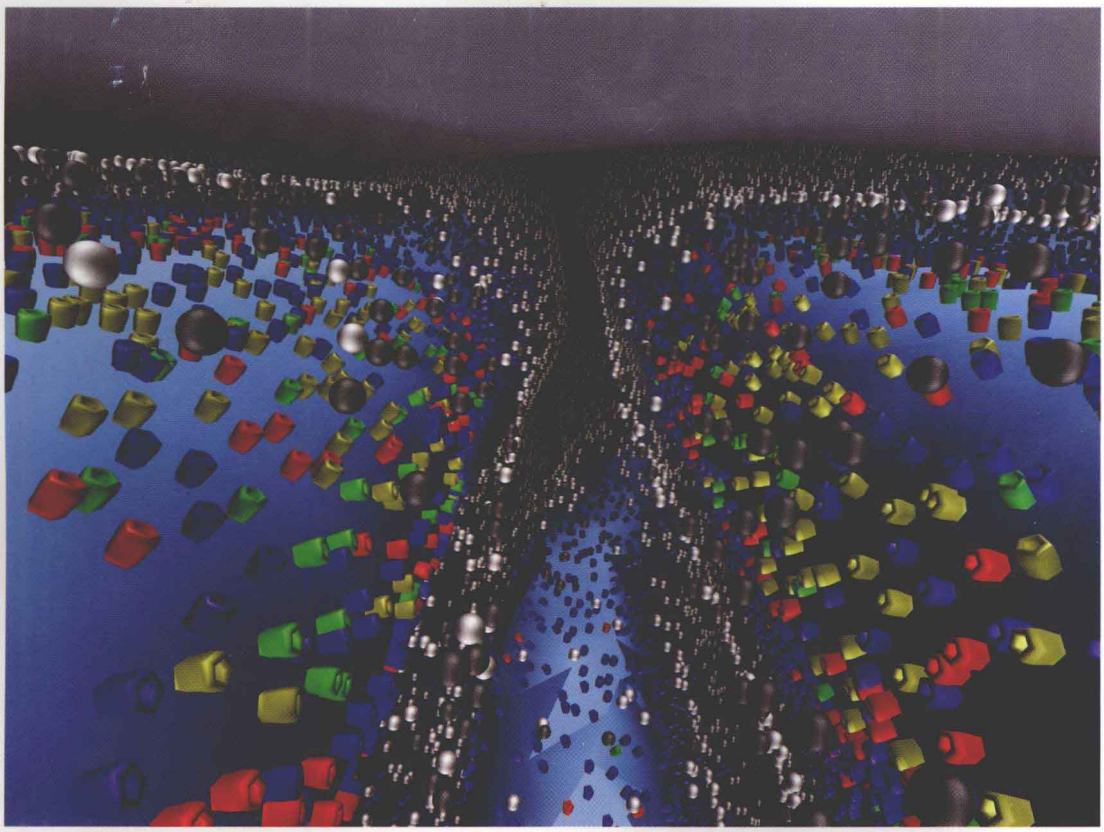
ANESTHESIA & ANALGESIA®



IARS International Anesthesia Research Society

Every minute, the loss of a mother shatters a family and reduces the life-chances of remaining children.

Above quote: The Lancet, Issue 380

FACT: Pregnancy and childbirth are the leading causes of death and disability among women worldwide. In some countries, a woman's chance of death during childbirth is one in seven. Worldwide, nearly half a million women will die each year from childbirth related complications.

FACT: One in 10 newborns will require resuscitation at birth. Each year, millions of babies are poorly resuscitated, leading to lifelong disability or death.

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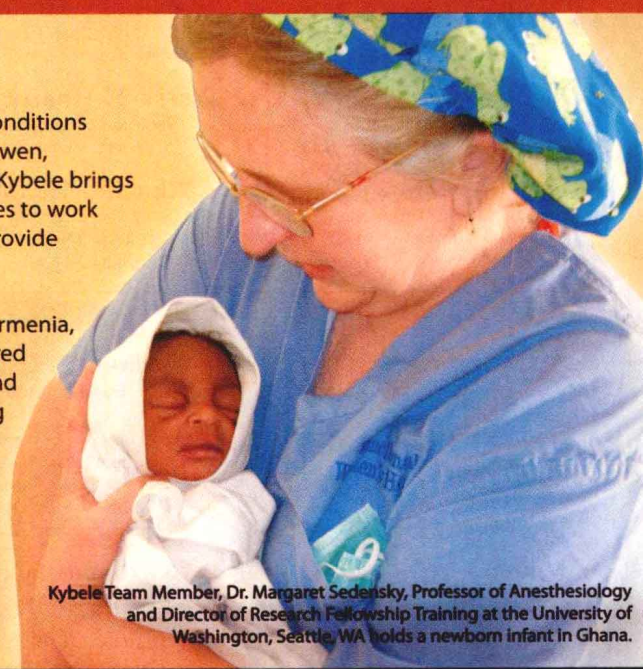

Kybele Team Member, Dr. Margaret Sedensky, Professor of Anesthesiology and Director of Research Fellowship Training at the University of Washington, Seattle, WA holds a newborn infant in Ghana.

Kybele is proudly supported by the Society for Obstetric Anesthesia and Perinatology (SOAP), the Obstetric Anaesthetists' Association (OAA), the International Anesthesia Research Society (IARS), the International Association for the Study of Pain (IASP), local and national foundations, corporations, academic institutions, medical professionals and individuals.

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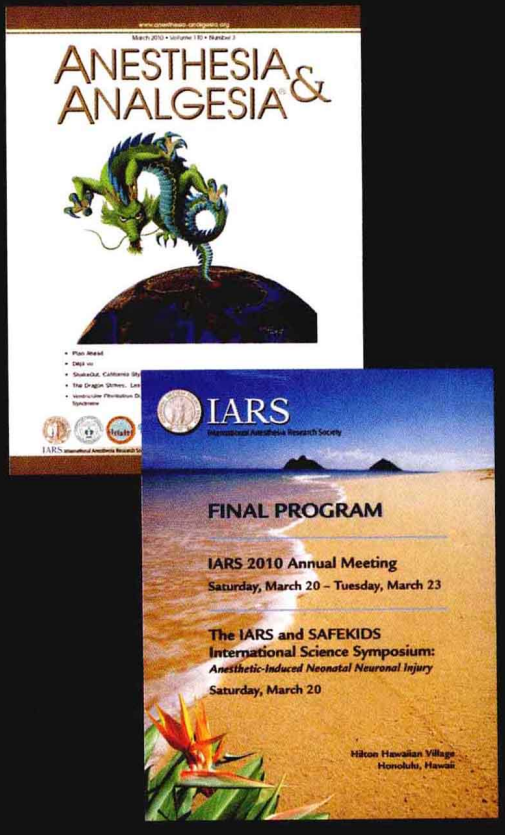

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New Safety Information

There have been adverse event reports of chondrolysis in patients receiving intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures. NAROPIN is not approved for this use. Please see dosage and administration details in Prescribing Information at www.naropin-us.com.

Please see accompanying brief summary of Prescribing Information.

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BRIEF SUMMARY

INDICATIONS AND USAGE Naropin is indicated for the production of local or regional anesthesia for surgery and for acute pain management. Surgical Anesthesia: epidural block for surgery including cesarean section; major nerve block; local infiltration. Acute Pain Management: epidural continuous infusion or intermittent bolus, e.g., postoperative or labor; local infiltration.

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

WARNINGS In performing Naropin blocks, unintended intravenous injection is possible and may result in cardiac arrhythmia or cardiac arrest. The potential for successful resuscitation has not been studied in humans. There have been rare reports of cardiac arrest during the use of Naropin for epidural anesthesia or peripheral nerve blockade, the majority of which occurred after unintentional accidental intravascular administration in elderly patients and in patients with concomitant heart disease. In some instances, resuscitation has been difficult. Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the probability of a successful outcome. Naropin should be administered in incremental 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 0.75% bupivacaine (another member of the amino amide class of local anesthetics) was inadvertently rapidly injected intravenously. Prior to receiving major blocks the general condition of the patient should be optimized and the patient should have an i.v. line inserted. All necessary precautions should be taken to avoid intravascular injection. Local anesthetics should only be administered by clinicians who are well versed in the diagnosis and management of dose-related toxicity and other acute emergencies that may arise from the block to be employed, and then only after ensuring 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, PRECAUTIONS, and MANAGEMENT OF LOCAL ANESTHETIC EMERGENCIES). 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 ropivacaine. Intra-articular infusions of local anesthetics following arthroscopic and other surgical procedures is an unapproved use, and there have been post-marketing reports of chondrolysis in patients receiving such infusions. The majority of reported cases of chondrolysis have involved the shoulder joint; cases of gleno-humeral chondrolysis have been described in pediatric and adult patients following intra-articular infusions of local anesthetics with and without epinephrine for periods of 48 to 72 hours. There is insufficient information to determine whether shorter infusion periods are not associated with these findings. The time of onset of symptoms, such as joint pain, stiffness and loss of motion can be variable, but may begin as early as the 2nd month after surgery. Currently, there is no effective treatment for chondrolysis; patients who experienced chondrolysis have required additional diagnostic and therapeutic procedures and some required arthroplasty or shoulder replacement. 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. Anesthesia to pinprick 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. Patients treated with class III antiarrhythmic drugs (e.g., amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be 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 events. 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 result in cardiovascular depression, particularly in the event of inadvertent intravascular injection. Tolerance to elevated blood levels varies with the physical condition of the patient. Debilitated, elderly patients and acutely ill patients 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 ropivacaine 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 (MH). 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 MH 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 an appropriate dose of epinephrine 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 shortacting amide anesthetic such as 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 Brachial Plexus Block:** Ropivacine plasma concentrations may approach the threshold for central nervous system toxicity after the administration of 300 mg of ropivacaine for brachial plexus block. Caution should be exercised when using the 300 mg dose. (See OVERDOSAGE.) The dose for a major nerve block must be adjusted according to the site of administration and patient status. Supraclavicular brachial plexus blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anesthetic used. **Use in Peripheral Nerve Block:** Major peripheral nerve blocks may result in the administration of a large volume of local anesthetic in highly vascularized areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption, which can lead to high plasma concentrations. **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 intra-arterial 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. **Drug Interactions:** Specific trials studying the interaction between ropivacaine and class III antiarrhythmic drugs (e.g., amiodarone) have not been performed, but caution is advised (see WARNINGS). 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. Cytochrome P4501A2 is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. *In vivo*, the plasma clearance of ropivacaine was reduced by 70% during coadministration of fluvoxamine (25 mg bid for 2 days), a selective and potent CYP1A2 inhibitor. Thus strong inhibitors of cytochrome P4501A2, such as fluvoxamine, given concomitantly during administration of Naropin, can interact with Naropin leading to increased ropivacaine plasma levels. Caution should be exercised when CYP1A2 inhibitors are coadministered. Possible interactions with drugs known to be metabolized by CYP1A2 via competitive inhibition such as theophylline and imipramine may also occur. Coadministration of a selective and potent inhibitor of CYP3A4, ketoconazole (100 mg bid for 2 days with ropivacaine infusion administered 1 hour after ketoconazole) caused a 15% reduction in *in-vivo* plasma clearance of ropivacaine. **Pregnancy Category B:** There are no adequate or well-controlled studies in pregnant women of the effects of Naropin on the developing fetus. Naropin should only be used during pregnancy if the benefits outweigh the risk. **Labor and Delivery:** Local anesthetics, including ropivacaine, rapidly cross the placenta, and when used for epidural block can cause varying degrees of maternal, fetal and neonatal toxicity (see CLINICAL PHARMACOLOGY and 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 patient'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:** The safety and efficacy of Naropin in pediatric patients have not been established. **Geriatric Use:** Of the 2,978 subjects that were administered Naropin Injection in 71 controlled and uncontrolled clinical studies, 803 patients (27%) were 65 years of age or older, which includes 127 patients (4%) 75 years of age and over. Naropin Injection was found to be safe and effective in the patients in these studies. Clinical data in one published article indicate that differences in various pharmacodynamic measures were observed with increasing age. In one study, the upper level of analgesia increased with age, the maximum decrease of mean arterial pressure (MAP) declined with age during the first hour after epidural administration, and the intensity of motor blockade increased with age. This drug and its metabolites are known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Elderly patients are more likely to have decreased hepatic, renal, or cardiac function, as well as concomitant disease. Therefore, care should be taken in dose selection, starting at the low end of the dosage range, and it may be useful to monitor renal function. (See PHARMACOKINETICS, Elimination.)

ADVERSE REACTIONS Reactions to ropivacaine are characteristic of those associated with other amidetype 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 clinical studies conducted in the U.S. and other countries. The reference drug was usually bupivacaine. The studies used a variety of premedications, sedatives, and surgical procedures of varying length. A total of 3,988 patients have been exposed to Naropin at concentrations up to 1.0% in clinical trials. Each patient was counted once for each type of adverse event. **Incidence ≥5%:** For the indications of epidural administration in surgery, cesarean section, postoperative pain management, peripheral nerve block, and local infiltration, the following treatment-emergent adverse events were reported with an incidence of ≥5% in all clinical studies (N=3988): hypotension (37.0%), nausea (24.8%), vomiting (11.6%), bradycardia (9.3%), fever (9.2%), pain (8.0%), postoperative complications (7.1%), anemia (6.1%), paresthesia (5.6%), headache (5.1%), pruritus (5.1%), and back pain (5.0%). **Incidence 1-5%:** Urinary retention, dizziness, rigors, hypertension, tachycardia, anxiety, oliguria, hypoesthesia, chest pain, hypokalemia, dyspnea, cramps, and urinary tract infection. **Incidence in Controlled Clinical Trials:** The reported adverse events are derived from controlled clinical studies with Naropin (concentrations ranged from 0.125% to 1.0% for Naropin and 0.25% to 0.75% for bupivacaine) in the U.S. and other countries involving 3,094 patients. Tables 3A and 3B list adverse events (number and percentage) that occurred in at least 1% of Naropin-treated patients in these studies. The majority of patients receiving concentrations higher than 5.0 mg/mL (0.5%) were treated with Naropin.

Table 3A
Adverse Events Reported in ≥1% of Adult Patients Receiving Regional or Local Anesthesia
(Surgery, Labor, Cesarean Section, Post-Operative Pain Management, Peripheral Nerve Block and Local Infiltration)

Adverse Reaction	Naropin total N=1661		Bupivacaine total N=1433	
	N	(%)	N	(%)
Hypotension	536	(32.3)	408	(28.5)
Nausea	283	(17.0)	207	(14.4)
Vomiting	117	(7.0)	88	(6.1)
Bradycardia	96	(5.8)	73	(5.1)
Headache	84	(5.1)	68	(4.7)
Paresthesia	82	(4.9)	57	(4.0)
Back pain	73	(4.4)	75	(5.2)
Pain	71	(4.3)	71	(5.0)
Pruritus	63	(3.8)	40	(2.8)
Fever	61	(3.7)	37	(2.6)
Dizziness	42	(2.5)	23	(1.6)
Rigors (Chills)	42	(2.5)	24	(1.7)
Postoperative complications	41	(2.5)	44	(3.1)
Hypoesthesia	27	(1.6)	24	(1.7)
Urinary retention	23	(1.4)	20	(1.4)
Progression of labor poor/failed	23	(1.4)	22	(1.5)
Anxiety	21	(1.3)	11	(0.8)
Breast disorder, breast-feeding	21	(1.3)	12	(0.8)
Rhinitis	18	(1.1)	13	(0.9)

Table 3B
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=1661		Bupivacaine total N=1433	
	N	(%)	N	(%)
Fetal bradycardia	77	(12.1)	68	(11.9)
Neonatal jaundice	49	(7.7)	47	(8.2)
Neonatal complication-NOS	42	(6.6)	38	(6.6)
Apgar score low	18	(2.8)	14	(2.4)
Neonatal respiratory disorder	17	(2.7)	18	(3.1)
Neonatal tachypnea	14	(2.2)	15	(2.6)
Neonatal fever	13	(2.0)	14	(2.4)
Fetal tachycardia	13	(2.0)	12	(2.1)
Fetal distress	11	(1.7)	10	(1.7)
Neonatal infection	10	(1.6)	8	(1.4)
Neonatal hypoglycemia	8	(1.3)	16	(2.8)

OVERDOSAGE Acute emergencies from local anesthetics are generally related to high plasma levels encountered, or large doses administered, 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: Therapy with Naropin should be discontinued at the first sign of toxicity. No specific information is available for the treatment of toxicity with Naropin; therefore, treatment should be symptomatic and supportive. 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 and during continuous infusion. At the first sign of change in mental status, 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. Circulation should be assisted as necessary. 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). Should cardiac arrest occur, prolonged resuscitative efforts may be required to improve the probability of a successful outcome. 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 human volunteers given intravenous Naropin, the mean (min-max) maximum tolerated total and free arterial plasma concentrations were 4.3 (3.4-5.3) and 0.6 (0.3-0.9) 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 aortocaval 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 nonpregnant patients and closed-chest cardiac compression may be ineffective. Rapid delivery of the fetus may improve the response to resuscitative efforts.

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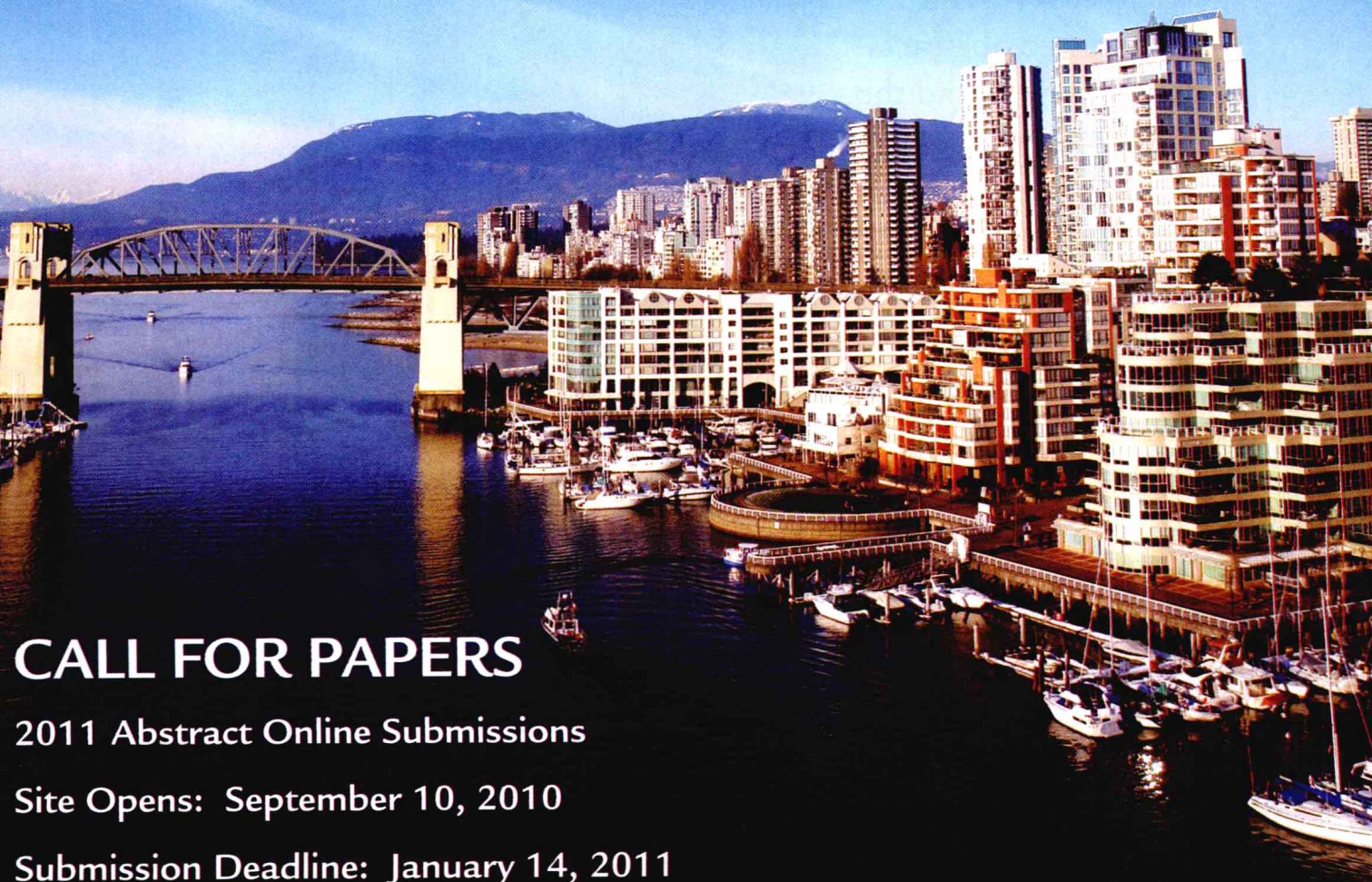

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Site Opens: September 10, 2010

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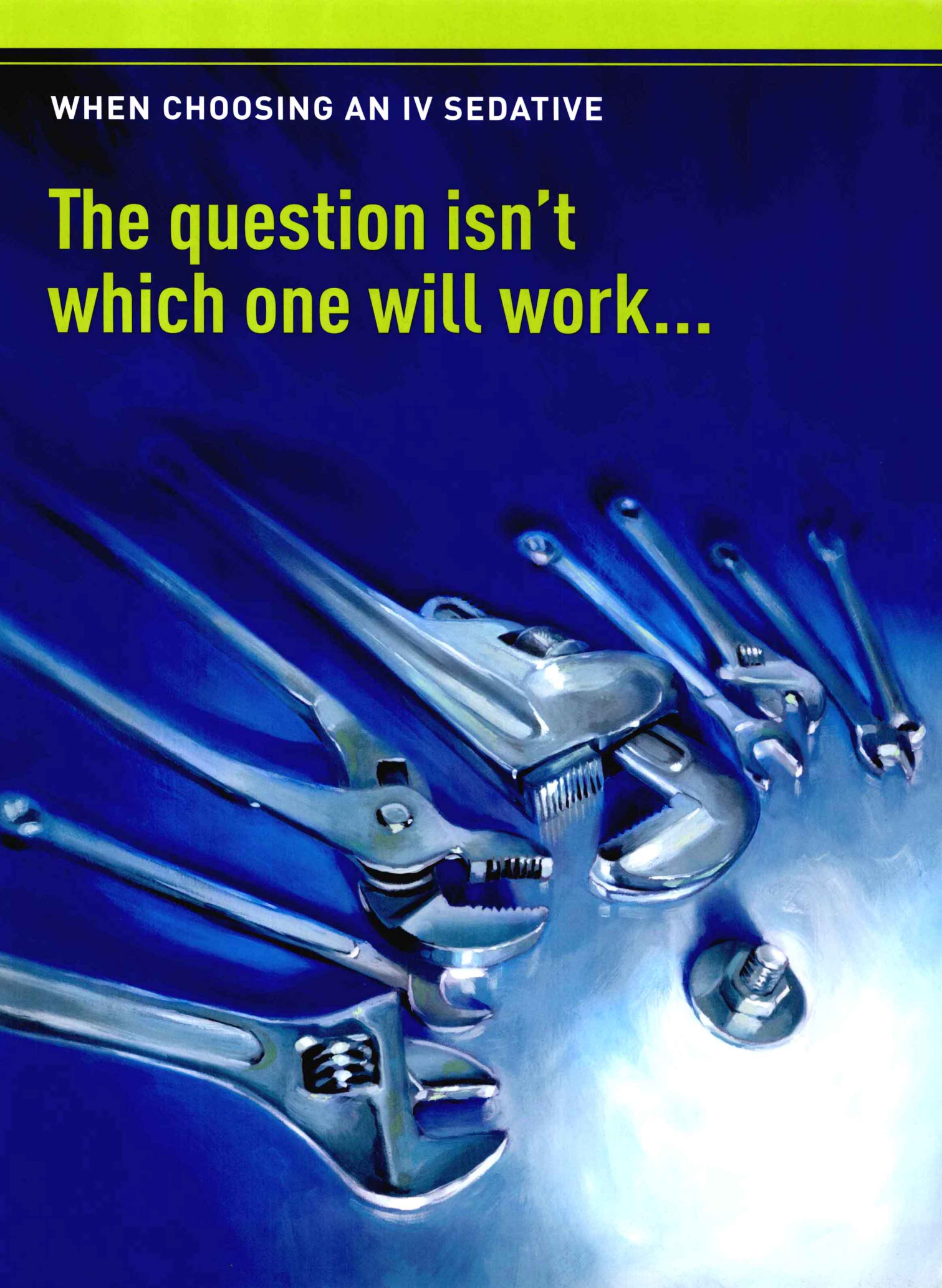
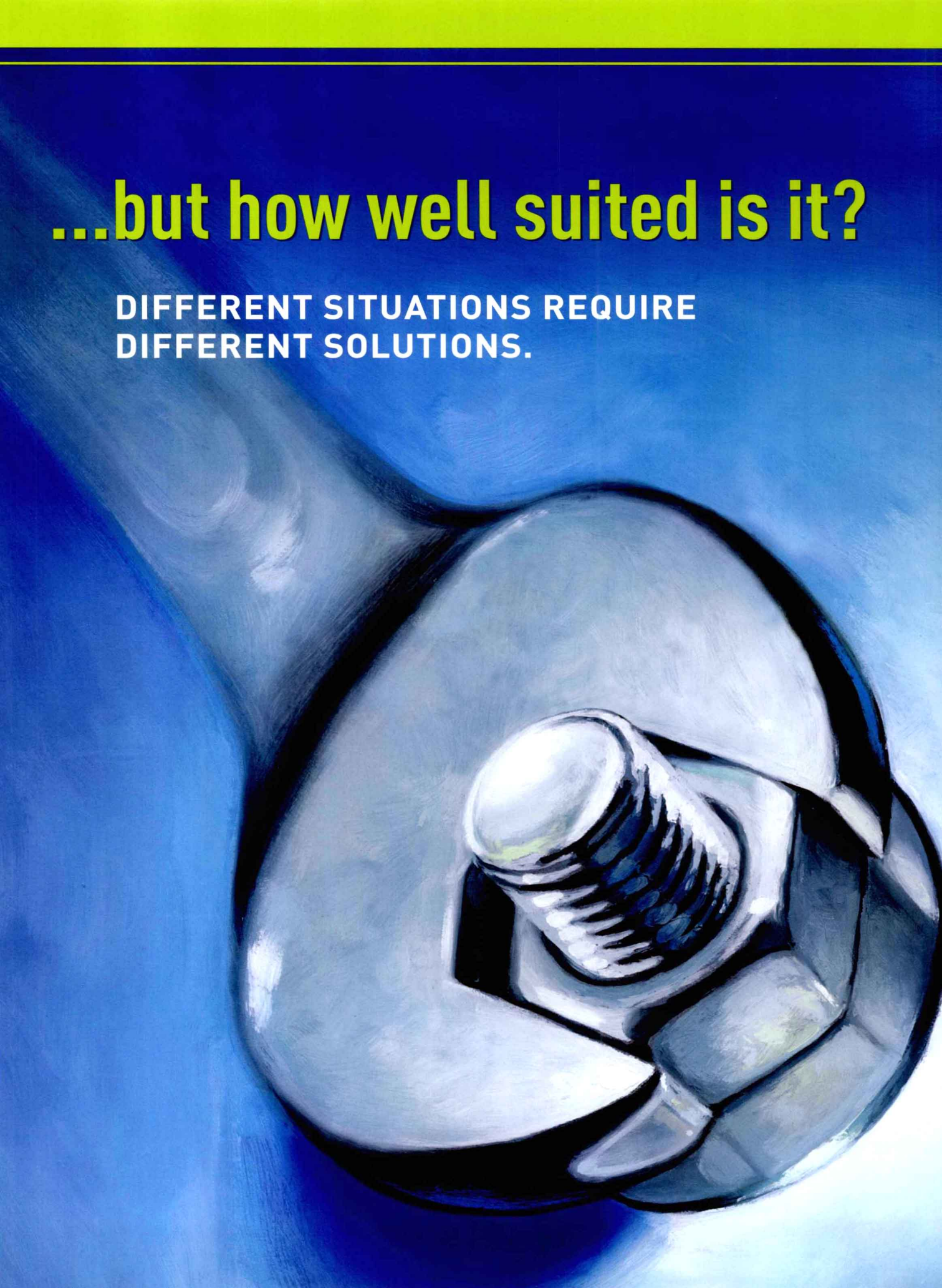
WHEN CHOOSING AN IV SEDATIVE

The question isn't which one will work...



...but how well suited is it?

DIFFERENT SITUATIONS REQUIRE DIFFERENT SOLUTIONS.



FASTEST GROWING IV SEDATIVE[1]

A right fit

FOR TODAY'S SEDATION MANAGEMENT PRACTICES

- The first and only alpha$_2$ agonist indicated for sedation[2,3]
  - —Nonintubated patients prior to and during surgical and other procedures[2]
  - —Intubated and mechanically ventilated patients during treatment in an intensive care setting[2]
- Can be used alone or in combination with other sedatives or opioid analgesics to provide sedation and added patient comfort.[2]
- Should be administered by continuous infusion not to exceed 24 hours.[2]
- Effective for intubated patients not just before—but also during—and after extubation.[2]
- More than 4.5 million vials administered to millions of patients since launch.[4]

IMPORTANT PRECEDEX SAFETY INFORMATION

- Clinically significant episodes of bradycardia, sinus arrest and hypotension have been associated with Precedex infusion and may necessitate medical intervention.
- Moderate blood pressure and heart rate reductions should be anticipated when initiating sedation with Precedex.

Please see the brief summary of Prescribing Information on adjacent page.

Precedex®
(dexmedetomidine HCl Injection)

The right fit

FOR TODAY'S SEDATION MANAGEMENT PRACTICES

FASTEST GROWING IV SEDATIVE[1]

Precedex®
(dexmedetomidine HCl Injection)

For step-by-step instructions on how to start using Precedex and what to expect, please visit us at **www.Precedex.com.**

- Moderate blood pressure and heart rate reductions should be anticipated when initiating sedation with Precedex.[2]
- Clinically significant episodes of bradycardia and sinus arrest have occurred in young, healthy volunteers with high vagal tone or with different routes of administration such as rapid intravenous or bolus administration.[2]
- Transient hypertension has been observed primarily during the administration of the loading dose. Treatment has generally not been necessary, although a reduction in loading dose infusion rate may be desirable.[2]
- Hypotension and bradycardia can occur and may necessitate medical intervention such as
  - —Decreasing or stopping Precedex infusion
  - —Increasing rate of IV fluid administration
  - —Elevating lower extremities
  - —Administering pressor agents such as atropine, ephedrine or glycopyrrolate[2]
- Use with caution in patients with advanced heart block or severe ventricular dysfunction.[2]
- The most common adverse effects (incidence >2%) are hypotension, bradycardia and dry mouth.[2]

Please see the brief summary of Prescribing Information on adjacent page.

References:
1. Based on increases in weight of active ingredient sold (either mcg or mg). IMS Health National Sales Perspective 2Q 2009. US nonretail market, all channels injectables.
2. Precedex [package insert]. Lake Forest, IL: Hospira, Inc; 2008. **3.** Kamibayashi T, Maze M. Clinical uses of α_2-adrenergic agonists. *Anesthesiology.* 2000;93:1345-1349.
4. Data on file. Hospira, Inc.

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Precedex®

(dexmedetomidine hydrochloride injection)

For Intravenous Use] Only

To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc. at 1-800-441-4100 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

1 INDICATIONS AND USAGE

1.1 Intensive Care Unit Sedation

Precedex® is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Precedex should be administered by continuous infusion not to exceed 24 hours.

Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Precedex prior to extubation.

1.2 Procedural Sedation

Precedex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Drug Administration

Precedex should be administered only by persons skilled in the management of patients in the intensive care or operating room setting. Due to the known pharmacological effects of Precedex, patients should be continuously monitored while receiving Precedex.

5.2 Hypotension, Bradycardia, and Sinus Arrest

Clinically significant episodes of bradycardia and sinus arrest have been reported with Precedex administration in young, healthy volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration.

Reports of hypotension and bradycardia have been associated with Precedex infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of Precedex, increasing the rate of intravenous fluid administration, elevation of the lower extremities, and use of pressor agents. Because Precedex has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (e.g., glycopyrrolate, atropine) should be considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine were effective in the treatment of most episodes of Precedex-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

Caution should be exercised when administering Precedex to patients with advanced heart block and/or severe ventricular dysfunction. Because Precedex decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension and in elderly patients.

In situations where other vasodilators or negative chronotropic agents are administered, co-administration of Precedex could have an additive pharmacodynamic effect and should be administered with caution.

5.3 Transient Hypertension

Transient hypertension has been observed primarily during the loading dose in association with the initial peripheral vasoconstrictive effects of Precedex. Treatment of the transient hypertension has generally not been necessary, although reduction of the loading infusion rate may be desirable.

5.4 Arousability

Some patients receiving Precedex have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.

5.5 Withdrawal

Intensive Care Unit Sedation

If Precedex were to be administered for more than 24 hours and stopped abruptly, withdrawal symptoms similar to those reported for another alpha-2-adrenergic agent, clonidine, may result. These symptoms include nervousness, agitation, and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

Procedural Sedation

Withdrawal symptoms were not seen after discontinuation of short term infusions of Precedex (<6 hours).

5.6 Hepatic Impairment

Since Precedex clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function [*see Dosage and Administration (2.2)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Use of Precedex has been associated with the following serious adverse reactions:

- Hypotension, bradycardia and sinus arrest [*see Warnings and Precautions (5.2)*]
- Transient hypertension [*see Warnings and Precautions (5.3)*]

Most common treatment-emergent adverse reactions, occurring in greater than 2% of patients in both Intensive Care Unit and procedural sedation studies include hypotension, bradycardia and dry mouth.

Intensive Care Unit Sedation

Adverse reaction information is derived from the continuous infusion trials of Precedex for sedation in the Intensive Care Unit setting in which 1007 patients received Precedex. The mean total dose was 7.4 mcg/kg (range: 0.8 to 84.1), mean dose per hour was 0.5 mcg/kg/hr (range: 0.1 to 6.0) and the mean duration of infusion of 15.9 hours (range: 0.2 to 157.2). The population was between 17 to 88 years of age, 43% ≥65 years of age, 77% male and 93% Caucasian. Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 2. The most frequent adverse reactions were hypotension, bradycardia and dry mouth [*see Warnings and Precautions (5.2)*].

Table 2: Adverse Reactions With an Incidence >2%—Intensive Care Unit Sedation Population

Body System/ Adverse Event	All Randomized Precedex N = 1007	Precedex N = 738	Placebo N = 400	Propofol N = 188
	n (%)	n (%)	n (%)	n (%)
Vascular Disorders				
Hypotension	248 (25%)	191 (24%)	48 (12%)	25 (13%)
Hypertension	123 (12%)	101 (13%)	76 (19%)	7 (4%)
Gastrointestinal Disorders				
Nausea	90 (9%)	73 (9%)	36 (9%)	20 (11%)
Dry mouth	35 (4%)	22 (3%)	4 (1%)	1 (1%)
Vomiting	34 (3%)	26 (3%)	21 (5%)	6 (3%)
Cardiac Disorders				
Bradycardia	52 (5%)	36 (5%)	10 (3%)	0
Atrial fibrillation	44 (4%)	37 (5%)	13 (3%)	14 (7%)
Tachycardia	20 (2%)	15 (2%)	17 (4%)	2 (1%)
Sinus tachycardia	6 (1%)	6 (1%)	2 (1%)	4 (2%)
Ventricular tachycardia	4 (0%)	4 (1%)	3 (1%)	9 (5%)
General Disorders and Administration Site Conditions				
Pyrexia	35 (4%)	31 (4%)	15 (4%)	8 (4%)
Hyperthermia	19 (2%)	16 (2%)	12 (3%)	0
Chills	17 (2%)	14 (2%)	13 (3%)	4 (2%)
Edema peripheral	4 (0%)	2 (0%)	2 (1%)	4 (2%)
Metabolism and Nutrition Disorders				
Hypovolemia	31 (3%)	22 (3%)	9 (2%)	9 (5%)
Hyperglycemia	17 (2%)	15 (2%)	7 (2%)	5 (3%)
Hypocalcemia	7 (1%)	7 (1%)	0	4 (2%)
Acidosis	6 (1%)	5 (1%)	4 (1%)	4 (2%)
Respiratory, Thoracic and Mediastinal Disorders				
Atelectasis	29 (3%)	23 (3%)	13 (3%)	12 (6%)
Pleural effusion	23 (2%)	16 (2%)	4 (1%)	12 (6%)
Hypoxia	16 (2%)	13 (2%)	8 (2%)	5 (3%)
Pulmonary edema	9 (1%)	9 (1%)	3 (1%)	5 (3%)
Wheezing	4 (0%)	4 (1%)	1 (0%)	4 (2%)
Psychiatric Disorders				
Agitation	20 (2%)	16 (2%)	11 (3%)	1 (1%)
Blood and Lymphatic System Disorders				
Anemia	19 (2%)	18 (2%)	7 (2%)	4 (2%)
Injury, Poisoning and Procedural Complications				
Post-procedural hemorrhage	15 (2%)	13 (2%)	10 (3%)	7 (4%)
Investigations				
Urine output decreased	6 (1%)	6 (1%)	0	4 (2%)

Procedural Sedation

Adverse reaction information is derived from the two trials for procedural sedation in which 318 patients received Precedex. The mean total dose was 1.6 mcg/kg (range: 0.5 to 6.7), mean dose per hour was 1.3 mcg/kg/hr (range: 0.3 to 6.1) and the mean duration of infusion of 1.5 hours (range: 0.1 to 6.2). The population was between 18 to 93 years of age, 30% ≥65 years of age, 52% male and 61% Caucasian.

Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 3. The most frequent adverse reactions were hypotension, bradycardia, and dry mouth [*see Warnings and Precautions (5.2)*]. Pre-specified criteria for the vital signs to be reported as adverse reactions are footnoted below the table. The decrease in respiratory rate and hypoxia was similar between Precedex and comparator groups in both studies.

Table 3: Adverse Reactions With an Incidence >2%—Procedural Sedation Population

Body System/ Adverse Event	Precedex N = 318	Placebo N = 113
	n (%)	n (%)
Vascular Disorders		
Hypotension[1]	173 (54%)	34 (30%)
Hypertension[2]	41 (13%)	27 (24%)
Respiratory, Thoracic and Mediastinal Disorders		
Respiratory depression[5]	117 (37%)	36 (32%)
Hypoxia[6]	7 (2%)	3 (3%)
Bradypnea	5 (2%)	5 (4%)
Cardiac Disorders		
Bradycardia[3]	45 (14%)	4 (4%)
Tachycardia[4]	17 (5%)	19 (17%)
Gastrointestinal Disorders		
Nausea	10 (3%)	2 (2%)
Dry mouth	8 (3%)	1 (1%)

1 Hypotension was defined in absolute and relative terms as Systolic blood pressure of <80 mmHg or ≤30% lower than pre-study drug infusion value, or diastolic blood pressure of <50 mmHg.

2 Hypertension was defined in absolute and relative terms as Systolic blood pressure >180 mmHg or ≥30% higher than pre-study drug infusion value or diastolic blood pressure of >100 mmHg.

3 Bradycardia was defined in absolute and relative terms as <40 beats per minute or ≤30% lower than pre-study drug infusion value.

4 Tachycardia was defined in absolute and relative terms as >120 beats per minute or ≥30% greater than pre-study drug infusion value.

5 Respiratory depression was defined in absolute and relative terms as respiratory rate (RR) <8 breaths or >25% decrease from baseline.

6 Hypoxia was defined in absolute and relative terms as SpO_2 <90% or 10% decrease from baseline.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Precedex. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypotension and bradycardia were the most common adverse reactions associated with the use of Precedex during post approval use of the drug.

Table 4: Adverse Reactions Experienced During Post-approval Use of Precedex

Body System	Preferred Term
Body as a Whole	Fever, hyperpyrexia, hypovolemia, light anesthesia, pain, rigors
Cardiovascular Disorders, General	Blood pressure fluctuation, heart disorder, hypertension, hypotension, myocardial infarction
Central and Peripheral Nervous System Disorders	Dizziness, headache, neuralgia, neuritis, speech disorder, convulsion
Gastrointestinal System Disorders	Abdominal pain, diarrhea, vomiting, nausea
Heart Rate and Rhythm Disorders	Arrhythmia, ventricular arrhythmia, bradycardia, hypoxia, atrioventricular block, cardiac arrest, extrasystoles, atrial fibrillation, heart block, t wave inversion, tachycardia, supraventricular tachycardia, ventricular tachycardia
Liver and Biliary System Disorders	Increased gamma-glutamyl transpepsidase, hepatic function abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase
Metabolic and Nutritional Disorders	Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, hypoglycemia
Psychiatric Disorders	Agitation, confusion, delirium, hallucination, illusion
Red Blood Cell Disorders	Anemia
Renal Disorders	Blood urea nitrogen increased, oliguria
Respiratory System Disorders	Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion
Skin and Appendages Disorders	Increased sweating
Vascular Disorders	Hemorrhage
Vision Disorders	Photopsia, abnormal vision

10 OVERDOSAGE

The tolerability of Precedex was studied in one study in which healthy subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hr. The maximum blood concentration achieved in this study was approximately 13 times the upper boundary of the therapeutic range. The most notable effects observed in two subjects who achieved the highest doses were first degree atrioventricular block and second degree heart block. No hemodynamic compromise was noted with the atrioventricular block and the heart block resolved spontaneously within one minute.

Five patients received an overdose of Precedex in the intensive care unit sedation studies. Two of these patients had no symptoms reported; one patient received a 2 mcg/kg loading dose over 10 minutes (twice the recommended loading dose) and one patient received a maintenance infusion of 0.8 mcg/kg/hr. Two other patients who received a 2 mcg/kg loading dose over 10 minutes, experienced bradycardia and/or hypotension. One patient who received a loading bolus dose of undiluted Precedex (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

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