Flumazenil: A specific benzodiazepine antagonist

BRIAN J. KASSON, CRNA, MHS
Cincinnati, Ohio

Flumazenil is a specific benzodiazepine (BZD) antagonist which inhibits the effects of BZD agonists by competing for the receptor site in the central nervous system. It has completed clinical trials in the United States and received final approval from the U.S. Food and Drug Administration for release in January 1992.

Following intravenous injection, clinically apparent arousal usually occurs within 1 to 5 minutes and is maintained for approximately 2 hours in patients either anesthetized or sedated with BZDs. This illustrates the potential for resedation and the importance of careful monitoring following administration.

Flumazenil does not possess clinically significant intrinsic pharmacologic activity. Because of its specificity for the BZD receptor, it has no effect on the actions of other non-BZD sedatives and anesthetics. Its efficacy has been established not only in conscious sedation and general anesthesia but also in the differential diagnosis of unknown/suspected BZD intoxication. To date, it has been well tolerated in most patients, with few reported side effects and has no effect on the pharmacokinetic profiles of coadministered drugs.

Flumazenil is a promising, effective, and short-acting BZD antagonist that should provide an additional degree of safety whenever the undesirable effects of BZD agonists occur.

Key words: Benzodiazepine antagonist, flumazenil, midazolam reversal.

Introduction
The compound flumazenil (Ro 15-1788) is a 1,4-imidazobenzodiazepine that is a potent specific antagonist of the central effects of benzodiazepines (BZD). Flumazenil antagonizes BZDs by competitively binding to the BZD receptor in the central nervous system following either parenteral or oral administration. It was synthesized and described in 1980 by Hunkeler and colleagues, and since that time it has received enormous attention in the fields of anesthesia and pharmacology. The availability of 2,500 papers in 2 years after its introduction illustrates its potential impact on the medical community.

Flumazenil's unique site of action at the central BZD receptor is what sets it apart from other pharmacological agents that have been implicated in reversing the effects of BZDs. For example, the centrally acting cholinesterase inhibitor physostigmine has been reported to reduce the somnolence and disorientation caused not only by diazepam, but also by ketamine, narcotics, and halothane. In practice, physostigmine's effectiveness in reversing BZDs is unreliable. Because these agents have different proposed mechanisms of action, the effect of physostigmine can be described as nonspecific physiologic antagonism.

The need for a specific and reliable reversal agent was underscored by the introduction of the BZD agonist midazolam, which has been used not only for conscious sedation but also for the induction and maintenance of general anesthesia. It has an affinity twice that of diazepam for the BZD receptor, resulting in a diazepam/midazolam potency...
ratio of 1:2. It possesses clinically significant hypnotic, anxiolytic, anticonvulsant, muscle relaxant, and amnestic properties.

However, all BZDs—including midazolam—are known to possess respiratory depressant properties mediated by the central nervous system. The slope of the ventilatory response curve to carbon dioxide is decreased, not shifted to the right, as is observed with respiratory depression induced by narcotics. This indicates an impairment of central carbon dioxide chemoreceptor sensitivity.

It has been noted that elderly patients are more susceptible to the effects of midazolam because of alternations in clearance and volume of distribution. In the same report it was found that in a trial of 74 patients of all ages, eight had prolonged elimination half-lives of greater than 10 hours. After its release in May 1986, numerous fatalities were reported as a result of excessive respiratory depression and resultant cardiac arrest. Despite U.S. Food and Drug Administration mandated reductions in recommended dose and widespread safety warnings, a total of 66 deaths had been reported by January 1988.

There is no doubt that midazolam can be employed safely for conscious sedation if the correct dosage is used, allowance is made for the patient’s age, and appropriate precautions are taken. However, as is the case with other potent central nervous system depressants, relative overdosage is a risk. Flumazenil offers an added degree of safety and security for the practitioner when these untoward effects occur.

This article will address the spectrum of pharmacodynamic and pharmacokinetic effects of flumazenil. In addition, its mechanism of action, side effects, and potential interactions will be discussed in detail.

Chemistry and structure

Flumazenil belongs to the imidazobenzodiazepine ring system (Figure 1). It is both less lipophilic and water soluble when compared to midazolam but still sufficient to produce an injectable aqueous solution. Commercial ampules have a pH of about 4. It causes little, if any, local irritation after intravenous injection.

Mechanism of action

Gamma aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the central nervous system, and it exerts its main effect via a GABAa receptor located on the Cl⁻ channel in the postsynaptic membrane. According to theory, there is a BZD receptor in close proximity to the GABAa receptor forming a complex. As a result of this proximity, activation of the BZD receptor modulates the function of GABAa receptors in several ways. BZDs increase the affinity of GABA for its receptor sites, as well as increasing the coupling of GABA receptors to the Cl⁻ channel. When the channel is opened, Cl⁻ diffuses inside, down its concentration gradient, and hyperpolarizes the cell membrane. This hyperpolarized membrane is then more resistant to neuronal excitation.

There appear to be at least three groups of BZD receptor ligands (Figure 2). In the first group are the classical agonists, which produce the charac-
teristic antianxiety, anticonvulsant, and sedative effects and include drugs like diazepam and midazolam. A second group is the BZD antagonists, which competitively bind to the receptor and inhibit the pharmacologic effects. The third group is a poorly understood one known as inverse agonists and contains compounds that cause the opposite effects of BZD agonists. Interestingly, the convulsant effects of these drugs have been reversed by flumazenil, implying an identical receptor.15

Pharmacodynamics

Midazolam has been widely used for the induction and maintenance of general anesthesia. Great individual variations have been reported in response to recommended doses, resulting in occasional delayed awakening or excessive postoperative sedation. In a double-blind study involving gynecologic ambulatory surgery patients who had anesthesia induced with midazolam, flumazenil given in the postoperative period was effective in improving psychodiagnostic tests of recovery, as well as pulse oxygen saturation and end-tidal carbon dioxide tension.14

Flumazenil injected intravenously in individually titrated doses has been clearly superior to a placebo in reversing BZD anesthesia.15 In a study by Lauven and associates in 1985, midazolam anesthesia was maintained by infusion.16 A single large dose of flumazenil caused the subjects to be fully oriented within 65 seconds and fully asleep again after 145 minutes. This illustrates the limited duration of action of flumazenil and the potential for resedation once the reversal has worn off.

Flumazenil has been found to be effective in reversing midazolam sedation in elderly patients after regional anesthesia.17 However, this improvement in alertness and recall started to diminish slowly after 5 to 15 minutes following flumazenil administration. If prolonged reversal is necessary, the use of continuous flumazenil infusions may prove useful.

The possibility that flumazenil has its own pharmacologic effects has been investigated, and the results have been inconclusive.18 However, it does appear as if flumazenil possesses very weak intrinsic activity in several behavioral, neurological, and electrophysiological tests in man.19 Depending on the dose, the basal clinical conditions, and experimental tests, flumazenil is reported to have both weak agonist-like and inverse agonist-like properties which might be explained by a modulation of GABAergic activity.20 These effects are generally minor and seem unlikely to detract from its use as an antagonist.21 The cardiovascular effects of flumazenil alone have also been studied in patients with ischemic heart disease and found to be negligible.22, 23

Flumazenil alone appears to have no effect on ventilation.24 Although the efficacy of flumazenil has been clearly established in reversing the sedative and hypnotic effects of BZD, some doubt exists as to its effectiveness in completely eliminating all aspects of the respiratory depression produced by BZD.25

Flumazenil has been found to be partially effective in reversing diazepam-induced depression of hypoxic ventilatory drive and central carbon dioxide chemoreceptor sensitivity.26 This incomplete action has been related to either the shorter elimination half-life of flumazenil or a possible agonistic action at another site.27 It remains to be seen if flumazenil is as effective in patients with chronic obstructive pulmonary disease, as they are the ones most likely to receive midazolam with sedation during regional anesthesia. Therefore, careful monitoring of ventilation into the postoperative period is still mandatory.28, 29

Studies of small numbers of patients admitted to intensive care units and emergency rooms have shown that, after 5 minutes, patients suffering from pure BZD overdose are fully awakened. However, reports of seizures and arrhythmias have appeared following the reversal of mixed drug overdoses. In a combined BZD/tricyclic overdose, the rapid elimination of BZD has unmasked the seizure-producing effects of tricyclic antidepressants, resulting in sustained seizure activity.30, 31 The same applies to BZD/chloral hydrate overdose, where flumazenil unmasks the arrhythmogenic effects of chloral hydrate producing uncontrollable ventricular arrhythmias.32

Despite inconclusive early studies, it has been established that flumazenil has no influence on psychomotor function in acute ethanol intoxication.33 An area of use that has been investigated and shows some promise is the use of flumazenil in the treatment of hepatic encephalopathy. It is postulated that increased GABA-mediated neurotransmission contributes to the mediation of hepatic encephalopathy. Flumazenil induced variable and transient, but distinct, improvements in the mental status of 10 of 14 patients with advanced cirrhosis. These findings strongly favor a prominent role of increased GABAergic tone and suggest that a positive response to flumazenil may be of prognostic value.34
Pharmacokinetics

High-performance liquid chromatography and, more recently, gas-liquid chromatography with nitrogen-phosphorous detection have been used to quantify flumazenil in the blood, which is readily absorbed after an oral dose and reaches its peak plasma concentration in 20-90 minutes. However, it undergoes significant first-pass metabolism in the liver, so that only 16% of an oral dose reaches the systemic circulation. Peak plasma concentration after intravenous administration is 6-10 minutes (Table I).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination half-life (hours)</td>
<td>0.7-1.3</td>
</tr>
<tr>
<td>Volume of distribution at steady state (L/kg)</td>
<td>0.6-1.6</td>
</tr>
<tr>
<td>Free fraction (%)</td>
<td>54-64</td>
</tr>
<tr>
<td>Plasma clearance (L/hr)</td>
<td>31-78</td>
</tr>
</tbody>
</table>

Flumazenil is extensively metabolized in the liver by hepatic microsomal oxidative mechanisms to an inactive free carboxylic acid and a corresponding glucuronide, with only 0.12% of a dose excreted unchanged in the urine. Three metabolites of flumazenil have been identified to date, and they are not known to possess any intrinsic pharmacologic activity.

The elimination half-life of between 49 and 58 minutes following both oral and intravenous administration results in a duration of action of 2 to 3 hours. This rapid hepatic elimination can be characterized both by the short half-life (0.7 to 1.3 hours) or better, by the high plasma clearance (0.5 to 1.3 L/min).

By comparison, midazolam has an elimination half-life of 1.5 to 3 hours and a plasma clearance of 0.35 to 0.5 L/min. The protein-bound fraction of flumazenil is approximately 40% to 50%, and its volume of distribution is 0.6 to 1.6 L/kg. The pharmacokinetics of flumazenil are not significantly affected by age, gender, or renal failure. Mean total clearance is decreased 40% to 75% of normal in patients with moderate to severe hepatic dysfunction.

Side effects and pharmacokinetic interactions

In studies conducted to date, the usual therapeutic doses of flumazenil have been well tolerated by most patients, and there is little if any pain on injection. A review of side effects in more than 1,700 patients noted that nausea and/or vomiting only occurred in more than 1% of patients. The incidence of side effects is significantly greater in those who receive flumazenil for BZD intoxication. The most frequent occurrence was agitation (6.5%), followed by unspecified discomfort (4.6%), tearfulness (4.2%), and anxiety (4.2%). Flumazenil has no influence on the pharmacokinetic parameters of coadministered BZDs or alcohol.

Conclusions

Flumazenil is a unique member of the BZD class of drugs that has been shown to possess the properties of a competitive antagonist, thereby reversing the central effects of other BZDs. Its baseline efficacy has been established in a wide range of clinical applications that have had a significant impact on the anesthesia community. The immediate onset of effect and the relatively short duration of action would seem to make flumazenil ideally suited for use in anesthesia. Clearly, flumazenil should not be used routinely; however, with its recent U.S. Food and Drug Administration approval, it should make a welcome addition to the armamentarium of drugs currently available to the anesthetia practitioner.

REFERENCES


AUTHOR

Brian J. Kasson, CRNA, MHS, received his nursing degree from Ohio State University College of Nursing, Columbus, Ohio, in 1986, and worked for three years in the cardiothoracic intensive care unit at Duke University Medical Center, Durham, North Carolina. He graduated from the Medical University of South Carolina's Anesthesia for Nurses Program in August of 1991 with a master in Health Sciences degree/certificate in Anesthesia. Mr. Kasson is currently a staff nurse anesthetist for Anesthesia Associates of Cincinnati, practicing at Christ Hospital, Cincinnati, Ohio.
In the countdown to recovery...

reversal you can count on

3 Performance Advantages
- Rapid reversal
- Conclusive patient evaluation in the O.R.¹
- Duration sufficient to cover the effects of today's short- and medium-acting, non-depolarizing muscle relaxants

2 Proven Ingredients
- A combination of edrophonium and atropine helps minimize side effects

1 Step Convenience
- Premixed in unit-dose packaging to simplify dosing

Enlon-Plus®
edrophonium chloride, USP & atropine sulfate, USP) Inj.

Anaquest

Please see brief summary of Prescribing Information on next page.
**Enlon-Plus**

**(edrophonium chloride, USP and atropine sulfate, USP) Injection**

**DESCRIPTION**

Enlon-Plus (edrophonium chloride, USP and atropine sulfate, USP) Injection is for intravenous use, as a sterile, nonpyrogenic, chloroform-free, aminopyrine-releasant agent. Enlon-Plus is a combination drug containing a safe and effective dose of edrophonium chloride, a neuromuscular blocking agent, and an atropinic鞍山 drug, atropine sulfate. Enlon-Plus contains in each mL of sterile solution: 10 mg edrophonium chloride and 0.14 mg atropine sulfate compounded with 2.0 mg sodium sulfate as a preservative and buffered with sodium citrate and citric acid. The pH is adjusted in the range of 4.4-4.8.

**INDICATIONS AND USAGE**

Enlon-Plus (edrophonium chloride, USP and atropine sulfate, USP) Injection is recommended as a reversal agent or a supportive agent in the management of patients undergoing neuromuscular-blocking agent-induced paralysis. Enlon-Plus has a specific fixed ratio of edrophonium and atropine in Enlon-Plus has not been evaluated in myasthenia gravis. Therefore, Enlon-Plus is not recommended for use in the differential diagnosis of this condition.

**CONTRAINDICATIONS**

Enlon-Plus (edrophonium chloride, USP and atropine sulfate, USP) Injection is not to be used in patients with known hypersensitivity to any of the components, or in patients with uranium or respiratory disease of mechanical type. Atropine sulfate is contraindicated in the presence of cardiovascular or obstructive lesions between the iris and lens of the eye, and pyloric stenosis.

**WARNINGS**

Enlon-Plus (edrophonium chloride, USP and atropine sulfate, USP) Injection should not be used with those patients as well as in jaundiced subjects receiving cholinergic blocking agents. In patients with cardiovascular disease, given the lack of specific antimuscarinic agent is contraindicated. The use of Enlon-Plus should be limited to patients with chronic lung disease.

**PRECAUTIONS**

**GENERAL**

As with any agent of nondepolarizing muscle relaxants, adequate recovery of voluntary respiratory function and resumption of normal spontaneous respiration should be obtained prior to the discontinuation of respiratory assistance. Should the patient develop "anoxicholinesterase insensitivity" or "resistance" to Enlon-Plus, the patient should be monitored and the dosage of anticholinesterase agents should be increased. If the patient again becomes sensitive to them, use with caution or discontinuation of anticholinesterase agents may be indicated.

When used in therapeutic doses, atropine can cause dryness of the mouth, skin, and eyes. In case of overdose, atropine should be used to combat the symptoms of atropine toxicity.

**DRUG INTERACTIONS**

Enlon-Plus (edrophonium chloride, USP and atropine sulfate, USP) Injection should not be administered prior to the administration of any nondepolarizing muscle relaxant. It should be administered 1 mg cautiously to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdose (cholinergic crisis)

Symptoms may mimic underdosage (myasthenic weakness), so the use of this drug may worsen the condition of these patients (see OVERDOSE section for treatment).

**DOSEAGE AND ADMINISTRATION**

**EDROPHONIUM CHLORIDE**

Enlon-Plus (edrophonium chloride, USP and atropine sulfate, USP) Injection range from 0.05-0.1 mg/kg given slowly over 45 seconds to 1 minute at a point of at least 5% recovery of twitch response to neuromuscular stimulation (95% block). The dosage delivered is 0.6-10 mg/kg of edrophonium chloride and 0.007-0.014 mg/kg of atropine sulfate. A total dose of 1.0 mg/kg of edrophonium chloride should rarely be exceeded.

**ADVERSE REACTIONS**

**CARDIOVASCULAR**

Arrhythmias: Frequency >10%: Bradycardia, AV block, 3 second R-R interval. Enlon-Plus contains in each mL of sterile solution: 10 mg edrophonium chloride and 0.14 mg atropine sulfate compounded with 2.0 mg sodium sulfate as a preservative and buffered with sodium citrate and citric acid. The pH is adjusted in the range of 4.4-4.8.

**GASTROINTESTINAL**

Diarrhea, nausea, vomiting, abdominal distension, increased peristalsis.

**NEUROLOGIC**

Convulsion, dysarthria, dizziness, and dysphagia.

**OTHER SENSORY ORGANS**

Dryness of the nose and mouth, thirst, blurred vision, photophobia, eye redness, strabismus, a transient decrease in visual acuity, or miosis.

**OVERDOSE**

**MUSCULOSKELETAL**

Weakness and fatigue.

**Miscellaneous**

Increased urinary frequency, diarrhea, increased lacrimation, papillary constriction, diplopia, and conjunctival hyperemia.

**TOXICITY AND EMERGENCY TREATMENT**

Upon injection into the subcutaneous tissue usually causes the following effects, which are not observed in the 235 patients treated with Enlon-Plus (edrophonium chloride, USP and atropine sulfate, USP) Injection.

**NEUROLOGIC**

Speech disturbances and restlessness with anesthesia.

**Dermatologic**

Flushed, dry skin, formation of a macula.

**MUSCULOSKELETAL**

Weakness and fatigue.

**Miscellaneous**

Increased urinary frequency, diarrhea, increased lacrimation, papillary constriction, diplopia, and conjunctival hyperemia.

Upon injection into the subcutaneous tissue usually causes the following effects, which are not observed in the 235 patients treated with Enlon-Plus (edrophonium chloride, USP and atropine sulfate, USP) Injection.

**NEUROLOGIC**

Speech disturbances and restlessness with anesthesia.

**Dermatologic**

Flushed, dry skin, formation of a macula.

**MUSCULOSKELETAL**

Weakness and fatigue.

**Miscellaneous**

Increased urinary frequency, diarrhea, increased lacrimation, papillary constriction, diplopia, and conjunctival hyperemia.

**REFERENCES**


4. Miller RD, Banski DR, Pahey MR, Pharmacokinetics of edrophonium and reserpine in man, a pregnant woman or can affect respiration of the newborn will be necessary, is not known. The effect of the combination drug on the later growth, development and functional maturation of the child is also unknown.

**NURSING MOTHERS:** The safety of Enlon-Plus during lactation has not been established.

**PEDIATRIC USE:** Safety and effectiveness in children have not been established. Pediatric patients may have increased vage tone. The effect of fixed ratio of edrophonium and atropine on heart rate in such patients has not been evaluated.

**ADVERSE REACTIONS**

**CARDIOVASCULAR**

Arrhythmias: Frequency >10%: Bradycardia, AV block, 3 second R-R interval. Enlon-Plus contains in each mL of sterile solution: 10 mg edrophonium chloride and 0.14 mg atropine sulfate compounded with 2.0 mg sodium sulfate as a preservative and buffered with sodium citrate and citric acid. The pH is adjusted in the range of 4.4-4.8.

**GASTROINTESTINAL**

Diarrhea, nausea, vomiting, abdominal distension, increased peristalsis.

**NEUROLOGIC**

Convulsion, dysarthria, dizziness, and dysphagia.

**OTHER SENSORY ORGANS**

Dryness of the nose and mouth, thirst, blurred vision, photophobia, eye redness, strabismus, a transient decrease in visual acuity, or miosis.

**OVERDOSE**

**MUSCULOSKELETAL**

Weakness and fatigue.

**Miscellaneous**

Increased urinary frequency, diarrhea, increased lacrimation, papillary constriction, diplopia, and conjunctival hyperemia.

**TOXICITY AND EMERGENCY TREATMENT**

Upon injection into the subcutaneous tissue usually causes the following effects, which are not observed in the 235 patients treated with Enlon-Plus (edrophonium chloride, USP and atropine sulfate, USP) Injection.
From Burroughs Wellcome Co.
A Long-Acting Neuromuscular Blocker

Excellent CV Stability

NUROMAX® INJECTION
(doxacurium chloride) 1 mg/mL

Please see brief summary of full prescribing information.
Emmott et al. compared the hemodynamic effects of Nuromax 0.037 and 0.075 mg/kg with the effects of pancuronium 0.09 mg/kg and vecuronium 0.075 mg/kg in 36 CABG patients (9 patients, each group).

Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration. All routine cardiac and vasoactive medications were continued up to the morning of surgery.

- doxacurium 0.037 mg/kg
- doxacurium 0.075 mg/kg
- pancuronium 0.09 mg/kg
- vecuronium 0.075 mg/kg
Longer acting than "high-dose" vecuronium

Clinically effective block (time to 25% recovery)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Time to Recovery</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED$_{95}$ (0.025 mg/kg)</td>
<td>~ 60 minutes (range 9-145)</td>
<td></td>
</tr>
<tr>
<td>2×ED$_{95}$ (0.05 mg/kg)</td>
<td>~ 100 minutes (range 39-232)</td>
<td></td>
</tr>
<tr>
<td>3×ED$_{95}$ (0.08 mg/kg)</td>
<td>160 minutes or more (range 110-338)</td>
<td></td>
</tr>
<tr>
<td>3×ED$_{eq}$ (0.2 mg/kg)</td>
<td>~ 68 minutes (range 50-106)</td>
<td></td>
</tr>
<tr>
<td>5×ED$_{eq}$ (0.3 mg/kg)</td>
<td>~ 111 minutes (range 62-208)</td>
<td></td>
</tr>
<tr>
<td>7×ED$_{eq}$ (0.4 mg/kg)</td>
<td>~ 115 minutes (range 35-191)</td>
<td></td>
</tr>
</tbody>
</table>

*This dose should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated.
†Numbers shown are not directly comparable since these data have been compiled from different study populations.

- Cardiovascular stability comparable with normal saline
- Noncumulative
- Ready-to-use solution
- Vials stored at room temperature, no refrigeration required
- Supplied as a 5 mL vial, 1 mg/mL

**NUROMAX**

(doxacurium chloride) 1 mg/mL

Excellent for Long CV Procedures

Please see brief summary of full prescribing information.
This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

Individualization of Dosages: In elderly patients or patients who have impaired renal function, the potential duration of block and the possibility of respiratory depression should be considered when determining the initial Nuromax dose. In general, the initial dose should not exceed 0.1 mg/kg. In these patients, a reduced dose may be required because of the potential for increased sensitivity to neuromuscular blocking agents and increased levels of some co-administered drugs. When used in combination with other agents, the potential for increased sensitivity and increased levels of other agents should be considered. In patients with neuromuscular diseases, the initial dose may have to be titrated according to the level of myasthenic syndromes present.

In patients with normal renal function, the usual initial dose of Nuromax is 1 mg. The initial dose may be increased by 1 mg increments q.10 minutes if clinically indicated. The maximum dose of Nuromax recommended for any patient is 6 mg. In patients with impaired renal function, the initial dose may have to be titrated to achieve the desired degree of block. In obese patients (patients weighing >30% more than ideal body weight for height), the Nuromax dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg = [106 + (6.8 x inches in height above 5 feet)]/2
Women: IBW in kg = [100 + (5.8 x inches in height above 5 feet)]/2

Dosages may be increased if necessary; some patients may require a higher than normal initial Nuromax dose to achieve clinically effective block. Once adequate block is established, the clinical duration of block may be prolonged in some patients relative to patients with normal renal function.

As with pancuronium, metocurine, and vecuronium, resistance to Nuromax, manifested by a reduced intensity and/or shortened duration of block, must be considered when Nuromax is selected for use in patients receiving phenothiazine or carbamazepine. In these patients, a reduced dose may be required because of the potential for increased sensitivity to neuromuscular blocking agents and increased levels of some co-administered drugs. In patients with CNS depression, excessive doses should not be administered. Overdosage: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment of an overdose is an anticholinesterase agent. However, with prolonged neuromuscular block, the use of an anticholinesterase agent may not be adequate or may be contraindicated. In such cases, the use of a nondecreasing anticholinesterase agent (e.g., edrophonium, pyridostigmine) in combination with a neuromuscular blocking agent may be effective in antagonizing the effects of the neuromuscular blocking agent.

There are no adequate and well-controlled studies of Nuromax during labor, vaginal delivery, or C-section. Nursing Mothers: It is not known whether Nuromax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nuromax is administered to a nursing woman. Pediatric Use: Nuromax has not been studied in children below the age of 2 years. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age. 

Adults: Initial Doses: When administered as a component of a balanced anesthetic regimen, the recommended dose of Nuromax is 1 mg for the awake patient and 0.1 mg/kg for the intubated patient to achieve adequate neuromuscular block during surgery. The duration of neuromuscular block may vary depending on the level of block achieved and the degree of anticholinesterase activity. In general, a single dose of Neo + 1 mg of Neostigmine will produce a 40% block and 1 mg of Atropine will produce a 20% block. In general, the dose of Nuromax should be based upon ideal weight (see Dosage and Administration subsection) unless individualized dosing is indicated due to the patient's medical condition.

Overdosage: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment of an overdose is an anticholinesterase agent. However, with prolonged neuromuscular block, the use of an anticholinesterase agent may not be adequate or may be contraindicated. In such cases, the use of a nondecreasing anticholinesterase agent (e.g., edrophonium, pyridostigmine) in combination with a neuromuscular blocking agent may be effective in antagonizing the effects of the neuromuscular blocking agent.

Antagonism of Neuromuscular Block: Antagonists (such as Neostigmine) should not be administered prior to the demonstration of some spontaneous recovery from neuromuscular block. T1/2 should be at least 70% before reversal is attempted. Prolonged neuromuscular block may be due to a number of factors, including the use of large doses of anticholinesterase agents, drugs that prolong the duration of block, and the administration of other agents that antagonize neuromuscular block. In these patients, the use of a nondecreasing anticholinesterase agent (e.g., edrophonium, pyridostigmine) in combination with a neuromuscular blocking agent may be effective in antagonizing the effects of the neuromuscular blocking agent.

In clinical trials, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg of pyridostigmine in antagonizing moderate to deep levels of neuromuscular block. Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal from moderate to deep levels of block (i.e., ≤45% T1 recovery). Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, Nuromax did not trigger MH. Nuromax has not been studied in MH-susceptible patients. Since MH can develop in patients with genetic predisposition to MH, patients with a family history of MH should be observed closely. Prolonged Neuromuscular Block: In patients with prolonged neuromuscular block, the use of a nondecreasing anticholinesterase agent (e.g., edrophonium, pyridostigmine) in combination with a neuromuscular blocking agent may be effective in antagonizing the effects of the neuromuscular blocking agent.

In general, the initial dose of Nuromax for the awake, intubated patient is 1 mg. For the intubated patient, the initial dose may be increased by 1 mg increments q.10 minutes if clinically indicated. The maximum dose of Nuromax recommended for any patient is 6 mg. In patients with impaired renal function, the initial dose may have to be titrated to achieve the desired degree of block. In general, the duration of block may be prolonged in some patients relative to patients with normal renal function.
Don't overlook this tremendous opportunity! We are seeking a Certified Registered Nurse Anesthetist to join our hospital-employed, self-managed department at Battle Creek Health System. We are proud of our good working relationship with our MDAs.

Battle Creek Health System is a 400-bed hospital formed through a joint venture four years ago of two acute care hospitals. We're a comprehensive medical system, with virtually every medical specialty, all types of anesthesia, and a full range of surgical services (pediatrics, general, neuro, vascular) excluding open heart.

A strong team of 10 CRNAs makes the call schedule reasonable. We also offer:

- One of the highest compensation packages in the area, with a generous signing bonus.
- Four weeks of vacation plus holidays.
- Malpractice insurance fully covered.
- $1500 allowance per year for continuing education, plus one week paid time off.
- Medical, dental, life insurance, retirement package.
- All interview and moving expenses paid.
- Day off after call.

Battle Creek is located in scenic southwestern Michigan, near many lakes and minutes from Lake Michigan. The area is rich in cultural resources and recreation. A local symphony, art center, and many golf courses are a few examples. The local economy is strong and stable. Battle Creek is home to The Kellogg Company, Post Cereal — division of General Foods, and others, and has developed a successful international industrial park complex. The area also has outstanding schools, both public and private. There are also educational opportunities through major colleges available locally. The area’s housing is rated sixth most affordable in the U.S. For those who enjoy life in a medium-sized city, Battle Creek is ideal. We are nearly half way between Chicago and Detroit, which are easily accessible by interstate or Amtrak train. A day or weekend trip for shopping or major sports is a breeze.

We'd like to personally show you our beautiful region of Michigan, and the great opportunity in Battle Creek. For more information, contact Yvonne Chapman at 300 North Avenue, Battle Creek, Michigan 49016, 800 926-2247, extension 8060.
IN THE AIR FORCE, NURSES RECEIVE QUALITY TREATMENT AS WELL.

We employ the latest procedures to insure the health of our nurses' careers. First, we put them in a stimulating environment. Next, we surround them with the best people we can find. Finally, we give their careers room to flourish, or even gain in responsibility. We'll even help them get the education they need to get ahead. With that kind of care, it's no wonder they respond. For more information about Air Force Nursing, call 1-800-423-USAF.

AIM HIGH
NURSING