Adenosine: Novel antiarrhythmic therapy for supraventricular tachycardia

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Detroit, Michigan

Adenosine (Adenocard®) is a unique new agent for the acute treatment of paroxysmal supraventricular tachycardia (PSVT). Administered by intravenous bolus, it has an onset and duration measured in seconds and greater than 90% efficacy. Its primary effect is to slow atrioventricular nodal conduction, thus converting reentrant forms of PSVT to normal sinus rhythm. Side effects quickly dissipate without treatment because of the short duration of action. Other uses include diagnosis of broad or wide QRS complex tachycardias and controlled intraoperative hypotension. Its short duration and high efficacy in converting select forms of PSVT make adenosine an excellent alternative to verapamil in patients with compromised hemodynamics. This article will review the clinical use and anesthetic implications for the administration of this drug.

Key words: Adenosine, antiarrhythmic, arrhythmia, supraventricular, tachycardia.

Introduction
Adenosine is an endogenous nucleoside found throughout the body which participates in a number of physiologic processes (Table I). Reports dating back to 1929 noted adenosine's possible therapeutic potential, yet only recently has its true clinical value become evident. Interest in adenosine's antiarrhythmic effect derives from its ability to slow sinoatrial (SA) node and, more importantly, atrioventricular (AV) nodal conduction, thereby terminating PSVT. Verapamil is currently the drug of choice for acute treatment of PSVT, but adenosine exhibits a similar efficacy and a safer adverse reaction profile.

Adenosine can also serve as a valuable diagnostic tool in differentiating the origin (supraventricular or ventricular) of broad QRS complex tachycardia. When combined with electrocardiographic analysis, it has a 92% predictive accuracy rate in differentiating the source of these arrhythmias.

Chemistry and pharmacokinetics
The chemical structure of adenosine is shown

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<td>Promotion of prostaglandin release</td>
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<td>Depression of cerebral and cardiac electrical activity</td>
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in Figure 1. It is an endogenous adenine nucleoside (6-amino-9-β-D-ribofluranosyl-9H-purine) with a molecular weight of 267. The onset of action of adenosine is 10-20 seconds, and its duration is approximately 1 minute. Its in vitro beta half-life is 10 seconds.\(^4\)\(^5\) After intravenous (IV) administration, adenosine is rapidly removed from the plasma by cellular uptake. Once inside the cell, it is phosphorylated to adenosine monophosphate.\(^6\)

![Figure 1](image1.png)

**Chemical structure of adenosine**

At higher concentrations, intracellular conversion to inosine, hypoxanthine, and, finally, uric acid can occur.\(^7\) The biotransformation of adenosine is shown in Figure 2.

Because of adenosine’s rapid plasma clearance, standard pharmacokinetic variables such as volume of distribution, protein binding, and elimination constants have not been determined. No dosing adjustments for renal or hepatic dysfunction are required, since adenosine’s clearance from plasma is by cellular uptake.

**Pharmacodynamics**

The effects of adenosine are produced by an agonist action on cell surface A\(_1\) purinergic receptors.\(^8\) The classification and function of purinergic receptors are shown in Figure 3.\(^9\)\(^10\) Endogenous secretion of adenosine produces coronary vasodilation. Another messenger system which mediates adenosine receptor function is cyclic adenosine monophosphate (cAmp).\(^9\) Adenosine receptors are differentiated in part by their ability to inhibit (A\(_1\)) or activate (A\(_2\)) the cAmp-producing enzyme complex adenyl cyclase. Ultimately, a cAmp-mediated decrease in calcium con-
duction probably accounts for the pharmacologic effect of the drug.¹¹

Pretreatment with atropine does not alter the electrophysiologic effects of adenosine in humans. As a result, muscarinic actions do not appear to contribute to the inhibitory effects of adenosine on the heart.²

**Clinical implications**

PSVT is characterized by the sudden onset of tachycardia with a QRS complex of supraventricular origin and rates in the range of 150-250 beats per minute.¹² Rates of 180-200 are most common in adults; however, they may exceed 250, especially in children. Because of these rapid rates, P waves are usually buried in the QRS complex. The QRS complex is generally of normal size and duration, however, broad QRS complex tachycardias may occur.¹³ Broad or wide complex tachycardias indicate a QRS interval of greater than 1.2 seconds. The term “paroxysmal” is used to indicate a tachycardia of sudden onset, changing from sinus rhythm to tachycardia in one beat, i.e., a premature atrial complex which initiates supraventricular tachycardia (SVT) (Figure 4).

There are several types of SVT, which are delineated by the arrhythmia circuit pathway¹⁴ (Figure 5). The most common SVTs include the AV node in the aberrant circuit. (See Figure 5: A, B, C, D.) Adenosine will convert more than 95% of these arrhythmias. SVT, which does not directly include the AV node, will usually not convert them. (See Figure 5: E, F, G, H.) However, the dose-dependent AV block produced by adenosine will slow ventricular response and may unmask atrial deflections in the ECG, which aids in arrhythmia diagnosis. The symptoms of SVT frequently include palpitations, anxiety, angina, syncope, and, in severe cases, shock. SVT-induced hypotension may result from a decrease in left ventricular end diastolic volume and stroke volume as the atrial contribution to ventricular filling is lost.¹²

**Treatment**

Nonpharmacologic approaches are usually attempted first. Maneuvers which increase vagal tone, such as carotid massage, valsalva, gagging, or ice water to the face (diving reflex), are occasionally effective.¹⁵,¹⁶

The drug of choice for acute termination of PSVT is intravenous verapamil in a dose of 5-10 mg. It is effective within about 10 minutes approximately 93% of the time.¹⁷,¹⁸ Although verapamil is generally safe, it has some limitations. Profound hypotension resulting from its negative inotropic action may occur in patients with congestive heart failure, reduced left ventricular function, or in those on concomitant beta-blocker therapy.¹⁹,²⁰ Precipitation of atrial fibrillation, ventricular fibrillation, and sudden death, have also been reported.²¹-²³

Additive myocardial depression should also be expected when verapamil is given with cardio-depressant anesthetic agents.²⁴ When problems do occur, the relatively long duration of action of verapamil (2-4 hours) may be a problem.²¹

The use of edrophonium and Neo-Synephrine® (phenylephrine) for acute therapy of SVT has been abandoned because of the high percentage of adverse outcomes.

Chronic therapy for prevention of recurrence may include digitalis, propranolol, verapamil, quinidine, procainamide, disopyramide, diltiazem, and amiodarone.¹³

**Adenosine.** The efficacy of adenosine compared to verapamil was studied in a prospective nonrandomized comparative trial in patients undergoing invasive cardiac diagnostic studies.¹⁷ Adenosine 0.125 mg/kg (mean dose) was compared to verapamil 0.145 mg/kg (mean dose). Success was determined by termination of tachycardia, absence of significant arrhythmia after conversion, and ability to unmask latent preexcitation. Adenosine terminated SVT in 20 out of 20 patients. Verapamil terminated tachycardia in 19 out of 20 patients.
Figure 5
Schematic representation of supraventricular tachycardias

Types A, B, C, and D have the atrioventricular node (AVN) as part of their circuitry and therefore are adenosine-terminable. In types E and F, the AV node only determines the ventricular response; therefore, the only effect of adenosine will be a transient decrease in the ventricular rate without affecting the tachycardia. Types G and H are rare; the AVN is not part of their mechanism and adenosine will not modify them in any way. (Reprinted with permission from Pinski SL, Maloney JD.14)

AP — Accessory pathway
AVN — Atrioventricular node
LA — Left atrium
NV — Nodoventricular
RA — Right atrium

However, two patients treated with verapamil experienced subsequent symptomatic arrhythmias (preexcitation atrial flutter in one and atrial tachycardia in the other). Adenosine unmasked intermittent or latent preexcitation in all instances, while verapamil identified preexcitation in only 25% of the patients. The investigators concluded that, overall, adenosine was satisfactory in 100% of the patients and verapamil in 70% (P < 0.05).

DiMarco et al, studied 46 patients with supraventricular tachyarrhythmias.25 Adenosine in increments of 37.5 μg/kg IV restored sinus rhythm within 20 seconds of administration in patients whose SVT involved the AV node (29 of 29). It did not restore sinus rhythm in patients with intra-atrial reentrant tachycardia, atrial fibrillation or flutter, SA nodal reentry, or automatic atrial tachycardia (17 patients). Overholt et al demonstrated similar results with adenosine in pediatric patients 6 hours to 17 years old.26

Adenosine is also useful in the diagnosis of broad complex tachycardias. Differentiating ventricular tachycardia (VT) from SVT is often difficult in emergency management of these arrhythmias. VT is frequently the presumptive, and erroneous, diagnosis.27 If the complex is VT and verapamil is given, the direct myocardial depression may lead to deleterious hemodynamic effects. Griffith et al administered adenosine to 26 patients with broad complex tachycardia.23 Eight of nine patients with VT converted to sinus rhythm or narrow complex SVT. Only one of 17 patients with VT converted to sinus rhythm; however, no adverse hemodynamic effects were observed, leading researchers to conclude that adenosine was useful in diagnosis and treatment of broad complex tachycardia.

Finally, it has been suggested that adenosine may be the agent of choice for treatment of SVT during pregnancy, although it has yet to be approved for this use.28 Its short half-life would make placental transfer highly unlikely and minimize potential fetal effects.

Dosage and administration

Adenosine (Adenocard®) is distributed in 2 mL vials containing 3 mg/mL (6 mg total). Rapid IV administration of a 6-mg bolus given in 1 or 2 seconds and immediately followed by a 10-mL saline flush is recommended.29 Use of a central IV line (if available) rather than a peripheral one is preferred because of its closer deposition to the heart. If administered slowly in a peripheral line, adenosine may undergo cellular uptake and degradation before it reaches the heart. Slow, continuous infusion may result in systemic vasodilation, hypotension, and undesirable reflex tachycardia, so this method of administration is not recommended for treating SVT. If the arrhythmia persists after 2 minutes, a second bolus of 12 mg is recommended. The 12-mg dose can be repeated after 2 minutes. Single doses exceeding 12 mg are not recommended.

Adverse effects, precautions, and contraindications

The most common adverse effects of adenosine are flushing (15-20%), dyspnea (12-20%), and chest pain (7-20%).28,29 Headache, nausea, coughing, and malaise have also been reported.30 Many short-lived arrhythmias, such as sinus arrest, sinus
exit block, sinus pause, and ventricular and junctional escape beats, may occur during conversion. Since all of these reactions are brief, usually lasting less than 1 minute, no intervention is required.

Prolonged sinus pause in patients with SA nodal dysfunction and an increase in ventricular response to PSVT in patients with certain types of Wolff-Parkinson-White syndrome have been reported. Caution is advised when administering adenosine to patients with these disorders.

Adenosine may induce bronchoconstriction and although no formal studies are available, it would appear prudent to use it with caution, if at all, in asthmatic patients. No absolute contraindications have been reported.

Drug interactions

Several drug interactions are of interest. Adenosine should not be used in patients receiving methylxanthine therapy, i.e., theophylline and caffeine. Methylxanthines are competitive antagonists of adenosine at cell surface adenosine receptors and completely block the drug's electrophysiologic effects. No data is available regarding the effect of beverages containing xanthine, such as coffee, tea, or cola, on the efficacy of adenosine.

Dipyridamole (Persantine®, etc.) competitively inhibits the transport of adenosine into cells, thereby preventing its subsequent deamination to inosine. This blockade of uptake and metabolism by dipyridamole results in a potentiation of adenosine's clinical effects. To avoid potentially severe bradycardias, initial doses of adenosine should not exceed 1 mg in patients receiving dipyridamole. Other bradycardia-producing drugs, such as calcium channel blockers, beta receptor blockers, and digitalis, may potentiate the negative chronotropic and dromotropic effect of adenosine, therefore, dosage reductions would appear prudent.

Preliminary data suggests that diazepam and possibly other benzodiazepines may also inhibit cellular uptake of adenosine, thereby potentiating its effect.

Anesthetic implications

The use of adenosine for termination of PSVT during anesthesia has not been reported. Discussion of the use of any antiarrhythmic agent during anesthesia should be preceded by three cautionary statements:

1. The etiology of the arrhythmia should be explored prior to instituting any treatment. Adequacy of ventilation, depth of anesthesia, acid-base, and fluid and electrolyte balance should be verified before appropriate therapy can be formulated.

2. The multiple drug administration which constitutes modern anesthesia practice may result in unexpected drug interactions.

3. Analysis of complex arrhythmias with the commonly used 3- or 5-lead ECG system during a surgical procedure is a less than ideal setting for proper diagnosis and treatment. Nonetheless, rhythm disturbances which compromise hemodynamic stability or may progress to more severe dysfunction must be addressed. The rapid onset, short duration, high efficacy, and safety of adenosine would appear to make it an excellent option for anesthetic use.

The use of adenosine infusion for controlled hypotension, as compared to nitroprusside during cerebral aneurysm surgery, has recently been reported. Hypotension was achieved with 252 ± 55.8 μg/kg/min adenosine infusion. Unlike nitroprusside, adenosine did not produce renin release and rebound hypertension after discontinuation of the infusion. Significant reductions in renal blood flow and glomerular filtration rate, which may be problematic in patients with impaired renal function, were observed. Four of 15 patients developed AV conduction disturbances. One patient exhibited first-degree AV block, two had nodal rhythms, and one had third-degree block followed by atrial flutter. All reverted to normal rhythm without treatment after adenosine was discontinued.

Sietz et al reported that adenosine produces a 49% reduction in halothane MAC in dogs. Other studies in animals have demonstrated sedative, analgesic, and anticonvulsant properties which may be of interest to anesthesiologists.

Summary

Adenosine adds a unique new choice to the list of drugs available for the treatment of SVT. Its quick onset and ultrashort duration of action allow for rapid control of reentrant forms of PSVT while minimizing prolonged undesirable effects. Although reports on its intraoperative effects have yet to emerge, it would appear to offer the benefit of a high efficacy with little chance for prolonged drug interactions with the anesthetic agents. Investigations into the sedative, hypotensive, and other potentially useful actions of adenosine are continuing.

REFERENCES


John Nagelhout, CRNA, PhD, is an assistant professor of Anesthesiology and Pharmaceutical Sciences, College of Pharmacy and Allied Health, Wayne State University, Detroit, Michigan, and a staff anesthetist at Detroit Receiving Hospital in Detroit.
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Since the vehicle (soybean oil in water emulsion) is capable of supporting rapid growth of microorganisms, strict aseptic technique must always be maintained while handling DIPRIVAN Injection. (See WARNINGS and DOSAGE AND ADMINISTRATION sections in the brief summary of prescribing information on the next page.)

DIPRIVAN is not recommended at this time for use in pediatric patients, nursing mothers, patients with increased intracranial pressure or impaired cerebral circulation, and in obstetrics, including cesarean section deliveries.

* Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound cardiovascular responses.


Please see next page for brief summary of prescribing information.
DIPRIVAN (propofol) injection

EMULSION FOR IV ADMINISTRATION

(Fr al rII-aI lortlhnein, re pacerg Iertn. A IDriat Sumaf ... dosageinformation, see CLINICAL PHARMACOLOGY-Individualization of Dosage.

Adults-healthy, less than 55 years of age

- Indications: DIPRIVAN Injection is indicated for the induction and maintenance of general anesthesia. It is not indicated for neuraxial anesthesia.

- Administration: DIPRIVAN Injection should be administered by intravenous injection over a period of at least 5 seconds. The dose of DIPRIVAN Injection is individualized for each patient, and the dose may need to be increased or decreased depending on the patient's response. DIPRIVAN Injection should be given slowly to prevent hypotension and bradycardia.

- Dosage and Administration: The dosage of DIPRIVAN Injection should be individualized for each patient. The dosage should be adjusted based on the patient's response, age, ASA classification, and other factors. The dosage should not exceed 4 mg/kg of body weight per minute. The maximum dosage of DIPRIVAN Injection for adults is 300 mg per minute. The dosage for children and adolescents should be calculated based on body weight.

- Adverse Reactions: The most common adverse reactions of DIPRIVAN Injection include hypotension, bradycardia, respiratory depression, nausea, vomiting, and transient hypotension. Other adverse reactions include dizziness, headache, and ventricular tachycardia. In rare cases, anaphylactic reactions may occur. Patients should be monitored for signs of respiratory depression, hypotension, and bradycardia. If these symptoms occur, the dosage of DIPRIVAN Injection should be reduced or stopped. In patients with a history of cardiovascular disease, DIPRIVAN Injection should be used with caution.

- Handling Precautions: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if the vial is cracked or if the rubber stopper is not intact. Discard any unused portion of the solution.

- Storage: Store at room temperature.

- Dosage and Administration: DIPRIVAN Injection is administered by intravenous injection. The dose should be individualized for each patient and adjusted based on the patient's response, age, ASA classification, and other factors. The maximum dosage of DIPRIVAN Injection for adults is 300 mg per minute. The dosage for children and adolescents should be calculated based on body weight.

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<table>
<thead>
<tr>
<th>Norcuron\textsuperscript{*} (vecuronium bromide) for injection</th>
<th>Atracurium besylate</th>
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<tr>
<td><strong>HEMODYNAMICS</strong></td>
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<tr>
<td>No significant variations in blood pressure, cardiac output, or systemic vascular resistance.\textsuperscript{1}</td>
<td>Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance.\textsuperscript{1} ($P&lt;.05$)</td>
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<td><strong>HISTAMINE</strong></td>
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<td>Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.\textsuperscript{1,4}</td>
<td>Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma).\textsuperscript{5}</td>
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<td><strong>RECOVERY</strong></td>
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<td>To 25% of control</td>
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<td><strong>DOSSING FLEXIBILITY</strong></td>
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<td>The initial recommended dose is 0.08-0.1 mg/kg.</td>
<td>Initial recommended dose is 0.4-0.5 mg/kg.</td>
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<td>Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.\textsuperscript{1,3,4}</td>
<td>A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P&lt;.05$) and 0.6 mg/kg.\textsuperscript{2,3,6}</td>
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<tr>
<td><strong>STORAGE &amp; SHELF LIFE</strong></td>
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<tr>
<td>2-year shelf life in lyophilized form at room temperature.\textsuperscript{4}</td>
<td>2-year shelf life under constant refrigeration.\textsuperscript{7}</td>
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<tr>
<td>Can be reconstituted with various IV solutions including Lactated Ringers.\textsuperscript{3}</td>
<td>Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.\textsuperscript{2}</td>
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\textsuperscript{*} Dose of atracurium above 0.5 mg/kg is not recommended.
\textsuperscript{†} As originally supplied by the respective manufacturers.
\textsuperscript{‡} Storage after reconstitution varies with solution. See package insert.

Norcuron® (vecuronium bromide) for injection

THE LOGICAL CHOICE FOR NEUROMUSCULAR BLOCKADE

See following page for brief summary of prescribing information.


**Norcuron®** (vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

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**CONTINUOUS MONITORING:** Norcuron® is contraindicated in patients known to have a hypersensitivity to it. Only physicians familiar with the continuous monitoring of patients under the supervision of experienced clinicians who are familiar with its actions and the possible complications that may develop in such patients should use Norcuron®. Some patients have experienced a syndrome characterized by signs and symptoms of skeletal muscle weakness, often followed by respiratory depression, after injection of quinidine during recovery from use of other muscle relaxants. Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent episodes of weakness may occur. If quinidine is to be used during recovery, close observation is indicated, and the patient should be carefully monitored for signs of skeletal muscle weakness. Quinidine should be used with caution during recovery in any patient who has received vecuronium or other nondepolarizing muscle relaxants. If the symptom of skeletal muscle weakness recurs, the patient should be treated with reversal agents and other appropriate supportive treatment.

**PRECAUTIONS:**

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1. **Neonates:** The drug has not been sufficiently studied in neonates, but neonates appear to be more sensitive to Norcuron® on a mg/kg basis than adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and a smaller maintenance dose compared with adults because of the generally shorter duration of action of vecuronium bromide in neonates.

2. **Overdosage:** If overdose occurs, treatment should be symptomatic and supportive. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an increase in the depth of muscle relaxation and a reduction in the rate of recovery from neuromuscular blockade. Overdosage may be managed by the use of reversal agents, which will increase the likelihood of respiration.

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**CONTRAINDICATIONS:** Norcuron® is contraindicated in patients known to have a hypersensitivity to it. It is contraindicated in patients who have received steroidal antiinflammatory agents and are at risk of developing a myasthenic crisis. Norcuron® is contraindicated in patients with known or suspected malignant hyperthermia.

**WARNINGS:**

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1. **Neonates:** In the presence of balanced anesthesia, clinically required neuromuscular blockade lasts approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is used, the rate of recovery may be increased.)

2. **Skeletal Muscle Weakness:** Potentially life-threatening skeletal muscle weakness may occur, sometimes in conjunction with respiratory arrest. The syndrome is not always reversible. It may occur days after Norcuron® administration. Thus, patients who may be susceptible should be observed during and after anesthesia. The potential for development of the syndrome should be considered before the drug is administered.

**INTERACTIONS:**

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**OVERDOSAGE:**

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1. **Adults:** Adults who receive Norcuron® in doses of 10 mg/kg or more are at risk for more profound neuromuscular blockade. If overdose occurs and treatment is required, reversal agents, such as pyridostigmine bromide, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate, should be used to reverse the neuromuscular blockade. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is used, the rate of recovery may be increased.)

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**DOSAGE AND ADMINISTRATION:**

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**Usual Adult Dosage:**

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