Nitrous oxide as an adjunct to local anesthesia: A study

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Nitrous oxide was first isolated, or identified, by Joseph Priestley (1733-1804). Horace Wells (1815-1848) attended a demonstration given by Gardner Q. Colton on December 10, 1844 on the effects of nitrous oxide. Wells noticed that a young shop assistant, Samuel Colley, cut his skin while under the influence of the gas, but felt no pain. On the following day, Wells convinced Colton to try the gas during a dental extraction, with himself as the patient and John Riggs as the dentist. The anesthetic worked, hailing “a new era in tooth pulling.”

Later, Wells gave a demonstration of nitrous oxide analgesia at Harvard Medical School. The patient, however, complained of pain, and Wells was hissed out of the room.

Over the years, anesthetic agents have been discovered, used, and set aside when they were replaced by new or superior agents. One agent, however, remains an integral part of most anesthetic techniques—nitrous oxide.

Today's trend in surgery is toward the development of ambulatory, or daycare, surgical procedures. Local anesthesia is the most preferable technique, but anxiety and discomfort during application of the local block necessitate pharmacological intervention. Narcotics, especially short acting ones and sedatives are employed routinely to decrease pain and anxiety. The disadvantages of this technique are prolonged sedation and/or some somnolence postoperatively.

Nitrous oxide appears to be highly suitable as a supplement to local anesthesia for in-hospital or daycare surgery. It is a good analgesic, while providing euphoria to relieve anxiety. The very low lipid solubility of nitrous oxide allows for rapid uptake and elimination. Nitrous oxide is a colorless gas with a faint odor and sweetish taste. It is known commonly as laughing gas because of the delirium it induces.

Nitrous oxide and its effects have been described by many authors. Grant described N₂O in the following excerpts from his book, Medical Gases, Their Properties and Uses.

“When inhaled in pure form, nitrous oxide (N₂O) is asphyxiating, but in high concentrations (80% or more) with sufficient oxygen present to avoid hypoxia, it induces rapid but shallow anesthesia. Loss of consciousness can be induced by nitrous oxide concentrations down to about 35%.”

“Nitrous oxide is non-irritant, gives no un-
pleasant aftermath, and is, in many ways, an ideal inhalation anesthetic. It is most often used as a background anesthetic, in conjunction with more potent agents, for major surgery or in dilute mixtures with oxygen as an analgesic.\textsuperscript{2}

The mechanism of anesthetics is poorly understood. Some theories of anesthetic action include "lipid solubility, thermodynamic activity in solution, clathrate formation, protein interaction, membrane permeability, and cellular enzyme effects."\textsuperscript{2} All these theories, however, fall short of a complete explanation of anesthetic action.

Eger et al. have shown (1971) that some correlation exists between narcotic action and oil/gas partition of a gas, the product of its oil/gas partition coefficient and its minimum alveolar-effective concentration (MAC) being roughly constant.\textsuperscript{2} Nitrous oxide is a relatively soluble gas. It is roughly 50 times more soluble in water than is air and even more soluble in organic liquids. The solubility in blood is about 0.43 liters per liter of blood (measured at 37° C 1 bar). A study done by Cozen et al. in 1920 on human autopsy samples demonstrated a slightly varying solubility in different human tissues.\textsuperscript{2}

The uptake and distribution of an inhalation agent is affected by three major variables: Alveolar concentration, lipid solubility, and cardiac output, or the matching of ventilation and perfusion.

Alveolar concentration is not necessarily inspired concentration. Functional residual capacity of the lung acts to dilute the inspired gases. Conditions which effectively increase the functional residual capacity, such as chronic obstructive pulmonary disease (COPD), tend to dilute the inspired gases to a greater extent.

Decreases in the functional residual capacity may be found in the at-term, gravid female. This decreases the dilution effect and increases the speed of induction with inhalation agents.

One method of increasing the rate of induction is called "overdriving," that is, administering a greater concentration, which increases the pressure gradient in the lung, thereby increasing diffusion and uptake by the blood.

Lipid solubility is important because the more soluble the substance in the blood, the less it leaves the blood to cross the blood-brain barrier into the brain. Highly soluble substances, such as ether or methoxyflurane, will remain in the blood until the necessary pressure gradient is developed to push the agent across the blood-brain barrier into the brain.

Highly soluble agents readily leave the alveoli for the blood. This rapidly decreases the concentration of the agent in the alveolus, thereby setting up a dilutional effect. The decrease of concentration in the alveolus serves to dilute the incoming gases in the next inspiration.

On the other hand, relatively insoluble agents such as nitrous oxide are driven across the alveolar membrane into the blood by the pressure gradient. Because the affinity for the blood is not as great, the agent readily leaves the blood across the blood-brain barrier, and equilibrium is reached more rapidly. The agent's exit follows the same steps in reverse.

Cardiac output, or matching ventilation to perfusion, also is important in the uptake and distribution of agent. The lung is neither ventilated nor perfused uniformly. In the upright position, the bases of the lung are more perfused and less ventilated than the upper lobes. Patients with pneumonia, alveolar destruction secondary to COPD, or atelectasis have areas of lung which are perfused but not ventilated.

Pulmonary emboli disrupt blood flow to areas of the lung. Though ventilation may continue, alveolar exchange of gases in the affected areas does not.

Unlike other inhalation agents, nitrous oxide exhibits few cardiovascular effects. The discharge of catecholamines from the sympathetic nervous system increases only slightly. The parasympathetic and peripheral nervous systems are unaffected. Cardiovascular effects show a slight decrease in vitro and in vivo myocardiac contractility and a slight increase in heart rate. The total peripheral resistance may undergo a slight increase, and the cardiac output may increase slightly. There is a small decrease in splanchnic flow.

Nitrous oxide does not affect carbon dioxide (CO\textsubscript{2}) response, bronchodilatation, or airway reflexes. The response to hypoxia is unknown.\textsuperscript{8}

Methods and materials

The success of nitrous oxide as an adjunct to local anesthesia has been well recognized. However, delivery may be more of an obstacle than the use itself.

In a series of cataract extractions, a modified Airlife® aerosol mask was used. Excess plastic around the nose bridge metal strip and mask sides was trimmed to allow maximum exposure for the ophthalmologist. The head strap was placed under the patient's ears and around the back of the head to allow prepping and draping without contamination of the surgical field. A 60-inch Ohio DABC® ventilator tube carried gas from the Ohio Unitrol® gas machine.
A 12-liter total flow rate was utilized, with a range of 50% to 60% nitrous oxide with oxygen. Not only did the mask provide adequate room for the surgical field, but it also kept the plastic Vidrape® from lying too close to the patient's face, rendering a feeling of stuffiness and discomfort. After approximately ten minutes, facial nerve and retrobulbar blocks were carried out. Oxygen at a flow rate of 6-8 L/minute was maintained during the surgical procedure.

The aforementioned type of mask also was modified for facial plastic surgical procedures. Two rhytidectomies were carried out using nitrous oxide/oxygen for analgesia during local injection. The mask was trimmed on all sides, including the headstrap holes. The mask was large enough to cover the nose and mouth and was held in place by the anesthetist for ten minutes before the injection to the first side of the face. Only one side of the face was injected at a time, because of the amount of time required to complete the procedure on one side. Two hours later, prior to the injection of the second side, nitrous oxide/oxygen again was applied for ten minutes. After block application, 100% oxygen was given for two to three minutes to prevent diffusion hypoxia.

A standard mask was used in Hickman catheter placement, herniography, and bilateral orchiectomy.

Procedure

Preoperatively the patient was interviewed, and the anesthetic procedure was discussed. The patient was assured that medication would be available should he or she desire further sedation. The intravenous infusion was started, and the patient was transported to the operating room.

Blood pressure was monitored using a Critikon Dinamap®, and the electrocardiogram was monitored using a Siemens 440 Sirecust®.

The nitrous oxide/oxygen mixture was applied at a 50% to 60% (nitrous oxide) concentration, depending on the patient's physical status. The younger, more robust patients received the higher concentration.

Once again, the patient was assured that all was proceeding according to plan and that medication was available if needed.

Conversation was maintained with the patient in order to assess the level of awareness. If any sign of confusion or disorientation appeared, the nitrous oxide concentration was decreased. After ten minutes, the local anesthetic was injected. Oxygen was provided for the remainder of the procedure.

Discussion

In all cases, analgesia was accomplished utilizing a nitrous oxide/oxygen mixture. Patient satisfaction rated high. Only two patients undergoing cataract surgery were dissatisfied with the technique. In both cases, their complaints were based upon degree of awareness, rather than on pain experienced. One patient was displeased with the technique because she could "hear talking," and the other was unhappy with being able to recall being in the operating room. Both denied any pain, but they were displeased with the recall. All other patients were quite satisfied with this technique. Of 30 plus patients, only four required any additional sedation. A diazepam and/or droperidol-fentanyl preparation was used.

The surgeons were pleased with the results of the technique, and several patients were allowed to return home the day of surgery.

The amounts of medication required for the facial plastic procedures were reduced greatly. Usual doses required during a narcotic/sedative technique were diazepam 5-10 mg, droperidol 0.25-5.0 mg, and fentanyl 0.05-0.350 mg. The two facial procedures required fentanyl 0.15 mg, fentanyl 0.10 mg, and diazepam 5 mg with no other sedation other than the nitrous oxide required.

This significant decrease in narcotics and sedatives permits the patient to go home the same day as surgery in most cases.

The most important component of the nitrous oxide technique is the reassurance of the patient. The anesthetist should tell the patient what he or she will experience even before it occurs. Some of the sensory effects of nitrous oxide are tingling of the extremities, giddiness, voices becoming increasingly distant, and a floating sensation. If the anesthetist describes the sensations to the patient before they occur, they will not be as alarming as if they were to occur without any warning. The anesthetist should reassure the patient that medication is available should it be needed. Maintenance of an ongoing conversation during the administration of the nitrous oxide is necessary to determine the level of consciousness and/or anxiety. The patient will be less apprehensive if he is in continuous verbal contact with the anesthetist. Once the administration of the local anesthetic is complete and the nitrous oxide is turned off, the patient returns to preoperative awareness. This is helpful for the procedure which requires patient cooperation.

Procedures such as septoplasty, rhinoplasty, or others in which blood drips into the oropharynx...
may pose a problem in airway management, such as coughing or gagging. With the patient quite responsive to verbal command and not very sedated, he or she is able to manage the continuous clearing of his airway. During cataract extraction, the elderly patient is better able to understand the importance of remaining very quiet.

Nitrous oxide can be considered an effective adjunct to local anesthesia due to its many advantages, including rapid elimination which allows the patient a quicker recovery. Understanding those techniques which are particularly useful in nitrous oxide administration can make the operative experience more agreeable for both the patient and the anesthetist.

REFERENCES

AUTHOR
Edward Dutkiewicz is a graduate of New Britain General Hospital School of Nursing. He received his anesthesia education at Fairfax Hospital School of Nurse Anesthesia and also received a BS degree from George Washington University in Washington, D.C. Currently, he is employed as a staff anesthetist by New Britain Anesthesia, P.C., in New Britain, Connecticut, and is attending Western New England College School of Law.

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Test Yourself Answers
(Questions appeared on page 350.)

1. The equipment should be removed from service and secured. The hospital biomedical department and/or the contracted service representative should be contacted immediately. The equipment should be inspected for proper function. Any service, repair or findings should be reported in writing to the medical director of the anesthesia department and the risk management office. Abnormal findings due to design, service or malfunction should be reported to the Food and Drug Administration and to the manufacturer.

2. To maintain objectivity in peer review, the case review and recommendations should be based upon pre-established criteria and department policy.

3. When a mishap occurs, the family, the risk management office, the insurance carrier(s) and the patient ombudsman/chaplain should be notified.

4. As studied by Cooper, critical incidents are significant occurrences that have either negative or positive effects in whatever setting the investigator is studying. Cooper studied preventable anesthesia mishaps (critical incidents) by interviewing staff and resident anesthesiologists. He labeled incidents as “critical” when it was clear that an occurrence could have led or did lead to an undesirable outcome.

5. To help reduce anesthesia mishaps, every department should develop a safety checklist for each anesthesia machine in the department, and compliance with daily checks must be enforced. Mandatory monitoring standards should be established through departmental policy. Inspired oxygen concentrations should be recorded on every anesthesia record.

New equipment should not be introduced into the department until it has been reviewed at a departmental inservice. The same holds true for new supplies, agents and drugs. Inservice programs should be taped so that staff members, who are unable to attend the inservice have a chance to review the new items as well.

Departments should consider coffee and meal break policies carefully, keeping in mind the fact that fatigue does seem to play a major factor in the occurrence of anesthesia mishaps.
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ACTIONS: Pavalon is a non-depolarizing neuromuscular blocking agent possessing all of the
characteristic pharmacological actions of this class of drugs (curare) on the myoneural
junction.

Pavulon (pancuronium bromide) is esterified by acetylcholine and anticholinesterases and
potassium on its action is increased by inhalational anesthetics such as halothane, diethyl ether,
enflurane and methoxyflurane, as well quinidine, magnesium salts, hypokalemia, some cancer-
omas, and certain antibiotics such as neomycin, streptomycin, cefalothin, kanamycin, gentami-
cin, and tetracycline. The action of Pavulon may be altered by dehydration, electrolyte imbalance
and base imbalance, renal disease, and concomitant administration of other neuromuscular
agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the
gas or to the bromide ion

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSEAGE BY OR
UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS
AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG
SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION,
OXGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST
BE PREPARED TO ASSIST OR CONTROL RESPIRATION

In patients who are known to have myasthenia gravis small doses of Pavulon may have
prolonged effects. A peripheral nerve stimulator is especially valuable in assessing the effects of
Pavulon in such patients

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect
to the possible adverse effects upon fetal development. Therefore, it should not be used in women
of childbearing potential and particularly during early pregnancy unless in the judgment of the
physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section) but reversal of pancuronium
may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because
magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as
indicated, in such cases

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing
pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is
particularly true of renal disease since a major portion of administered Pavulon is excreted
unchanged in the urine

ADVERSE REACTIONS: Neuromuscular: The most frequently noted adverse reactions consist pri-
marily of an extension of the drug's pharmacological actions beyond the time period needed for
surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged
skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of
the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon
(pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by
manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted

Respiratory: Salivation is sometimes noted during very light anesthesia especially if no

Skin: An occasional transient rash is noted accompanying the use of Pavulon

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthesia, has
been reported

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in
patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether,
enflurane and methoxyflurane

Prior administration of succinylcholine, such as that used for endotracheal intubation,
enhances the relaxant effect of Pavulon and the duration of action of succinylcholine is increased.
If succinylcholine is administered before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows
signs of wearing off

DOSEAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of
experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for
suggested dosages

CAUTION: Federal law prohibits dispensing without prescription

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This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Although Tracrium is a less potent histamine release than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactic reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by beta-adrenergic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or cardiovascular disease.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane, isoflurane, halothane, certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quindine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular block induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short-term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenetics assay at up to 3 mg/kg, paralyzing doses. A low response was observed in the mouse lymphoma assay under conditions (50 and 100 μg/ml, in the absence of metabolic activation) which killed over 60% of the treated cells; there was no mutagenicity at 60 μg/ml and lower concentrations which killed up to 50% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic years to lifetime exposure in an effort to determine potential carcinogenicity of a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that furosemide delivery may be necessary.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients with a history of magnesium therapy, a neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see WARNINGS).

The incidence of clinically important adverse reactions was 7/18% or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December 1983. Subsequently reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:

Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodepression (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Adults: A Tracrium dose of 0.4 to 0.5 mg/kg (1.7-2.2 times the ED₉₀), given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, a high percentage of neuromuscular block in adults (over 90%) can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes. Recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of any inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The initial maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age). Dosage may be administered at regular intervals for each patient, ranging approximately from 15 to 25 minutes for infants with even or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with history (e.g., severe anaphylactic reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or cardiovascular in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. No Tracrium dosage adjustments are required for patients with renal disease.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended for adults following the use of succinylcholine for induction under balanced anesthesia. Further reductions may be desirable with the use of potent inhalation anesthetics. The patient should be permitted to recover from the effects of succinylcholine prior to Tracrium administration. Insufficient data are available for recommendation of a specific initial Tracrium dose for administration following the use of succinylcholine in children and infants.

U.S. Patent No. 4179507

Printed in U.S.A.

Get more new information on TRACRIUM® INJECTION (atracurium besylate) at American Association of Nurse Anesthetists Meeting Washington, DC August 11-13, 1986

TRACRIUM® INJECTION
(atracurium besylate) 85TRA12E
In Reversal of nondepolarizing muscle relaxants, don’t look for what’s better...
...look for what’s best

Regonol®
(pyridostigmine bromide injection, USP)
when compared to neostigmine

- Clinically fewer side effects
- Significantly lower degree and incidence of:
  1) Bradycardia
  2) Salivation
  3) Gastrointestinal stimulation
- Wide margin of safety

Organon Pharmaceuticals
Organon A Division of Organon Inc.
West Orange, N.J. 07052
OR-5091
Regoflol (pyridostigmine bromide injection USP)

BRIEF SUMMARY—(Please consult full package insert, enclosed in every package, before using Regoflol)

INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents, intestinal and urinary obstructions of mechanical type.

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in a occasional patient, atropine and antishock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiration assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. It is管理体系 concerned about the adequacy of recovery from the effects of the nondepolarizing muscle relaxant; artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuation of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSEAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneously with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg/kg. Usually 10 or 20 mg of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurracization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme dehydration, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

HOW SUPPLIED—Regoflol is available in:
- 5 mg/ml: 2 ml ampules — boxes of 25—NDC-0052-0460-02
- 5 ml vials — boxes of 25—NDC-0052-0460-05

REFERENCES:

Jackson Memorial Hospital has immediate openings for CRNA's (or board/eligible graduates) to join our staff. Jackson Memorial is a progressive teaching hospital affiliated with the University of Miami. We are a 1,250-bed tertiary care facility offering a wide variety of anesthesia experience in all surgical specialties. We offer an on-going approved continuing education program, and tuition reimbursement, as well as other benefits. We currently have 20 OR's, 5 DR's and have opened a new 3 OR out patient surgical department.

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Professor and Service Chief
Jeff Davis Anesthesia Service
1801 Allen Parkway, Rm. 107, OB Annex
Houston, TX 77019
(713) 751-8127
An equal opportunity employer
See for yourself.

The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...

ideal for your patients, including those at risk.¹⁻⁵
See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials. In fact, even at 12 times effective doses, under halothane anesthesia, NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.

Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED₉₅.⁵

NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range. In contrast, other nondepolarizing neuromuscular blocking agents given at normal clinical doses do increase histamine release to levels at which hypotension and tachycardia tend to occur.⁵

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>%ED₉₅</th>
<th>Histamine</th>
<th>Mean Arterial Pressure</th>
<th>Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubocurarine</td>
<td>0.5</td>
<td>1</td>
<td>410</td>
<td>78</td>
<td>116</td>
</tr>
<tr>
<td>Metocurine</td>
<td>0.5</td>
<td>2</td>
<td>212</td>
<td>79</td>
<td>119</td>
</tr>
<tr>
<td>Atracurium</td>
<td>0.6</td>
<td>3</td>
<td>192</td>
<td>80</td>
<td>108</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1</td>
<td>1.7</td>
<td>117</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.2‡</td>
<td>3.5</td>
<td>87</td>
<td>99</td>
<td>102</td>
</tr>
</tbody>
</table>

*Adapted from Basta et al.⁶

†Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.06 to 0.1 mg/kg.
### Performance unaffected by renal function.

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.

<table>
<thead>
<tr>
<th>Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset (min)</td>
</tr>
<tr>
<td>Duration of time (min) to 90% recovery</td>
</tr>
<tr>
<td>Recovery index (min)</td>
</tr>
</tbody>
</table>

* Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.

† Adapted from Miller et al.

### The surgical muscle relaxant ideal for virtually all patients including those at risk.

**Norcuron®**

*(vecuronium bromide) injection*

See full prescribing information on following page.

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**References:**


**NORCURON® (vecuronium bromide) injection**

**DESCRIPTION:** NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as 1-[2-[3a, 6α-dihydro-6α-hydroxy-1, 2, 3, 4, 6, 7, 8, 8a-octahydro-8, 8a-dimethoxy-1-naphthalenyl]ethyl]-1-piperidinium, 1H-pyridinium, 1, 3, 7-triazacyclododecyl-2-ylacetate monobromide hydrate with the empirical formula of C₂₃H₂₆BrN₂O₂. The drug is a white or pale yellow, odorless, practically inactive, stable, non-hygroscopic oily liquid when stored at room temperature.

**Indications and Usage:** NORCURON® injection is indicated for initial intubating dose and for maintenance of neuromuscular blockade in patients 1 year of age and older for intubation and surgical procedures requiring neuromuscular blocking agents. NORCURON® should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents.

**Warnings:** Hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other associated with changes in blood pressure or heart rate may occur when NORCURON® is administered. Repeated administration of maintenance doses of NORCURON® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeated doses can be administered at relatively regular intervals with predictable neuromuscular blockade recovery. Adverse reactions may be due to either too low or too high a dose of the drug. Incidence and nature of adverse reactions are increased during clinical trials.

**Dosage and Administration:** Maintenance dose is 0.010 to 0.015 mg/kg, generally required within 25 to 40 minutes; subsequent maintenance dose may be administered at relatively regular intervals with neuromuscular blockade recovery. Norcuron should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of NORCURON® has not been studied. Repeated administration of maintenance doses of NORCURON® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeated doses can be administered at relatively regular intervals with predictable neuromuscular blockade recovery. Adverse reactions may be due to either too low or too high a dose of the drug. Incidence and nature of adverse reactions are increased during clinical trials.

**ADVERSE REACTIONS:** Bronchospasm, flushing, redness, hypotension, tachycardia, and other associated with changes in blood pressure or heart rate may occur when NORCURON® is administered. Repeated administration of maintenance doses of NORCURON® has little or no cumulative effect on the duration of neuromuscular blockade.

**Drug Interactions:** Administration of NORCURON® with other drugs that cause respiratory depression may result in respiratory depression. Administration of NORCURON® with drugs which also cause respiratory depression should be avoided. There are insufficient data to support concomitant use of NORCURON® and other competitive muscle relaxants.

**Special Considerations:** Delay of 2 to 3 minutes between NORCURON® administration and intubation is recommended. Prior administration of succinylcholine may enhance the neuromuscular blocking effect of NORCURON® and its duration of action. With succinylcholine as the relaxing agent, initial doses of 0.04 to 0.06 mg/kg of NORCURON® may produce complete neuromuscular block with clinical duration of action of 25 to 30 minutes. Succinylcholine is used prior to NORCURON® administration, the administration of NORCURON® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of NORCURON® has not been studied. Repeated administration of maintenance doses of NORCURON® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeated doses can be administered at relatively regular intervals with predictable neuromuscular blockade recovery. Adverse reactions may be due to either too low or too high a dose of the drug. Incidence and nature of adverse reactions are increased during clinical trials. NORCURON® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine bromide, neostigmine, or edrophonium. Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with NORCURON® as with all nondepolarizing neuromuscular blocking agents.

**Formulation:** NORCURON® injection is available in 5 ml vials (contains 10 mg of active ingredient) only. DIUENT (Sterile Water for Injection) DILUTION: NORCURON® injection is supplied as a sterile, aqueous solution for injection containing 10 mg/ml. The pH of the solution is approximately 7.4. The solution may be stored in refrigerator or kept at room temperature not to exceed 30ºC.

**Storage:** Store in a tightly closed container and protect from light. Solution may be stored in refrigerator or kept at room temperature not to exceed 30ºC.