ROCURON®

Rocuronium Bromide INN

PRESENTATION

Each vial contains Rocuronium Bromide INN 50 mg injection. Rocuron is supplied in a vial as a clear, aqueous solution for intravenous injection.

DESCRIPTION

Rocuronium Bromide is a fast onset, intermediate acting non-depolarizing neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of medicines (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

The clinical duration with 0.6mg/kg Rocuronium Bromide is 30-40 minutes. The total duration is 50 minutes. The mean time of spontaneous recovery of twitch response from 25 to 75% (recovery index) after a bolus dose of 0.6mg/kg Rocuronium Bromide is 14 minutes. With lower dosages of 0.3-0.45mg/kg Rocuronium Bromide, onset of action is slower and duration of action is shorter. With high doses of 2mg/kg, clinical duration is 110 minutes.

INDICATIONS

Rocuron is indicated -

- As an adjunct to general anesthesia to facilitate tracheal intubation during routine induction, and during rapid sequence induction when suxamethonium is contraindicated
- To provide skeletal muscle relaxation during surgery
- As an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation

DOSAGE & ADMINISTRATION

Dosage

Like other neuromuscular blocking agents, Rocuron should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these agents. The dosage of Rocuron should be individualized in each patient. The method of anesthesia and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other medicines that are administered concomitantly and the condition of the patient should be taken into account when determining the dose. The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery. Inhalational anesthetics do potentiate the neuromuscular blocking effects of Rocuron. This potentiation, however, becomes clinically relevant in the course of anesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with Rocuron should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Rocuron during long lasting procedures (longer than 1 hour) under inhalational anesthesia. In adult patients the following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures, and for use in the intensive care unit.

Surgical Procedures

Tracheal Intubation: The standard intubating dose during routine anesthesia is 0.6mg Rocuronium Bromide per kg body weight, after which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0mg Rocuronium Bromide per kg body weight is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anesthesia, after which adequate intubation conditions are also established within 60 seconds in nearly all patients. If a dose of 0.6mg Rocuronium Bromide per kg body weight is used for rapid sequence induction of anesthesia, it is recommended to intubate the patient 90 seconds after administration of Rocuronium Bromide. In patients undergoing Caesarean section it is recommended to only use a dose of 0.6mg Rocuronium Bromide per kg body weight, since a 1.0mg/kg dose has not been investigated in this patient group.

Maintenance Dosing: The recommended maintenance dose is 0.15mg Rocuronium Bromide per kg body weight; in the case of long-term inhalational anesthesia this should be reduced to 0.075-0.1mg Rocuronium Bromide per kg body weight. The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height, or when 2-3 responses to train of four stimulation are present.

Continuous Infusion: If Rocuronium Bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6mg Rocuronium Bromide per kg body weight and, when neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height, or to maintain 1 to 2 responses to train of four stimulation. In adults under intravenous anesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6mg/kg/hr and under inhalational anesthesia the infusion rate ranges from 0.3-0.4mg/kg/hr. Continuous monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Dosing in Paediatric Patients: Children (1-14 years) and infants (1-12 months) under halothane anesthesia manifest similar sensitivity to Rocuronium Bromide as adults. Onset of action is faster in infants and children than in adults. Clinical duration is shorter in children than in adults. For continuous infusion in paediatrics, the infusion rates, with exception of children, are the same as for adults. For children higher infusion rates might be necessary. For children the same initial infusion rates as for adults are recommended and this should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to train of four stimulation during the procedure. There are insufficient data to support dose recommendations for the use of Rocuronium Bromide in neonates (0-1 month). The experience with Rocuronium Bromide in rapid sequence induction in paediatric patients is limited. Rocuronium Bromide is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

Dosing in Geriatric patients and patients with Hepatic and/or Biliary tract disease and/or Renal Failure: The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anesthesia is 0.6mg Rocuronium Bromide per kg body weight. A dose of 0.6mg per kg body weight should be considered for rapid sequence induction of anesthesia in patients in which a prolonged duration of action is expected. Regardless of the anesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1mg Rocuronium Bromide per kg body weight, and the recommended infusion rate is 0.3-0.4mg/kg/hr.

Dosing in Overweight and Obese Patients: When used in overweight or obese patients (defined as patients with a body weight of 30% or more above ideal body weight) doses should be reduced taking into account ideal body weight.

Intensive Care Procedures

Tracheal Intubation: For tracheal intubation, the same doses should be used as described above under surgical procedures.

Maintenance Dosing: The use of an initial loading dose of 0.6mg Rocuronium Bromide per kg body weight is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train of four stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80-90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3-0.6mg/kg/hr during the first hour of administration, which will need to be decreased during the following 6-12 hours, according to the individual response. Thereafter, individual dose requirements remain relatively constant. A large between patient variability in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2-0.5mg/kg/hr depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Administration up to 7 days has been investigated.

Special Populations: Rocuronium Bromide is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and geriatric patients due to a lack of data on safety and efficacy.

Administration

Rocuronium Bromide is administered intravenously either as a bolus injection or as a continuous infusion.

CONTRAINDICATIONS

Hypersensitivity to Rocuronium or to the Bromide ion or to any of the excipients.

WARNINGS & PRECAUTIONS

Since Rocuronium Bromide causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this agent until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. In case of intubation difficulties resulting in a clinical need for immediate reversal of Rocuronium Bromide induced neuromuscular block, the use of sugammadex should be considered. As with other neuromuscular blocking agents, residual curarization has been reported for Rocuronium Bromide. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Other factors which could cause residual curarization after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of sugammadex or another reversal agent should be considered, especially in those cases where residual curarization is more likely to occur. Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross-reactivity to neuromuscular blocking agents has been reported. In general, following long term use of neuromuscular blocking agents in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or over dosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, neuromuscular blocking agents should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Myopathy after long term administration of other non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported regularly. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of the neuromuscular blocking agent should be limited as much as possible. If suxamethonium is used for intubation, the administration of Rocuronium Bromide should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium. The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Rocuronium Bromide:

Hepatic and/or Biliary tract disease and Renal failure: Because Rocuronium Bromide is excreted in urine and bile, Rocuronium Bromide should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6mg Rocuronium Bromide per kg body weight.

Prolonged Circulation Time: Conditions associated with prolonged circulation time such as cardiovascular disease, old age and edematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. The duration of action may also be prolonged due to a reduced plasma clearance.

Neuromuscular Disease: Like other neuromuscular blocking agents, Rocuronium Bromide should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Rocuronium Bromide may have profound effects and Rocuronium Bromide should be titrated to the response.

Hypothermia: In surgery under hypothermic conditions, the neuromuscular blocking effect of Rocuronium Bromide is increased and the duration prolonged.

Obesity: Like other neuromuscular blocking agents, Rocuronium Bromide may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight.

Burns: Patients with burns are known to develop resistance to non-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of Rocuronium Bromide: Hypokalaemia (e.g. after severe vomiting, diarrhoea and diuretic therapy), hypermagnesemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

Pregnancy and Lactation

Pregnancy: For Rocuronium Bromide, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing Rocuronium Bromide to pregnant women.

Caesarean section: In patients undergoing Caesarean section, Rocuronium Bromide can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anesthetic agent is administered or following suxamethonium facilitated intubation. Rocuronium Bromide, administered in doses of 0.6mg/kg, has been shown to be safe in parturient undergoing Caesarean section. Rocuronium Bromide does not affect Apgar score, foetal muscle tone nor cardio-respiratory adaptation. From umbilical cord blood sampling it is apparent that only limited placental transfer of Rocuronium Bromide occurs which does not lead to the observation of clinical adverse effects in the newborn.

Lactation: It is unknown whether Rocuronium Bromide is excreted in human breast milk. Animal studies have shown insignificant levels of Rocuronium Bromide in breast milk. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Rocuronium Bromide should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

ADVERSE EFFECTS

In clinical trials, the most common adverse reactions (2%) are transient hypotension and hypertension. Other are -

- o Anaphylaxis
- o Residual paralysis
- o Myopathy
- o Increased pulmonary vascular resistance

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Rocuronium Bromide, have been reported. Anaphylactic/anaphylactoid reactions are: bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse - shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume they may occur and take the necessary precautions.

Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematosus reactions at the site of injection and/or generalized histaminoid (anaphylactoid) reactions (see also under Anaphylactic Reactions above) should always be taken into consideration when administering these agents.

In clinical studies only a slight increase in mean plasma histamine levels has been observed following rapid bolus administration of 0.3-0.9mg/kg Rocuronium Bromide.

Prolonged neuromuscular block: The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the agent's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnoea.

Myopathy: Myopathy has been reported after the use of various neuromuscular blocking agents in the ICU in combination with corticosteroids.

Local injection site reactions: During rapid sequence induction of anesthesia, pain on injection has been reported, especially when the patient has not yet completely lost consciousness and particularly when propofol is used as the induction agent. In clinical studies, pain on injection has been noted in 16% of the patients who underwent rapid sequence induction of anesthesia with propofol and in less than 0.5% of the patients who underwent rapid sequence induction of anesthesia with fentanyl and thiopental.

DRUG INTERACTIONS

The following agents have been shown to influence the magnitude and/or duration of action of non-depolarizing neuromuscular blocking agents:

Effect of other agents on Rocuronium Bromide

Increased Effect: Halogenated volatile anesthetics potentiate the neuromuscular block of Rocuronium Bromide. The effect only becomes apparent with maintenance dosing. Reversal of the block with anti-cholinesterase inhibitors could also be inhibited. Long-term concomitant use of corticosteroids and Rocuronium Bromide in the ICU may result in prolonged duration of neuromuscular block or myopathy.

Other drugs:

Antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.

Diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lidocaine i.v., bupivacaine epidural) and acute administration of phenytoin or ?-blocking agents.

Recurarization has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium.

Decreased Effect: Prior chronic administration of phenytoin or carbamazepine. Protease inhibitors (gabexate, ulinastatin)

Variable Effect: Administration of other non-depolarizing neuromuscular blocking agents in combination with Rocuronium Bromide may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used. Suxamethonium given after the administration of Rocuronium Bromide may produce potentiation or attenuation of the neuromuscular blocking effect of Rocuronium Bromide.

Effect of Rocuronium Bromide on other drugs

Rocuronium Bromide combined with lidocaine may result in a quicker onset of action of lidocaine.

OVERDOSAGE

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. In this situation there are two options for the reversal of neuromuscular block: (1) Sugammadex can be used for reversal of intense (profound) and deep block. The dose of sugammadex to be administered depends of the level of neuromuscular block. (2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine), with appropriate vagolytic (e.g atropine) can be used at reappearance of T2 or at the first signs of clinical recovery and should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of Rocuronium Bromide, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

PRECAUTIONS

Instructions for use/handling

Compatibility studies with the following infusion fluids have been performed. In nominal concentrations of 0.5mg/mL and 2.0mg/mL, Rocuronium Bromide has been shown to be compatible with: 0.9% NaCl, 5% dextrose, 5% dextrose in saline, sterile water for injections, Lactated Ringers and Haemaccel. Administration should be commenced immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

For use/handling

If Rocuronium Bromide is administered via the same infusion line that is also used for other medicines, it is important that this infusion line is adequately flushed (e.g. with 0.9% NaCl) between administration of Rocuronium Bromide and medicines for which incompatibility with Rocuronium Bromide has been demonstrated or for which compatibility with Rocuronium Bromide has not been established.

STORAGE

Rocuron should be stored in the refrigerator at 2-8 °C and not be frozen.

Commercial Packaging

Each box contains 1 vial of 50 mg Rocuronium Bromide INN.

Manufactured by
Incepta Pharmaceuticals Ltd
Dhaka, Bangladesh
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V.N. 01
RCI

W = 120 mm L = 290 mm