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Review Article

Clinical Pharmacology of Rocuronium in Infants and Children

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Abstract

The main clinical use of the neuromuscular blocking agents is an adjuvant in surgical anaesthesia to obtain relaxation of skeletal muscle, particularly of the abdominal wall, to facilitate surgical manipulations. Rocuronium can be used instead of suxamethonium to provide rapid muscle paralysis during tracheal intubation but the recovery is much slower. Rocuronium is administered intravenously to infants and children. In infants, rocuronium is administered at a dose of 450 µg/kg for providing muscle relaxation for laryngeal intubation. To provide sustained paralysis, rocuronium is given at a dose of 600 µg/kg. In children, the neuromuscular blockade is obtained with 600 µg/kg followed by an intravenous infusion of 150 µg/kg per hour. For assisted ventilation in intensive care, rocuronium is administered at a dose of 600 µg/kg followed by an intravenous infusion of 300 to 600 µg/kg per hour. The effects of rocuronium have been extensively studied in infants and children. Rocuronium is converted into 17-desacetyl rocuronium. The pharmacokinetics of rocuronium have been studied in infants and children and the mean residence time is 55.6 and 25.6 min (P-value < 0.01) in infant and children, respectively. Rocuronium interacts with drugs, the treatment of infants and children with rocuronium has been studied, and rocuronium poorly crosses the human placenta. The aim of this study is to review the published data on rocuronium dosing, pharmacokinetics, and treatment in infants and children, and rocuronium metabolism and transfer across the human placenta.

Key Words: rocuronium; dosing; effects; metabolism; pharmacokinetics; treatment; placental-transfer; infants; and children

Introduction

Mechanism of action of neuromuscular blocking agents

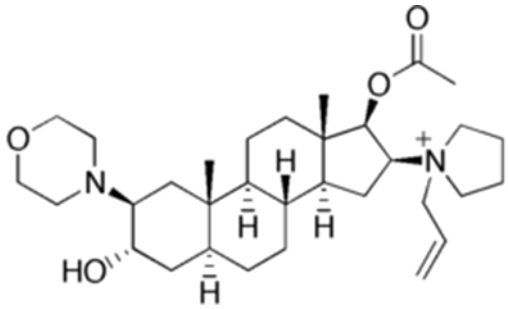
Competitive antagonists bind the nicotine acetylcholine receptor in skeletal muscle and thereby competitively block the binding of acetylcholine. The depolarizing agents, such as succinylcholine, depolarize the membrane by opening channels in the same manner as acetylcholine. However, they persist longer at the neuromuscular junction primarily because of their resistance to acetylcholine. The depolarisation is thus longer lasting, resulting in a brief period of repetitive excitation that may elicit transient and repetitive muscle excitation (fasciculations), followed by blocking of neuromuscular transmission and flaccid paralysis (called phase I block). The block arises because, after an initial opening, perjunctional Na^+ channels close and will not reopen until the end plate is repolarized. At this point, neural release of acetylcholine results in the binding of acetylcholine to receptors on an already-depolarized end plate. These closed perjunctional channels keep the depolarization signal from effecting downstream channels and effectively shield the rest of the muscle from activity at the motor end plate. This sequence is influenced by such factors as the anaesthetic agent used concurrently, the type of muscle, and the rate of drug administration. Under clinical condition, with increasing concentrations of succinylcholine and over time, the block may convert slowly from a depolarizing phase I block to a non-depolarizing phase II block. While the response to peripheral stimulation during phase II block by administration of anti-acetylcholine agents (e.g., neostigmine) is difficult to predict and should be undertaken cautiously. Many drugs and toxins block neuromuscular transmission by other mechanisms, such as interference with the synthesis or realised acetylcholine, but most of these agents are not employed clinically for neuromuscular blockade. One exception is the group of botulinum toxins, which are administered locally into muscles of the orbit in the management of ocular blepharospasm and strabismus and have been used to control other muscle spasm and to facilitate facial muscle relaxation. This toxin also has been injected into the lower oesophageal sphincter to treat achalasia [1].

Muscular relaxation of neuromuscular blocking agents

The main clinical use of the neuromuscular blocking agents is an adjuvant in surgical anaesthesia to obtain relaxation of skeletal muscle, particularly of the abdominal wall, to facilitate operative manipulations. With muscle relaxation no longer dependent on the depth of general anaesthesia, a much lighter level of anaesthesia suffices. Thus, the risk of respiratory and cardiovascular depression is minimized, and post-anaesthetic recovery is shortened. Neuromuscular blocking agents of short duration often are used to facilitate endotracheal intubation and have been used to facilitate laryngoscopy, bronchoscopy, and esophagoscopy in combination with a general anaesthetic agent. Neuromuscular blocking agents are administered parenterally, nearly always intravenously. These agents may be administered by continuous infusion in the intensive care setting for improving chest wall compliance and eliminating ventilator dyssynchrony [1].

Clinical use of rocuronium

Rocuronium can be used instead of suxamethonium to provide rapid muscle paralysis during tracheal intubation, but the recovery is much slower. Vecuronium is a similarly long-acting paralytic agent but takes longer to work. Atracurium and mivacurium are useful (but slower acting) alternatives when short-term paralysis is all that is required, but are more likely to trigger histamine release [2]. Rocuronium is used for muscle relaxation/paralysis in patients requiring endotracheal intubation. Rocuronium is an aminosteroid non-depolarizing neuromuscular blocking agent that is an analogue of vecuronium with 10 to 15% of its potency. It has a rapid to intermediate onset depending on the dose and intermediate duration. It acts by competing for cholinergic receptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine and edrophonium. The plasma levels of rocuronium follow a three compartment open model following intravenous administration. The rapid distribution half-life is 1 to 2 min and the sower distribution half-life is 14 to 18 min. Onset of clinical effect usually occurs within 2 min and the duration ranges from 20 min to 2 hours. Larger doses (900 to 1,200 µg/kg) lead to more rapid onset and larger duration of clinical effect. It can have differential effects on various muscle groups (e.g., laryngeal versus adductor pollicis versus diaphragm). The onset of laryngeal adductor paralysis is significantly slower with rocuronium compared to succinylcholine. Despite this difference, rocuronium has the fastest onset of any currently available non-depolarizing muscle relaxant. The average half-life in newborns is 1.1 hours. Rocuronium is approximately 30% protein bound, and is primary excreted by the liver [3].



Rocuronium molecular structure (molecular weight = 529.7742 grams/mole)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: “rocuronium dosing infants, children“, “rocuronium effects infants, children, “rocuronium adverse-effects infants, children”, “rocuronium metabolism”, “rocuronium pharmacokinetics infants, children”, “rocuronium drug interactions”, “rocuronium treatment infants, children”, and “rocuronium placental transfer”. In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] have been consulted.

Results

Administration schedules or rocuronium to infants and children

Intravenous administration to infants [2]

Brief use to effect intubation: 450 µg/kg of rocuronium provides the muscle relaxation needed to effect easy laryngeal intubation within a min in infants < 1 year old, but recovery may take 1 hour. A larger dose does not speed the onset of paralysis and may double recovery time in a young infants.

Use to provide sustained paralysis: Start giving 600 µg/kg of rocuronium by intravenous injection. Most infants continue to comply with the imposed ventilator rate as they wake from this first paralysing dose (especially if a moderately fast rate and a relatively short inspiratory time is used) but a few require prolonged paralysis. The standard repeat dose is a quarter to half the initial dose given intravenously every 2 to 4 hours as necessary but some older infants seem to require a higher maintenance dose. Paralysed infants should always be sedated. An infusion of 300 to 600 µg/kg per hour adjusted according to the response is an alternative to intermittent dosing.

Intravenous administration for neuromuscular blockade (intermediate duration) during surgery [4]

Children. Give initially 600 µg/kg, and then (by intravenous injection) 150 µg/kg, repeat the dose if necessary, alternatively (by intravenous infusion) 300 to 600 µg/kg per hour, adjust the dose according to the response.

Intravenous administration for assisted ventilation in intensive care [4]

Children. Give initially 600 µg/kg, initial dose is optimal, and then (by intravenous infusion) give 300 to 600 µg/kg per hour for the first hour, and then (by intravenous infusion) adjust the dose according to the response.

Effects of rocuronium in infants and children

Rocuronium facilitates successful intubation and provided clinical paralysis quickly in term and preterm infants [5]. Six-hundred µg/kg of rocuronium has a rapid onset of effect in infants and prolonged duration of action in infants compared to children [6]. Neuromuscular blockade induced by rocuronium can be effectively reversed with sugammadex 2 mg/kg in children aged 1 to 12 years [7]. A dose of 450 µg/kg

rocuronium results in rapid relaxation and safe ventilation in paediatric patents undergoing rigid bronchoscopy [8]. Rocuronium at intubating doses of 450, 600 or 1,000 µg/kg is effective in producing rapid-onset neuromuscular blockade with an intermediate duration of action in paediatric patients during sevoflurane induction/isoflurane maintenance anaesthesia [9]. Intramuscular rocuronium does not consistently provide satisfactory tracheal intubating conditions in infants and children and is not an adequate alternative to intramuscular succinylcholine when rapid intubation is necessary [10]. Deltoid injections of rocuronium at a dose of 1,000 µg/kg in infants and 1,800 µg/kg in children rapidly permit tracheal intubation in infants and children, despite a light plane of anaesthesia [11]. The emergency recovery following an average 94.5±4.8% neuromuscular blockade established by rocuronium is roughly similar in infants and children. Thus, one ED_{95} dose of rocuronium, unlike vecuronium, acts as an intermediate-acting agent in infants and children [12]. Rocuronium has a rapid onset and intermediate duration of action in children aged 4 to 12 years and appears to devoid significant adverse-effects [13]. Rocuronium reduces the frequency of oculocardiac reflex mainly by reducing the incidence of supraventricular and ventricular premature beats [14]. Rocuronium given at a dose of 300 µg/kg during halothane anaesthesia causes neuromuscular depression and has a longer duration of action in infants than in children older than 2 years [15].

Adverse-effects caused by rocuronium in infants and children [4]

Uncommon adverse-effects

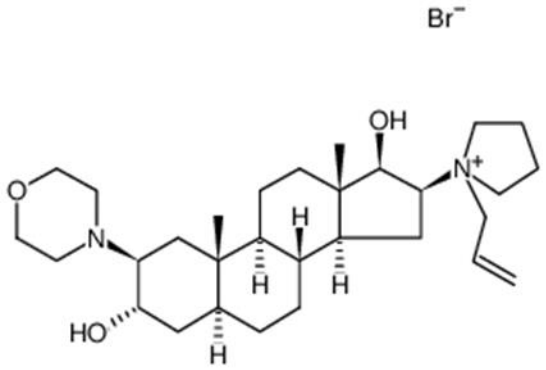
Procedural complications and tachycardia.

Rare or very rare adverse-effects

Angioedema, circulatory collapse, face oedema, malignant hyperthermia, paralysis, and shock.

Metabolism of rocuronium

In literature there is only one study on rocuronium metabolism and it has been reported by Proost et al. [16]. In samples of human urine, bile, and faeces only small amounts of rocuronium metabolite 17-desacetyl-rocuronium have been found.



17-Desacetyl Rocuronium bromide molecular structure (molecular weight = 567.6 grams/mole)

Pharmacokinetics of rocuronium in infants and children

Wierda et al. [17] studied the pharmacokinetics of rocuronium in 5 infants aged 0.1 to 0.8 years and in 5 children aged 2.3 to 8 years. Rocuronium was intravenously infused at a dose of 600 µg/kg per min to infants and at a dose of 900 µg/kg per min to children. Table 1 provides the surgical procedures and subject's demographic characteristics and table 2 summarizes the pharmacokinetics of rocuronium.

Value	Infants	Children
Surgical procedure (N)		
Tracheal resection	2	---
Aortic valvulotomy	1	---
Aortic coarctation resection	2	---
Atrial septum closure	---	4
Ventricular septum closure	---	1
Age (years)	0.5 (0.1 – 0.8)	5.4 (2.3 – 8.0)
Body-weight (kg)	6.0±2.1 (4.7 – 9.6)	19.1±4.9 (13.8 – 27.0)

Table 1: Subject data and surgical procedures. Figures are the subject number or mean±SD, and (range) by Wierda et al. [17].

Variable	Infants	Children	*P-value
Cl_{pl} (ml/min/kg)	4.19±0.43 (3.88 – 4.93)	6.66±1.05 (5.65 – 8.09)	< 0.01
Cl_{12} (ml/min/kg)	15.1±4.0 (8.8 – 19.2)	10.4±2.2 (7.5 – 13.2)	NS
Cl_{13} (m/min/kg)	3.24±3.55 (1.31 – 9.57)	1.69±0.63 (0.64 – 2.16)	NS
V_1 (ml/kg)	35.4±5.4 (28.0 – 43.6)	34.7±12.8 (16.1 – 44.8)	NS
V_2 (ml/kg)	87.0±37.0 (49.0 – 142)	44.0±16.0 (26.0 – 62.0)	< 0.05
V_3 (ml/kg)	108±16 (89.0 – 133)	86.0±34.0 (49.0 - 139)	NS
V^{ss} (ml/kg)	231±32.0 (202 – 283)	165±44.0 (120 – 214)	< 0.05

MRT (min)	55.6±9.9 (41.0 – 66.9)	25.6±8.9 (14.8 – 37.9)	< 0.01
K_{eo} (min^{-1})	0.25±0.08 (0.17 – 0.34)	0.32±0.06 (0.24 – 0.37)	NS
EC_{50} (mg/L)	1.19±0.38 (0.79 – 1.62)	1.65±0.38 (1.20 – 2.02)	< 0.05
γ	5.74±1.28 (4.78 – 7.97)	3.91±0.51 (3.12 – 4.56)	< 0.01
ED_{50} (mg/kg)	0.261±0.066 (0.190 – 0.300)	0.335±0.077 (0.255 – 0.451)	NS

Table 2: Pharmacokinetic parameters of rocuronium which are obtained in 5 infants and in 5 children. Figures are the mean±SD and (range), by Wierda et al. [17].

Cl_{pl} = plasma clearance. Cl_{12} and Cl_{13} = distribution clearance to the second and third compartment, respectively. V_1, V_2, and V_3 = volume of the central, second and third compartments, respectively. V^{ss} = distribution volume at steady-state. MRT = mean residence time after an intravenous bolus dose. K_{eo} = rate constant of equilibration between central and peripheral compartments. EC_{50} = the concentration in the effect compartment at 50% neuromuscular block. γ = slope of the concentration-effect relationship in the effect compartment. ED_{50} = calculated bolus dose resulting in 90% block. NS = not significant. *Mann-Whitney U test.

This table shows that the plasma clearance is greater in children than in infants, the volume of the second compartment is lower in children, the distribution volume at the steady state and the mean residence time are lower in children, and the concentration in the peripheral compartment at 50% neuromuscular block is greater in children, the slope of the concentration-effect relationship in the effect compartment is lower in children.

Interaction of rocuronium with drugs

The co-administration of rocuronium with cisatracurium results in a synergic effect [18]. Rocuronium inhibits the formation-rate of temazepam and desmethyldiazepam by 20% and 15%, respectively, in human liver microsomes [19]. Magnesium potentiates the neuromuscular effect of rocuronium and shifts the concentration-response curve to the left [20]. The calculated doses producing 50% depression (ED_{50}) of the twitch height for rocuronium, pancuronium, pipecuronium and vecuronium were 144.8, 32.4, 27.1, and 23.7 µg/kg, respectively. Corresponding doses producing 95% depression (ED_{95}) of twitch height were, respectively, 322.1, 58.1, 48.7, and 39.9 µg/kg. Based on the estimate of ED_{50}, the relative potency is 1:4, 5:5, and 4:6, respectively. The interaction between rocuronium and vecuronium, pipecuronium or pancuronium is found to be additive [21]. Chronic therapy with anticonvulsant drugs reduces the duration of action of rocuronium [22]. Phenytoin acutely augments the neuromuscular block produced by rocuronium without altering its plasma concentration or its binding to plasma proteins [23].

Treatment of infants and children with rocuronium

Children born full-term or with birthweight > 2.5 kg in the cerebral palsy cohort requires more rocuronium than preterm and low birthweight counterparts [24]. Three-hundred µg/kg of rocuronium is better than a lower dose of 150 µg/kg for clinically acceptable intubating conditions in paediatric ambulatory surgery during remifentanil-propofol-based anaesthesia at the doses used in the study [25]. Sub-paralyzing doses of rocuronium show a distinct effect on muscular endurance as opposed to momentary force. These findings support the hypothesis that low doses of rocuronium act mainly by reducing muscular endurance, thereby facilitating, for example, tracheal intubation [26]. A total of 300 µg/kg of rocuronium is sufficient for tracheal intubation for children aged 1 to 6 years under sevoflurane induction [27]. During inhalation induction with 8% sevoflurane in 60% nitrous oxide, rocuronium 290 µg/kg optimizes intubation conditions for surgery of short duration [28].

Transfer of rocuronium across the human placenta

In literature there is only one investigation of the transfer of rocuronium across the human placenta and it is reported by Abouleish et al. [29]. Rocuronium was injected at a dose of 600 µg/kg to 32 pregnant women at delivery.

Parameter	Mean±SEM	Range	Median	Ratio of means
Maternal venous blood (ng/ml)	2,412±180	1,120 – 6,300	2,200	---
Umbilical venous blood (ng/ml)	390±27.8	50 – 931	349	---
Umbilical arterial blood (ng/ml)	271±34.7	72 - 495	277	---
Umbilical vein to maternal ratio	---	---	---	0.191
Umbilical arterial to maternal ratio	---	---	---	0.620

Table 3: Maternal and fetal plasma concentrations of rocuronium which are obtained in 32 maternal and fetal pairs. Figures are the mean±SEM, range, and median, by Abouleish et al. [29].

This table shows that rocuronium poorly crosses the human placenta and rocuronium concentration is higher in the umbilical vein blood than in the umbilical arterial blood.

Discussion

The main clinical use of the neuromuscular blocking agents is an adjuvant in surgical anaesthesia to obtain relaxation of skeletal muscle, particularly of the abdominal wall, to facilitate surgical manipulations. Neuromuscular blocking agents of short duration often are used to facilitate endotracheal intubation and have been used to facilitate

laryngoscopy, bronchoscopy, and esophagoscopy in combination with a general anaesthetic agent [1]. Rocuronium can be used instead of suxamethonium to provide rapid muscle paralysis during tracheal intubation, but the recovery is much slower. Vecuronium is a similarly long-acting paralytic agent but takes longer time to work. Atracurium and mivacurium are useful (but slower acting) alternatives when short-term paralysis is all that is required, but are more likely to trigger histamine release [2]. Rocuronium is used for muscle relaxation/paralysis in patients requiring endotracheal intubation. Rocuronium is an aminosteroid non-depolarizing neuromuscular blocking agent that is an analogue of vecuronium with 10 to 15% of its potency. It has a rapid to intermediate onset depending on dose and intermediate duration. Rocuronium acts by competing for cholinergic receptors at the motor end-plate. Rocuronium can have differential effects on various muscle groups (e.g., laryngeal versus adductor pollicis versus diaphragm). The onset of laryngeal adductor paralysis is significantly slower with rocuronium compared to succinylcholine. Despite this difference, rocuronium has the fastest onset of any currently available non-depolarizing muscle relaxant [3]. Rocuronium is administered intravenously to infants and children. In infants, the dose to produce a brief effect for intubation is 450 µg/kg and the dose for providing a sustained paralysis is 600 µg/kg [2]. In children, the dose for neuromuscular blockade is 600 µg/kg followed by 150 µg/kg [4]. The effects caused by rocuronium have been extensively studied in infants and children [5-15]. Rocuronium is used to provides clinical paralysis to facilitates intubation in term and preterm infants [5], a dose of 600 µg/kg rocuronium has a more prolonged onset of effect in infants than in children [6], the neuromuscular blockade induced by rocuronium is reversed by 2 mg/kg sugammadex [7], a dose of 450 µg/kg results in a rapid relaxation in paediatric patients undergoing rigid bronchoscopy [8], rocuronium at a dose of 450, 600, or 1,000 µg/kg produces neuromuscular blockade in paediatric patients during anaesthesia [9], intramuscular rocuronium does not provide satisfactory tracheal intubation conditions in infants and children and is not alternative to succinylcholine [10], deltoid injections of rocuronium at a dose of 1,000 µg/kg to infants and 1,800 µg/kg to children permit tracheal intubation [11], the emergency recovery of neuromuscular blockade established by rocuronium is similar in infants and children [12], rocuronium produces neuromuscular blockade in children without producing adverse-effects [13], rocuronium reduces the frequency of oculocardiac reflex in children [14], and a rocuronium dose of 300 µg/kg causes neuromuscular depression in infants and children undergoing anaesthesia [15]. Rocuronium is converted into 17-desacetyl rocuronium and this metabolite appears in small amounts in urine, bile, and faeces [16]. The pharmacokinetics of rocuronium have been studied in infants and children and the mean residence time of rocuronium is 55.6 and 25.6 hours (P-values < 0.01) in infants and children, respectively. The volumes of the central, second, and third compartments are 35.4, 87.0, and 108 ml/kg in infants and 34.7, 44.0, and 86.0 ml/kg in children [17]. Rocuronium interacts with drugs [18-23]. The co-administration of rocuronium with cisatracurium results in a synergistic effect [18], rocuronium inhibits the formation-rate of temazepam and desmethyldiazepam [19], magnesium potentiates the neuromuscular effect of rocuronium [20], the interaction between rocuronium and vecuronium, pipecuronium or pancuronium is additive [21], anticonvulsants drugs reduce the duration of rocuronium effect [22], and phenytoin augments the neuromuscular block produced by rocuronium [23]. The treatment of infants and children with rocuronium has been studied [24-28]. Children requires more rocuronium than infants [24], a rocuronium dose of 300 µg/kg is better than a dose of 150 µg/kg for intubation paediatric patients undergoing surgery [25], low rocuronium doses act mainly by reducing muscular endurance facilitating the tracheal intubation [26], a 300 µg/kg rocuronium dose is sufficient for tracheal intubation in children [27], and a dose of 290 µg/kg rocuronium optimizes the intubation conditions for surgery [28]. Rocuronium poorly crosses the human placenta [29].

In conclusion, rocuronium is a neuromuscular agent and is used in surgical anaesthesia to reduce the relaxation of skeletal muscle, particularly of the abdominal wall, to facilitate surgical manipulations. Rocuronium is administered intravenously to infants and children. In infants, the muscular relaxation necessary for easy laryngeal intubation is obtained with 450 µg/kg and a dose of 600 µg/kg is necessary for surgery. In children, the neuromuscular blockade is obtained with 600 µg/kg followed by 150 µg/kg. The effects caused by rocuronium in infants and children have been extensively studied. Rocuronium is converted into 17-desacetyl rocuronium. The pharmacokinetics of rocuronium have been studied in infants and children and the mean residence time of rocuronium is 55.6 and 25.6 hours (P-value <0.01) in infants and children, respectively. Rocuronium interacts with drugs and the treatment of infants and children with rocuronium has been studied in infants and children and rocuronium is poorly transferred across the human placenta. The aim of this study is to review the clinical pharmacology of rocuronium in infants and children.

Conflict of interests

The authors declare no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts, and honoraria.

This article is a review and drugs have not been administered to men or animals.

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