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REVIEW ARTICLE

ROCURONIUM FOR MUSCLE RELAXATION IN AMBULATORY PATIENTS

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INTRODUCTION

Although ambulatory surgery has been performed for decades, recently it has gained new interest and popularity worldwide. This has come about because new anesthetic drugs have been developed, characterized by a short duration of action and less side-effects, and because surgical techniques have also been improved. Health economics, in particular the need to reduce costs, stimulated the development of day-care centers, frequently a separate unit as part of a general hospital.

Selection for suitability of a procedure to be performed under day-care conditions is, among other things, based on the following criteria: the expected length of the procedure, the nature of the required postoperative care, the incidence of surgery-related serious postoperative morbidity, such as pain, nausea and vomiting, and the availability of an adequate environment to guarantee care after discharge.

Once ambulatory treatment is planned, the anesthesiologist has to decide about the anesthetic technique. Many interventions can be performed under either loco-regional or general anesthesia. The anesthesiologist has to balance the pro's and con's for a specific technique taking into account patient- and treatment-related factors and the preference of the patient. Regional anesthesia is usually considered to be associated with less risks and side-effects, such as nausea, vomiting and lethargy, and a reduced need for postoperative anesthetic care. However, regional techniques have their own disadvantages which may interfere with timely discharge from a day-care ward, such as urine retention, spinal headache, or persistent sympathetic block. The additional need for sedation may further delay discharge of loco-regional patients.

Persistent post-operative nausea and vomiting (PONV) is frequently associated with a prolonged stay in a day-care unit and sometimes even responsible for an overnight hospital admission. Many factors may play a role in PONV, such as type of surgery, ingestion of blood, and use of opioids, nitrous oxide and/or other drugs, associated with an increased frequency of nausea and vomiting (vide infra).

Use and avoidance of certain anesthetics may reduce the incidence of PONV. The administration of propofol has been associated with reduced nausea and vomiting[1], whereas also recently more potent anti-emetic drugs have been introduced. In particular ondansetron, a central-acting 5-hydroxy-tryptamine-3 antagonist, appears to be an improvement over existing anti-emetic drugs, like droperidol which causes drowsiness and drysphoria, and metoclopramide which is associated with dystonic reactions[2,3]. Ondansetron, seemingly devoid of clinically relevant side-effects, however, is an expensive drug, whose wide acceptance in the future will be dependent on further information regarding its cost-efficacy relationship.

CHOICE OF THE ANESTHETIC TECHNIQUE

As stated before, ambulatory interventions may be performed under regional or general anesthesia. A regional anesthetic technique has frequently been considered advantageous, because side-effects and risks associated with general anesthesia, such as nausea and lethargy, are precluded, whereas the need for postanesthetic care may be reduced. The regional anesthesia-related risks and side-effects (vide supra) should, however, be taken into account, when making a cost-benefit analysis between the two anesthetic techniques. Finally "the time till street fitness" after a loco-regional technique will probably not differ from that following general anesthesia using drugs with a rapid intrinsic rate of recovery allowing fast emergence from anesthesia.

PROCEDURES REQUIRING THE USE OF GENERAL ANAESTHESIA AND INTUBATION / RELAXATION

Several procedures still require general anesthesia, although not all of them necessitate endotracheal

intubation. Mask ventilation can be performed and/or spontaneous breathing can be allowed during a variety of interventions. The laryngeal mask is an elegant piece of equipment creating a hands-free airway in spontaneously breathing patients. The laryngeal mask, however, does not protect against (silent) aspiration and the anesthesiologist should be aware of the risk of an airway obstruction by interposition of the epiglottis.

For a variety of reasons intubation and/or relaxation may be justified during treatment. Increased risk of regurgitation, prone position during treatment and "remote control" anesthesia require endotracheal intubation, whereas some procedures like physical examinations, abdominal or oropharyngeal surgery or fracture reposition may only be successfully performed under relaxation. "Remote control" anesthesia, i.e., anesthesia under circumstances where the patient (or the patient's airway) is out of reach for the anesthesiologist, frequently occurs during angiography, magnetic resonance imaging and computerized tomography.

CHOICE OF THE MUSCLE RELAXANT

The classification of neuromuscular agents proposed by the FDA and presented in table 1 is a practical tool to describe the pharmacological profile of the various relaxants.

Table 1. The classification of neuromuscular blocking agents according to onset time and duration of action of twice the ED_{95} dose.

	Onset time (min)	Clinical duration (min)
Ultrashort	<l	8
Short	2	20
Intermediate	4	_50
Long	4	>50

In general all muscle relaxants, except those with a long time course of action. are suitable for ambulatory surgery, under certain conditions. Two recently developed non-depolarizing neuromuscular blocking agents, mivacurium and rocuronium, may now replace atracurium and vecuronium, currently widely used for surgical interventions for various reasons. Although suxamethonium remains popular, being the only ultrashort muscle relaxant, mivacurium and rocuronium may be attractive alternatives in many interventions requiring intubation and/or relaxation lasting 15 min or more. For mivacurium this is based on its short duration and fast recovery[4], whereas for rocuronium the attractiveness is its rapid rate of block development[5], allowing reduction of the intubating dose without delaying intubation to an unacceptable extent. This reduction of the intubating dose of rocuronium leads to a shorter duration of action and a faster recovery. The preference for a non-depolarizing muscle relaxant is based particularly on the discomfort reported following the use of suxamethonium in surgical out-patients[6,7]. Low doses of mivacurium (<2x ED_{90}) will result most probably in unacceptable intubation conditions, whereas high doses of rocuronium (>2x ED_{90}) may result in a period of relaxation easily exceeding the average duration of the ambulatory intervention. The main advantages and disadvantages of these three products have been listed in table 2.

Table 2. Advantages and disadvantages of suitable muscle relaxants for healthy patients, ASA Class I to II, scheduled for ambulatory interventions.

Muscle relaxant	Advantages	Disadvantages
Suxamethonium	Ultrashort onset	Muscle pain
	Ultrashort duration	Cardiovascular effects
		Malignant hyperthermia
		Pseudocholinesterase dependent
Mivacurium	Non-depolarizing	Intermediate onset
	Short duration	Histamine release
		Pseudocholinesterase dependent
Rocuronium	Non-depolarizing	Intermediate duration ($2x ED_{90}$)
	Short onset	Reversal required

Results from various clinical studies permit comparison of mivacurium and rocuronium in doses, that have a similar duration till full clinical recovery, i.e., a train-of-four value above 70% [4,8-10].

Table 3. The neuromuscular blocking profiles of rocuronium and mivacurium following equilasting doses (25-30 min) with respect to time from end of injection until spontaneous recovery of the train-of-four ratio till the value of 70%.

	Rocuronium	Mivacurium
Dose(mg kg^{-1})	0.3	0.15
Onset (min)	5.0	6.0
Block (%)	85	97
Intubation (min)	2.0-2.5	2.5-3.0
Dur_{25}(min)	13	17
R.I.sp (min)	7	6
Dur_{TOF70}^{sp} (min)	25-30	25-30
$R.I._{ind}$ (min)	2-4	2-4
Dur_{TOF70}ind (min)	15-20	20-25

Dur_{25} = (clinical) duration till 25% recovery of the twitch height: R.I.sp or R.I.ind recovery index, the time between 25% and 75% recovery of the twitch height, spontaneously or induced by a reversal agent:

Dur_{TOF70}sp or Dur_{TOF70}ind = the duration to full clinical recovery (TOF 70/%). spontaneously or induced by a reversal agent.

In table 3 neuromuscular blocking data of these so-called "equilasting doses.' of mivacurium and

rocuronium, resulting in a spontaneous full clinical recovery of the neuromuscular function within 25-30 min, have been listed. These values are guide numbers based on intravenous anesthesia with barbiturates. Further shortening of the duration till full recovery following these doses with approximately 10 min can be obtained by administering an adequate dose of neostignine (20-40 u g kg^{-1}).

In table 4 neuromuscular blocking data of "equilasting doses" of mivacurium and rocuronium resulting in a neostigmine (20-40 ug kg^{-1}) induced full clinical recovery of the neuromuscular function within 25-30 min have been listed. These values are guide numbers based on intravenous anesthesia with barbiturates. If spontaneous recovery is preferred, this will prolong the duration till full recovery with 5-10 min.

Table 4. The neuromuscular blocking profiles of rocuronium and mivacurium following equilasting doses (25-30 min) with respect to time from end of injection until induced recovery of the train of four ratio till the value of 70%.

	Rocuronium	Mivacurium
Dose (mg kg^{-1})	0.45	0.25
Onset (min)	3.5	3.5
Block(%)	98	.100
Intubation (min)	1.5-2.0	2.0-2.5
Dur_{25} (min)	21	21
R.I.sp (min)	9	7
Dur_{TOF70}sp (min)	35-40	30-35
R.I.ind (min).	2-4	2-4
Dur_{TOF70}ind (min)	25-30	25-30

Dur_{25} = (clinical) duration till 25% recovery of the twitch height;

R.I.sp or R.I.ind recovery index, the time between 25% and 75% recovery of the twitch height, spontanecucly or induced by a reversal agent;

Dur_{TOF70}sp or DuR_{TOF70}ind = the duration to full clinical recovery (TOF 70%), spontaneously or induced by reversal agent.

REVERSAL OF NEUROMUSCULAR BLOCK

Reversal of neuromuscular block following mivacurium and rocuronium should not be performed before recovery of the twitch height till approximately 5-10% of control has been obtained. For mivacurium early administration of neostigmine may result in a delayed recovery due to inhibition of its metabolism by pseudocholinesterase in plasma[11]. For rocuronium it has been shown that reversal with neostigmine is most efficacious if the twitch height has recovered to at least 5% of control [12].

It has been suggested that neostigmine reversal is associated with an increase in nausea and vomiting (PONV) [13] (table 5), although other investigators found rather a reduction of PONV in the group of patients, in which residual curarization was reversed with neostigmine [14,15] (table 6).

*Table 5. The incidence of postoperative nausea and vomiting in elderly patients after hip or knee replacement following an anesthetic technique with methohexital, morphine, halothane, d-tubocurarine and nitrous oxide. Patients received neotigmine, 2.5 mg and atropine, 1.2 mg to reverse the residual neuromuscular block * = p<0.O5. Data from King et al. [13].*

Group	Number	Nausea	Vomiting
Induced recovery	19	13	9
Spontaneous recovery	19	6 *	2 *

*Table 6. The incidence of postoperative nausea and vomiting in adult patients after inguinal hernia repair or saphenous vein stripping following an anesthetic technique with thiopental, fentanyl, halothane, vecuronium, and nitrous oxide. Patients received neostigmine, 1.5 mg, and atropine, 0.5 mg to reverse the residual neuromuscular block. Patients were encouraged to drink and mobilize early. * = p<0.05. Data from Boeke et al. [15].*

Group	Number	Nausea	Vomiting	Anti-emetics
Induced recovery	20	14	10	4
Spontaneous recovery	20	18	15	12 *

Of these studies, the study of Boeke et al. may more reliably predict the effects of reversal on PONV in ambulatory surgery, due to an adequate number of patients undergoing a day-case procedure with early mobilization and drinking (inguinal hernia repair or saphenous vein stripping), a good randomization and stratification regimen, and a current anesthetic technique with adequate doses of atropine and neostigmine (20-30 ug kg^{-1})[15]. These authors conclude that the propulsive action of neostigmine on the intestinal tract may be responsible for the reduced incidence of vomiting in the reversal group. Neostigmine has recently been associated with an higher incidence of postoperative nausea and vomiting (PONV) than edrophonium [16]. However, the difference in PONV observed in this study may rather be caused by the difference in that concurrently administered vagolytic drugs, i.e., glycopyrrolate and atropine to antagonize the vagomimetic effects of neostigmine and edrophonium, respectively, as in earlier investigations glycopyrrolate has been shown to produce more PONV than atropine [17,18].

PONV has also been associated with a large number of other factor such as type of surgery, ingestion of blood,

47use of opioids, nitrous oxide, and (high doses of) antimuscarinic agents. Other factors such as the use of propofol for induction and maintenance of anesthesia or sedation [1] and replacement of opioids by non-opioid analgesics like ketorolac [19] may effectively reduce PONV in ambulatory patients. Finally, in case of PONV ondansetron (vide supra) has been shown to be highly effective [2] and superior to metoclopramide and droperidol in the treatment of postoperative nausea, particularly by a significant reduction of the incidence of vomiting [3].

THE USE OF ROCURONIUM IN PATIENTS SCHEDULED FOR AMBULATORY TREATMENT

Neuromuscular monitoring, at least the use of a nerve stimulator, appears to be indicated to enable the optimal use of muscle relaxants and reversal agents for ambulatory surgery. The availability of a relatively cheap and reliable monitor, the TOF-Guard, based on accelerographic measurement of an indirectly elicited contraction of a peripheral muscle, enables the anesthesiologist to titrate the muscle relaxant as well as the reversal agent with greater precision.

For ultrashort anesthetic procedures, requiring relaxation for intubation and/or the intervention itself. only suxamethonium is currently a suitable alternative. Recently published data, however, suggest that in the near future shorter acting non-depolarizing muscle relaxants, like Org 9487, may become available for these procedures [20].

For interventions lasting between 15 and 30 min rocuronium may be administered in a low dose (0.30-45 mg kg^{-1}), permitting intubation within two min after administration. Residual curarization, i.e., fade of the train-of-four response should be reversed by titration of a reversal agent.

For interventions lasting more than 30 min an intubating dose of rocuronium (0.6 mg kg^{-1}) may be administered allowing intubation usually within 1 minute, followed by maintenance doses or a target-controlled infusion if further relaxation is required.

CONCLUSION

Rocuronium (Esmeron or Zemuron) is a new non-depolarizing muscle relaxant characterized by a rapid development of neuromuscular block and an intermediate time-course of action. Its rapid onset of action and predictable degree of block permit a reduction of the intubating dose, thereby shortening the duration of action. Rocuronium may. therefore, be an attractive alternative for relaxation in ambulatory patients for all interventions requiring or allowing a period of relaxation equal to or longer than 15-20 min.

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