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New muscle relaxants for anesthesia during 1-day surgery

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Abstract

In the last few years, the growth of 1-day surgery and the introduction of new techniques have increased the need for general anesthesia with endotracheal intubation and mechanical ventilation. The end point of 1-day anesthesia is early patient discharge home. Therefore, new muscle relaxant agents have been propounded to anesthetists to achieve this. In this paper, we analyze pharmacological and clinical characteristics of available newer muscle relaxants and evaluate their possible use in 1-day surgery.

Keywords: Anesthesia; Muscle relaxant; Neuromuscular block; Surgery

1. Introduction

In the last few years, 1-day surgery has progressively gained importance. In fact, 60% of the patients in the US scheduled for surgery are at present treated in an outpatient setting [1].

The aim of 1-day surgery is to achieve a good therapeutic result and an early patient discharge from hospital. This makes it necessary to adapt '1-day anesthesia' which includes adequate patient selection and anesthesia that provides a rapid recovery of patient autonomy. The introduction of new surgical techniques (laparoscopic surgery, for instance) extends the indications for 1-day surgery and increases the need for general anesthesia with endotracheal intubation. Therefore, muscle relaxants are of major importance in the clinical practice of 1-day anesthesia, since they permit tracheal intubation and mechanical ventilation and facilitate the surgical procedures [2].

Muscle relaxants act on the neuromuscular junction and can be classified into two groups: agonists or depolarizing muscle relaxants and competitive or non-depolarizing muscle relaxants.

Depolarizing muscle relaxants bind to the receptor and mimic the action of acetylcholine, a neuromuscular mediator. Since these drugs are not inactivated by acetylcholinesterase, they bind to the receptor for a longer time than acetylcholine. The consequence is a prolonged depolarization of the end plate and a neuromuscular block through a mechanism of desensibilization [3,4].

Non-depolarizing muscle relaxants have a competitive action with acetylcholine at the receptor site. After binding to the postsynaptic receptor, they block the ion channel and the ion flow through it. Therefore, the membrane is not depolarized and the muscle becomes flaccid [3–5]. They are classified in benzylisoquinolinium compounds, quaternary amines and aminosteroid compounds [3].

In the last 4 years, four new non-depolarizing muscle relaxants (pipecuronium, rocuronium, doxacurium and mivacurium) have been commercially available. They have been synthesized in an attempt to find the drug with the ideal pharmacokinetic and pharmacodynamic profile for specific surgical needs. Moreover, other muscle relaxants such as cisatracurium, a stereoisomer of atracurium, have been clinically tested.

In this paper, we analyze the pharmacological characteristics of these new muscle relaxants for anesthesia and their possible use for anesthesia during 1-day surgery.

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1.1. Pipecuronium

Pipecuronium is a long-acting muscle relaxant which provides an ideal condition for tracheal intubation approximately 150–300 s after the administration of a dose of 0.05–0.07 mg/kg [4,6]. The time of recovery from neuromuscular block varies significantly in the different studies, which is also due to the diverse parameters considered. At a dose of 0.07 mg/kg, the recovery of 25% of the response to the first twitch of train of four (T_1 25%) is 95 min, while the recovery of T_1 75% is 136 min [6]. At a lower dose (0.05 mg/kg) the recovery of 90% of the response to the first twitch of the train of four (T_1 90%) is 90 min [4]. Pipecuronium is an aminosteroid with an elevated renal excretion (38%) and a reduced hepatic elimination (2%) [7]. In patients with renal impairment, the prolonged half-life of elimination (275 vs. 127 min in healthy patients) and the reduced clearance (1.5 vs. 2.5 ml/kg per min) make this drug unsuitable [8]. Pipecuronium, like other aminosteroids, is deacetylated in the liver, and its clearance may thus be prolonged in patients with hepatic impairment. Even though the percentage of drug excreted in bile in 24 h is low, its elimination may be reduced by an extrahepatic biliary obstruction [3].

1.2. Doxacurium

Doxacurium is a benzylisoquinolinium compound with a very slow onset of action: the onset time is 6 min at a dose of 0.05 mg/kg [9] and 10–14 min at a dose of 0.025 mg/kg [4]. The duration of action is long. The recovery of T_1 75% is 116 min at the dose of 0.05 mg/kg, while the recovery of T_1 90% is 80–100 min at the dose of 0.025 mg/kg [4,9]. Plasma hydrolysis is not significant since this drug is excreted unchanged through the kidney at percentages ranging from 25 to 90% [2,10,11]. Renal impairment reduces its clearance and prolongs the half-time of elimination [10], increasing the pharmacodynamic effects [12]. The contemporary use of volatile anesthetic agents reduces the required dose of doxacurium by 20–40% if compared with the administration of N_2O and fentanyl [13]. It releases little histamine and has no cardiovascular effects [4].

1.3. Rocuronium

Rocuronium is a monoquaternary aminosteroid compound with a rapid onset time and an intermediate duration of action [14–18]. The onset time of the neuromuscular blockade after the administration of a bolus of 0.6 mg/kg is about 60–70 s with a duration of action measured by T_1 25% and T_1 75% of 43 and 66 min, respectively [17,18]. This drug does not seem to induce significant variations in histamine release and guarantees, therefore, a good hemodynamic stability [4,19]. Some authors, however, suppose an important vagolytic effect [18]. The potency of rocuronium is a seventh of that of vecuronium [4] and approximately 30–33% of the drug is excreted through the kidney [20,21]. The pharmacodynamic effects of the drug are similar in patients with renal impairment and in healthy subjects even if an increased distribution volume of the compound and a prolonged half-time of elimination have been observed in patients with renal impairment [22]. Other authors hypothesize that the administration of rocuronium in these patients prolongs the clinical effects [21]. This drug has been used at a dose of 6 mg in 50 patients as a pretreatment 60 s before induction of anesthesia with succinylcholine (1.5 mg/kg). In these patients, fasciculation due to depolarization was reduced to 8% and the incidence of myalgia within the 4th postoperative day decreased to 20–28.6%, making it significantly more efficacious than vecuronium [23].

1.4. Cisatracurium

Cisatracurium is a non-depolarizing benzylisoquinolinium muscle relaxant of intermediate duration of action. It is a purified stereoisomer of atracurium 3 times more potent but with a slower onset of action [24–28]. Its elimination occurs spontaneously in an organ-dependent manner by non-enzymatic hydrolysis (Hofmann elimination: degradation rate depends on the patient's pH and temperature producing laudanosine and a monoquaternary acrylated metabolite which undergoes hydrolysis by a non-specific plasma esterase). However, hydrolysis of cisatracurium by plasma esterases is not the most important pathway for the elimination of the drug [29,30] and this drug can, therefore, be used in patients with renal and/or hepatic impairment [31]. A lower histamine release than with atracurium has been described [32].

1.5. Mivacurium

Mivacurium is the only non-depolarizing muscle relaxant with a short duration of action. This drug is a bis-benzylisoquinolinium diester which is rapidly hydrolyzed by plasma cholinesterases at a percentage of about 88% compared with succinylcholine [33] and is degraded to only partially active metabolites [34,35]. At equipotent doses, the onset time of mivacurium is comparable to that of atracurium [11,33]. The onset time is not always predictable since it is influenced by some factors difficult to evaluate, such as muscular perfusion and circulation [36]. The induction bolus (0.20–0.25 mg/kg) provides good conditions for endotracheal intubation (abolition of 95–100% of T_1) within a time period ranging from 90 to 150 s from the administration [4]. Other authors report that the mean onset time

of mivacurium is longer (229 s) [37]. The duration of action is 6–8 min if measured with the recovery index (time for recovery of T_1 from 25 to 75%) and 25 min if measured with the recovery of T_1 90% [4]. The functional recovery from neuromuscular blockade is 2–3 times faster with mivacurium than with atracurium [11,33]. These data are confirmed by other authors who demonstrated that the clinical duration and the recovery from neuromuscular blockade assessed by means of the recovery index are significantly shorter with mivacurium (13 and 6 min, respectively) than with rocuronium (28 and 11 min, respectively), administered in a single dose during a general balanced anesthesia [37]. In order to maintain an adequate neuromuscular block, mivacurium can also be administered by continuous infusion since its short plasma half-life does not determine accumulation at doses of 6–7 μg/kg per min. The association of volatile anesthetic agents (halothane and isoflurane) and children increases the potency of the curare, reducing the dose requirements of infusion by 32 and 70% from the initial infusion rate after 30 and 80 min, respectively [38]. The short duration of action of mivacurium does not usually make the use of antagonists necessary [39]. Many authors report a functional inhibition of plasma cholinesterases due to the administration of anticholinesterase drugs such as neostigmine. Therefore, in cases requiring the use of an antagonist, edrophonium should be administered, because it does not interfere with the plasma cholinesterase activity and it provides a much faster recovery from neuromuscular block than neostigmine [39,40]. Others disagree with the use of edrophonium and suggest the use of neostigmine–pyridostigmine [41–43]. In patients with renal or hepatic impairment, plasma cholinesterase activity is reduced [44] and the distribution volume increased. Consequently, the duration of the block in these patients is increased by 30–50%. The recovery from neuromuscular blockade is shorter in small children (< 10 min), and prolonged in the elderly, in renal- or hepatic-impaired patients and in heterozygotes for plasma cholinesterase. Known or probable homozygosis (about 1:2500 to 1:3000 patients) is a contra-indication for the use of this drug since variably prolonged blocks (> 3 h) may appear [45].

2. Therapeutic considerations

Before the introduction of the non-depolarizing muscle relaxants with intermediate duration of action, succinylcholine was the most used neuromuscular blocker in 1-day surgery [2], due particularly to its short onset and offset time. On the one hand, succinylcholine has unquestionable advantages but, on the other hand, its clinical use over the years has evidenced many problems. Its parasympathetic mimetic activity may be responsible for sinus bradycardias (especially in children) and for episodes of bradyasystolic arrest described after a repeated dose in adults [2,4]. Besides, the incidence of myalgia after the administration of this drug varies from 0.2 to 89%, with a higher frequency in females and after minor surgery in outpatients, where the analgesic consumption is reduced. These muscular pains may be of severe intensity and last up to 4 days. Many authors suppose a correlation between muscle pain and muscle damage caused by a desynchronized contraction (fasciculation) which appears in the first phase of pharmacological muscle paralysis [2–4,24,46–50]. There are also many reports which describe the occurrence of hyperkalemia after administration of succinylcholine, especially significant in the presence of some pathologies such as burns, trauma, neuromuscular diseases, head injury, abdominal infections and renal impairment where a marked release of potassium could cause cardiac arrest [2,3,51,52]. Succinylcholine seems also to be responsible for increased intragastric, intra-ocular and intracranial pressures [2–4,53–55]. Finally, this drug is one of the main trigger substances of malignant hyperthermia, a rare but potentially fatal muscular disorder [56].

The non-depolarizing muscle relaxants currently used in 1-day surgery (vecuronium and atracurium) have specific advantages over succinylcholine in terms of adverse effects, but they also have a slower onset of action and a longer duration of action.

Among the new muscle relaxants, pipecuronium and doxacurium do not appeal to anesthetists practising '1-day anesthesia'. In fact, these drugs are long acting [57] and do not allow a rapid recovery and an early discharge of patients.

Rocuronium and cisatracurium, which are intermediate-acting muscle relaxants, seem to be more interesting in the clinical setting of 1-day anesthesia. Rocuronium has the most rapid onset of action compared with the other non-depolarizing agents, providing good intubating conditions within 60 s [23]. It seems to guarantee a good hemodynamic stability [4,19] and its onset of action, which is almost as rapid as that of succinylcholine, may be useful in patients with residual gastric contents [4]. Besides, rocuronium pretreatment is particularly effective in reducing fasciculation and myalgia due to succinylcholine and, in this respect, rocuronium is superior to vecuronium [23]. Cisatracurium may be considered the compound of choice for patients with renal or hepatic failure [31], and produces lower histamine release than atracurium [32].

There is no doubt that the muscle relaxant of major interest for use in 1-day surgery is represented by mivacurium, because of its short offset time. The onset of action is similar to that of atracurium and vecuronium, but recovery from the blockade is much more rapid [4]. Mivacurium appears to be the drug of choice

when a rapid and spontaneous recovery from neuromuscular blockade is indicated [37]. Besides, as reported by some authors [58,59], avoiding the administration of antagonists (neostigmine/atropine, neostigmine/glycopyrrolate) decreases the incidence of postoperative nausea and vomiting, adverse effects that limit an early patient discharge. Transient significant histamine plasma levels with consequent cutaneous flushes and transient hemodynamic changes after a rapid administration (5 s) of boluses of mivacurium have been reported by some authors [19,60], but no statistically significant alterations of the hemodynamic values (heart rate and arterial pressure) were reported after slower infusion of boluses (15 s) either in young or in elderly patients [60].

In conclusion, all old and new non-depolarizing intermediate or short-acting muscle relaxants may be considered for intermediate or long lasting 1-day surgical procedures, but mivacurium chloride represents today the first choice for short procedures, due to its pharmacokinetic and pharmacodynamic characteristics.

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