Development of New Neuromuscular Blocking Agents

Hiroshi Sunaga · Cynthia A. Lien

Abstract Increased understanding of structure–activity relationships has allowed the development of neuromuscular blocking compounds and reversal agents that are unique and offer pharmacokinetic and dynamic improvements over their predecessors. Compounds have been developed that have a short duration of effect, a rapid clearance and a decrease in adverse effects. The fumarates comprise one of the series of compounds that have resulted from this research. These compounds are inactivated through a mechanism that is completely new for neuromuscular blocking agents—that of cysteine adduction. The work has also led to the development of alternative ways to enhance recovery of neuromuscular function. Sugammadex encapsulates steroidal neuromuscular blocking compounds making them unable to interact with the acetylcholine receptor and reversing their effect within minutes. Recovery from gantacurium- or CW002-induced neuromuscular block can be shortened by administration of L-cysteine. These new neuromuscular blocking and reversal agents allow for maintenance of an adequate depth of neuromuscular block intraoperatively and almost immediate recovery of neuromuscular function, a sensible goal as the risks of residual neuromuscular block are increasingly appreciated.

Keywords Fumarates · Gantacurium · CW002 · L-Cysteine

Introduction

In an editorial in 1975, Savarese and Kitz [1] described the need for new neuromuscular blocking agents. In that article a need for neuromuscular blocking agents with three different pharmacodynamic profiles was outlined: there was a need for a short-acting compound with a rapid onset of effect, an intermediate-acting compound that had no cumulative effects and a long-acting compound that was free of hemodynamic side effects. Since then, many compounds have been introduced into clinical practice that have met several facets of the requirements described in 1975. Identification of the short-acting compound with a rapid onset of effect though, remains elusive and, for this reason, of the compounds available for use in 1975, succinylcholine, is the one that is still used commonly in clinical practice.

Succinylcholine has been available since 1952 in the US. It was the one of the earliest neuromuscular blocking agents introduced into clinical practice—following the introduction of d-tubocurarine ten years earlier [2, 3]. As a depolarizing neuromuscular blocking agent, it offered a pharmacodynamic profile that was very different than that of its nondepolarizing predecessors and was rapidly incorporated into clinical practice. Because of the combination of its rapid onset of effect and short duration of action, it is still—in spite of its adverse effect profile—commonly used in clinical practice.

The well-known adverse effects of succinylcholine, which range from fasciculations to hyperkalemia and cardiac arrest, are largely attributable to its depolarizing nature of action and have continued to fuel an interest in finding a nondepolarizing equivalent. Additionally, as quantitative monitors of neuromuscular block have become increasingly available and the adverse of residual neuromuscular block more appreciated, there is a renewed interest in identifying compounds that will allow for reliable and complete recovery of neuromuscular function.

Identification of several key compounds has provided essentially the building blocks to allow development of

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neuromuscular blocking agents to move forward. Development of these key neuromuscular blocking agents will be briefly reviewed as an understanding of their structure–activity relationships has contributed to the development of the newest compounds.

Onset of Neuromuscular Block

Impact of Mechanism of Neuromuscular Block on Onset of Neuromuscular Block

The rapid onset of succinylcholine-induced block has been attributed to a combination of four different factors; its mechanism of action, its potency, its clearance, and the dose administered for a rapid sequence induction. In the 1990's Feldman theorized that, while a nondepolarizing neuromuscular blocking agent had to block 80 % of receptors for the block to occur, a depolarizing agent could cause a block with occupancy of less than 20 % of receptors [4]. Shortly thereafter, in a comment on the inherent margin of safety in neuromuscular transmission, Fauvel [5] stated that "if block occurs with 75–90 % occupancy, twitch requires only 10–25 % occupancy". As the adverse effects of succinylcholine are due to the depolarizing nature of its block, this has not been a characteristic sought in new neuromuscular blocking agents.

Impact of Potency on Onset of Neuromuscular Block

Paton and Waud [6] found that neuromuscular block was not detectable until 80 % of acetylcholine receptors had been blocked and that neuromuscular block was maximal once 90 % of receptors had been bound by a nondepolarizing neuromuscular blocking agent. Because of the concentration of acetylcholine receptors at the neuromuscular junction and the percentage of these receptors that have to be blocked before a decrease in muscle strength is appreciable, potency of a neuromuscular blocking agent will impact its onset of effect. Since fewer molecules of a compound are administered when a potent neuromuscular blocking agent is used, there is less of a driving force to move these molecules into the neuromuscular junction where they will have their effect.

Succinylcholine is not a potent neuromuscular blocking agent. Its lack of potency contributes to its rapid onset of effect. Its ED_{95} has been reported to be between 0.3 and 0.63 mg/kg [7, 8]. The relationship between slower onset and greater potency has been demonstrated with steroidal neuromuscular blocking agents [9], benzylisoquinoliniums [10] and equipotent doses of long acting neuromuscular blocking agents of different structures [11].

Impact of Clearance on Onset of Neuromuscular Block

Clearance is another factor postulated to contribute to the speed of onset of neuromuscular block. In an article describing the onset of neuromuscular blocking agents, Bevan stated that "if drug metabolism or redistribution is very rapid, plasma concentrations will decrease quickly so that the time to equilibration of the drug in the effect compartment occurs rapidly" [12]. A study of the concentration effect of succinylcholine demonstrated that it had a rapid clearance (37 ml/min/kg) and a short elimination half-life of less than 1 min [13]. As the k_{e0} values were similar to what is found for nondepolarizing neuromuscular blocking agents, the rapid onset of effect of succinylcholine was found to be due to its rapid clearance. As anticipated from the relationship between clearance and onset, when succinylcholine is administered to patients who are homozygous for atypical butyrylcholinesterase, its onset of effect is slower than it is in patients with normal enzymatic activity [14].

Recovery of Neuromuscular Function

The ultrashort-duration of action of succinylcholine is recognized as an advantage in the "cannot intubate–cannot ventilate" scenario. A similar pattern of recovery of neuromuscular function would also be of benefit after a routine general anesthetic in which neuromuscular blockade had been administered and maintenance of neuromuscular blockade was not required. The impact of subtle degrees of neuromuscular block on a patient's ability to breath was described in the 1970s by Ali et al. [15]. Observed changes were small and determined to be clinically insignificant. Approximately ten years later, small precurarizing doses of nondepolarizing agents were noted to cause measurable decreases in the train-of-four response to stimulation. Importantly, these slight changes in response to neuromuscular stimulation were associated with, in addition to visual disturbances, a feeling of malaise and a sense that it was difficult to breathe and swallow [16, 17]. Considerably later, the potential adverse effects of residual neuromuscular blockade during and after emergence from general anesthesia were explored. The adverse effects of residual neuromuscular block, ranging from visual disturbances, to hypoxia in the PACU to aspiration and decreased patient satisfaction, have now been documented in several studies [18–20, 21••, 22••]. Perhaps more importantly, clinicians are beginning to recognize that a train-of-four ratio of ≥0.90 prior to extubation of a patient's trachea, is important in the care of their patients [23]. A number of factors currently render this goal difficult, if not impossible, to obtain. They include a lack of wide spread availability of

quantitative monitors of neuromuscular function, a nondepolarizing neuromuscular blocking agent with an ultrashort duration of action and, in the United States, a reversal agent that will quickly antagonize any depth of neuromuscular block.

Newer Neuromuscular Blocking Agents

Over the previous 25 years, development of several new neuromuscular blocking agents and one selective relaxant binding agent have contributed to understanding of the structural elements required to create a nondepolarizing neuromuscular blocking agent that does not cumulate, has a rapid onset of effect and is free of adverse side effects. The intermediate-acting compounds, vecuronium and atracurium, were both introduced in the 1980s. Both had shorter elimination half-lives than any nondepolarizing neuromuscular blocking agent previously available. Vecuronium is very similar to pancuronium in its structure. However, its different pharmacodynamic characteristics were due to the removal of the quaternizing methyl group at the 2-piperidine substitution. Its duration of action was shortened, its renal elimination decreased, and its metabolism in the liver increased when compared to pancuronium. Importantly, the hemodynamic effects of pancuronium were eliminated with the structural revision of the compound [24]. In fact, vecuronium set a new standard for absence of hemodynamic effects—that has only been matched by the development of the long-acting compound pipecuronium. The development of atracurium introduced an entirely new means for these compounds to be inactivated in ways other than end-organ metabolism. The short elimination half-life and rapid clearance of atracurium was due to Hoffman elimination and ester hydrolysis [25]. While it caused histamine release like the benzylisoquinolines that preceded it, d-tubocurarine and metocurine, its propensity to do so was considerably decreased [26].

The second generation of intermediate-acting compounds, cisatracurium and rocuronium, reflects both improvements in the capacity to manufacture a single isomer of a compound on a large scale and an appreciation of the impact of potency on the onset of neuromuscular blockade. In developing rocuronium, the steroidal structure was revised to incorporate different cyclic substitutions at the 2 and 16 positions of the molecule so that its potency for neuromuscular blockade was decreased. While an ED_{95} is 0.3 mg/kg [27–29], it is a relatively impotent neuromuscular blocking agent and remains the only available compound with an onset of effect similar to that of succinylcholine [30]. Administration of 0.6 mg/kg rocuronium ($2\times$ the ED_{95}) causes 100 % neuromuscular block in, on average, 1.5 min. Doubling the dose shortens the onset to

just under a minute, comparable to 1 mg/kg succinylcholine. Not unexpectedly, as the dose of rocuronium is increased to shorten its onset of effect, its duration of action becomes increasingly prolonged. The clinical duration of action (the time from administration of the neuromuscular blocking agent to 25 % recovery of twitch height) is essentially doubled from 37 to 73 min by increasing the dose from 0.6 to 1.2 mg/kg [30]. Of note, 25 % twitch height is the earliest point at which antagonism of residual neuromuscular block should be considered.

Cisatracurium, one of 10 isomers of atracurium, is an example of the potential impact of the selection of a structural element on the pharmacodynamics and adverse effect profile of a neuromuscular blocking agent. Cisatracurium is the 1-R-cis, 1-R'-cis isomer that constitutes 10 % of the isomers of which atracurium is composed. With an ED_{95} of 0.05 mg/kg [31], it is significantly more potent than atracurium. Because of its potency, its onset is, not surprisingly, substantially slower than that of atracurium. Like atracurium, it undergoes Hofmann elimination. Interestingly, it does not, even when administered rapidly in large doses, cause the release of histamine [32]—making it unique among the benzylisoquiloliniums in terms of its side effect profile.

Development of the short-acting neuromuscular blocking compound, mivacurium, introduced yet another means of metabolizing nondepolarizing compounds. Like succinylcholine, it is metabolized by butyrylcholinesterase. Its clearance is faster than that of succinylcholine [33]. Its clearance is due to the rapid metabolism of its potent cis–trans and trans–trans isomers by butyrylcholinesterase. In spite of its clearance, its onset of effect is slower than that of succinylcholine [34]. Its slower onset of effect, in spite of its more rapid clearance, has been attributed to its greater potency [12]. Administration of larger doses to shorten onset of neuromuscular block is limited by the histamine release caused with administration of doses larger than $2.5\times ED_{95}$ [35].

Rapacuronium was the most recent neuromuscular blocking agent to be introduced into clinical practice in the USA. Like succinylcholine and rocuronium, it had a rapid onset of effect. Although the duration of action was not as short as that of succinylcholine, it was shorter than that of mivacurium [36]. Its ED_{90} of 1 mg/kg meant that it was not a potent neuromuscular blocking agent. Given this, its onset following administration of 1.5 mg/kg, of approximately 1 min was not unexpected. In addition to its low potency as a neuromuscular blocking agent, the rapid clearance of rapacuronium contributed to its rapid onset of effect. Its clearance of 8 ml/kg/min [37] is almost twice that of the intermediate-acting neuromuscular blocking agents cisatracurium and vecuronium.

From a pharmacodynamic point of view, this was a very interesting and promising compound. In clinically relevant doses, however, rapacuronium interacted with the M_2 receptors and the M_3 receptors of the airway. This meant that the negative feedback of M_2 muscarinic acetylcholine receptors of the airway on parasympathetic nerves was inhibited, resulting in excessive release of acetylcholine [38], stimulation of the M_3 receptors and bronchoconstriction. Additionally, rapacuronium caused allosteric potentiation of M_3 muscarinic acetylcholine receptors on the smooth muscles of the airway, also contributing to bronchoconstriction [39]. With administration of clinically-recommended doses of rapacuronium, the observed increase in pulmonary artery pressures is due to its effects on M_2 and M_3 muscarinic acetylcholine receptors [40, 41]. Rapacuronium was withdrawn from the market in 2001, shortly after its introduction into practice.

New Means of Reversing Neuromuscular Block

Sugammadex is a selective relaxant binding agent, that encapsulates rocuronium rendering it inactive in the plasma and unable to bind to the acetylcholine receptor at the neuromuscular junction [42, 43]. While anticholinesterases cannot effectively antagonize profound neuromuscular block, sugammadex can reverse profound rocuronium-induced block [44, 45]. Its dynamics have been well-described. When administered 3 min after administration of an intubating dose of rocuronium, recovery of neuromuscular function occurs very quickly—as if rocuronium were a short-acting neuromuscular blocking agent [44]. The rocuronium–sugammadex complex is eliminated through renal mechanisms [46]. As one molecule of sugammadex binds one molecule of rocuronium, it is possible to give an inadequate dose of sugammadex to completely reverse neuromuscular block [47, 48•]. Doses of 8–16 mg/kg have been recommended for rapid reversal of profound neuromuscular block.

Its unique means of activity means that this cyclodextrin may have other uses clinically. Neuromuscular blocking agents are the most common causes of anaphylaxis during clinical anesthesia, and rocuronium is the nondepolarizing neuromuscular blocking agent most frequently implicated in these anaphylactic reactions. [49–51]. Since sugammadex encapsulates rocuronium, which is the allergen, it could be another form of treatment [52–55]. Interestingly, though, studies failed to demonstrate the efficacy of sugammadex in the setting of anaphylaxis [56•, 57]. In addition, there have been reports of allergic reaction to sugammadex [58, 59] and 48 cases of anaphylaxis or anaphylactoid reaction in reaction to sugammadex were been reported between April, 2010 through January, 2012

in Japan. This being said, more than 1 million patients have received sugammadex to reverse neuromuscular block induced with rocuronium or vecuronium without occurrence of an adverse event.

Because of the cost of sugammadex, should it be introduced into practice in the United States, it is unlikely that it will be rapidly incorporated into routine clinical practice. It is more likely that it will be used in the "cannot intubate–cannot ventilate" scenario or in cases where a surgical procedure ends far sooner than had been anticipated.

Ongoing Development of Neuromuscular Blocking and Reversal Agents

The search for an ideal neuromuscular blocking agent is ongoing. A majority of recent work has focused on the development of a new series of fumarate, olefinic isoquinolinium diester, compounds. Within this class of compounds are agents that have varying potency, different onsets of effect and durations of action and different side effect profiles. All are inactivated through a unique mechanism, that of adduction of L-cysteine (Fig. 1). Two of these compounds have undergone volunteer trials.
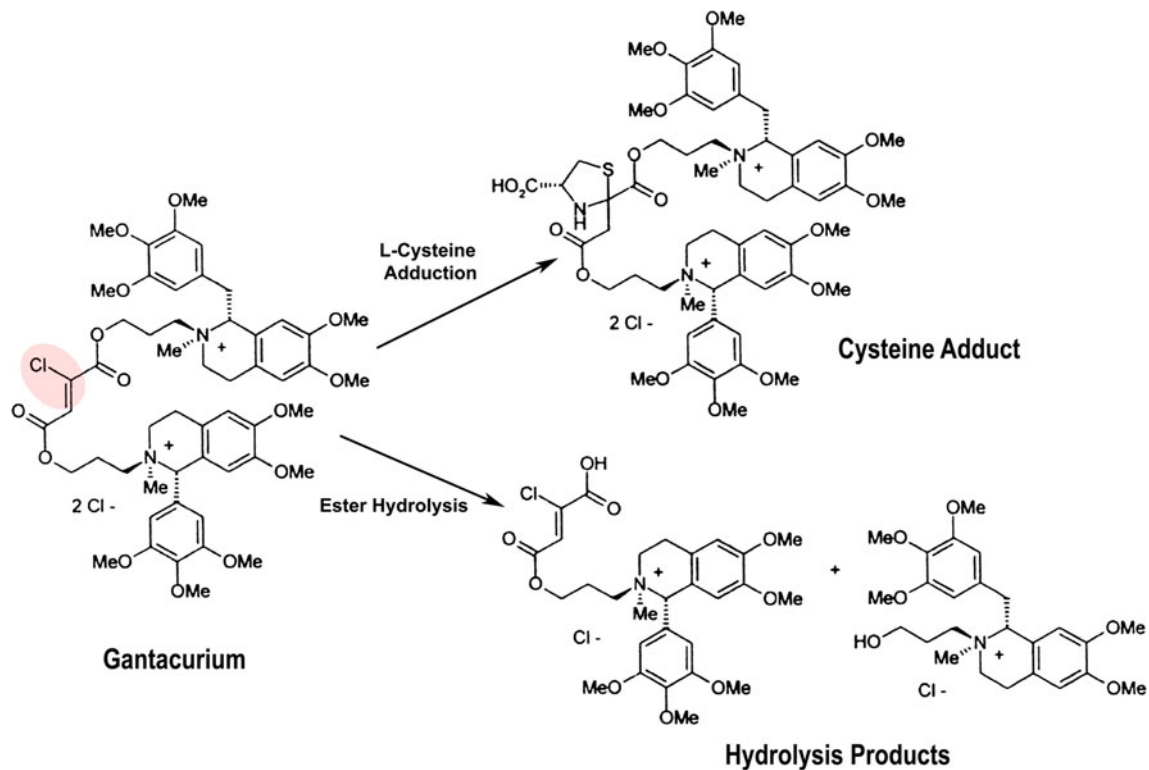
Gantacurium

Structure

Gantacurium (Fig. 1) is an asymmetrical isoquiolinium diester of chlorofumaric acid [60]. Gantacurium rapidly combines with L-cysteine in vitro to form a presumably less-active degradation product (a cysteine adduct) [61••]. One of the central double-bonded (olefinic) carbons is activated (so that it has an increased electrophilic character) by a strongly electronegative chlorine substitution that was designed to accelerate the adduction reaction. Gantacurium itself and its adduct may undergo further breakdown by nonenzymatic alkaline hydrolysis.

Pharmacology

Gantacurium, the first of the olefinic isoquinolinium diester compounds to be studied in humans, is a nondepolarizing neuromuscular blocking agent with ED_{95} that was 0.19 mg/kg [62]. It has a rapid onset of effect, resulting in maximal block in 90 s following administration of 0.3 mg/kg ($1.5\times$ the ED_{95}) and 60 s following 0.3–0.4 mg/kg. This rapid onset is likely due to its relative lack of potency as well as its rapid clearance [62]. Following administration of 0.54 mg/kg, onset of 100 % block at the laryngeal

Fig. 1 The chemical structure of gantacurium (GW 280430A) and its breakdown products. Inactivation takes place at the olefinic bond (indicated by the *red circle*) through adduction of cysteine in a rapid reaction to yield an adduct. A slower process of inactivation occurs through hydrolysis to yield two hydrolysis products. From Savarese et al. [60], with permission from Wolters Kluwer Health (Color figure online)

adductors occurred in 0.9 min while that following 1 mg/kg succinylcholine was 0.8 min [63•]. Increasing the dose of gantacurium from 0.3 to 0.72 mg/kg did not change the total duration of action (minutes from administration to a train-of-four ratio ≥0.9) of the neuromuscular blocking agent which remained at 14–15 min. Similarly, the 5–95 % recovery interval (the time from 5 % recovery of the first response in the train-of-four to 95 % recovery) remained constant at 7 min in this dose range.

Reversal

The ultra-short duration of action of gantacurium is likely due to the adduction of endogenous L-cysteine. This rapid recovery can be further shortened by the administration of edrophonium. When edrophonium, 0.5 mg/kg, was administered at 10 % recovery of T1, the total duration of action of gantacurium, 0.4 mg/kg, was shortened from 15.5 to 5.7 min. When edrophonium was administered to monkeys 1 min after gantacurium, it was not as effective a reversal agent. In contrast, when L-cysteine, 10 mg/kg, was administered to monkeys 1 min after 0.5 mg/kg gantacurium, 5× ED$_{95}$, it rapidly restored neuromuscular function, reducing the total duration of action from 10.4 to 3.0 min (Fig. 2). When administered at the very beginning of recovery, 2 %

twitch height, exogenous L-cysteine also significantly shortened recovery of neuromuscular function [61••].

Adverse Effects

While gantacurium will, when administered in doses of approximately 3–4× ED$_{95}$, cause histamine release and its associated hemodynamic changes [62], its propensity to do so is less than that of mivacurium [64]. Unlike rapacuronium, gantacurium does not cause bronchoconstriction via interaction with M2 and M3 muscarinic receptors even at doses several times greater than those required for muscle paralysis in guinea pigs [65].

CW002

Structure

The unique pharmacology of gantacurium led to the development of nonhalogenated olefinic isoquinolinium compounds. The absence of chlorine in the compound results in less activation of the olefinic carbons, which are then influenced only by the two relatively weakly electronegative adjacent alpha-carboxyl (ester) groups located on both sides of the central olefinic double bond causing the adduction of
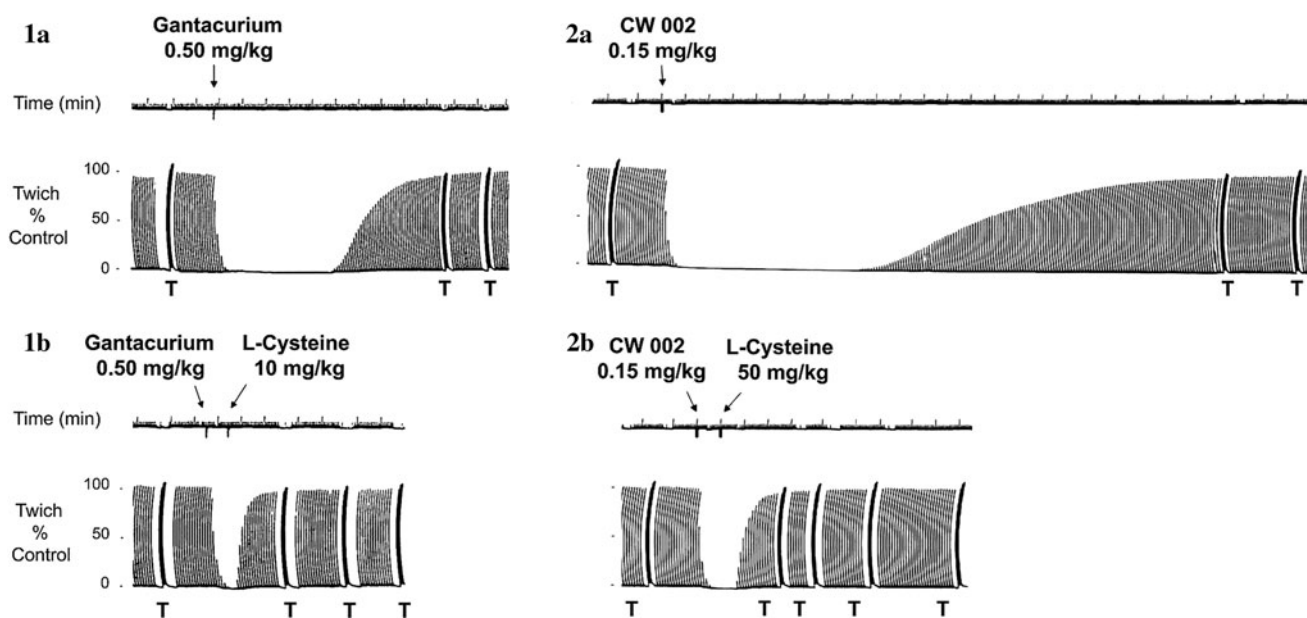
Fig. 2 Twitch recordings in individual monkeys demonstrating in **1a** spontaneous recovery from gantacurium, 0.50 mg/kg and in **2a** spontaneous recovery from CW002, 0.15 mg/kg. Complete spontaneous recovery from gantacurium-induced block occurs in approximately 11 min and from CW002-induced block, 25 min. Recovery is shortened by the administration of L-cysteine, as demonstrated in panels **1b** and **2b**. Administration of L-cysteine, 10 mg/kg, 1 min after 0.50 mg/kg gantacurium shortens the time from administration of the neuromuscular blocking agent to complete recovery from 11 to approximately 3 min in this one animal. As demonstrated in panel **2b**, administration of L-cysteine, 50 mg/kg, 1 min following CW002 shortened recovery from 25 to 4 min

L-cysteine to occur more slowly. CW002, a nonhalogenated, symmetrical, benzylisoquinolinium fumarate diester compound, is the first of these compounds to undergo human trials. To date, ten volunteers have participated in the trial of this compound. Based on the results of animal trials and in vitro studies, its duration of action will be longer because of slower L-cysteine adduction.

Pharmacology

CW002 is a potent nondepolarizing neuromuscular blocking agent, with an ED_{95} in monkeys receiving isoflurane and nitrous oxide anesthesia of 0.042 mg/kg [61••]. The time from administration of an approximate $4\times$ ED_{95} dose of CW002 to recovery of 95 % twitch height is 28 min, approximately half that of cisatracurium (58.0 min) and three times longer than that of gantacurium (10.4 min). This appears comparable to recovery to a train-of-four ratio of 90 % following administration of $5\times$ ED_{90} of rocuronium, which is 28 min [66]. The 5–95 % recovery interval of CW002 after $4\times$ ED_{95} dose is 10.8 min, shorter than that of cisatracurium following a $1.25\times$ ED_{95} dose (20.3 min).

Reversal

Neostigmine, 0.05 mg/kg, will shorten recovery from CW002-induced neuromuscular block when administered at moderate levels of neuromuscular block, 2 % recovery of twitch height. It is not effective in antagonizing block when administered 1 min following administration of CW002. In contrast, L-cysteine, 30–50 mg/kg, administered 1 min after $4\times$ ED_{95} of CW002 rapidly restores neuromuscular function in less than 3 min (Fig. 2). When administered at 2 % recovery of twitch height, L-cysteine, 50 mg/kg, also shortens the 5–95 % recovery interval to 2.1 min, which is significantly shorter than recovery following neostigmine [61••].

Adverse Effects

CW002, like gantacurium, does not interact with M2 or M3 receptors of the airway [65]. Therefore, CW002 should not cause bronchoconstriction. Current clinical trials have been designed to look for changes in peak airway pressure that may, in the absence of a rise in histamine levels, be indicative of the occurrence of bronchoconstriction through this mechanism.

In dogs, sequential increasing dosing of CW002 to supratherapeutic levels produced a small but significant reduction of mean arterial pressure (MAP) [67]. In this model, dose-related reductions were also evident in heart rate and cardiac output starting at $50\times$ ED_{95} and mean pulmonary arterial pressure at $100\times$ ED_{95}. In contrast to the direct relationship between the dose of CW002 and changes in hemodynamic variables, a similar relationship

did not exist for histamine release. That may be due to the fact that for modeling in this study, administration of progressively larger doses of CW002, was not optimal to demonstrate histamine release. There is the possibility that with bolus administration of a larger single dose, histamine release will become apparent.

L-Cysteine Reversal

L-Cysteine is a nonessential amino acid in adults and conditionally essential in preterm infants because of the enzymatic immaturity of the *trans*-sulfuration pathways that convert methionine to cysteine [68]. As such, L-cysteine is commonly infused at doses up to 80 mg/kg/day to supplement parenteral nutrition in preterm infants [69].

As previously described, the olefinic isoquinolinium diester compounds gantacurium and CW002 are chemically inactivated by the adduction of L-cysteine to its central double bond. L-cysteine adduction occurs at different rates in the compounds because of their different structures, accounting for their different durations of action. Intravenous administration of exogenous L-cysteine shortens recovery by increasing the amount of L-cysteine available to bind to the neuromuscular blocking agents.

The dose of L-cysteine required for rapid antagonism of $5\times$ ED_{95} of gantacurium is 10 mg/kg. This dose is smaller than that required for rapid antagonism of $4\times$ ED_{95} of CW002, 50 mg/kg [61••]. This difference can be explained by the differences in structure of the compounds. The chlorine substitution in gantacurium accelerates L-cysteine adduction to the olefin, and is likely the reason it has ultrashort duration of action and is rapidly antagonized with administration of relatively low doses of L-cysteine. Of note, neuromuscular block induced by cisatracurium is not antagonized by L-cysteine.

L-Cysteine, in doses up through 50 mg/kg, shows a dose-dependent relationship for antagonism of CW002 [70•]—with larger doses resulting in greater degrees of recovery 1 min after administration of L-cysteine. Administration of larger doses of L-cysteine does not further shorten any recovery parameter. When administered after reversal of CW002-induced block with L-cysteine, additional doses of CW002 have a shorter duration of action.

Increasing the dose of L-cysteine from 10 to 100 mg/kg tends to increase MAP and reduce the heart rate. The increases in MAP, though, are not clearly dose related. These hemodynamic changes are, on average, less than 10 %, even following administration of 100 mg/kg L-cysteine. There is a multiphasic response to administration of this large dose of L-cysteine, with an initial vasodilation followed by a more sustained vasoconstriction. The mechanism of this response remains unclear.

Toxicologic evaluation of L-cysteine in rats indicates that intraperitoneal administration of L-cysteine at doses 24–30 times greater than required for reversal of CW002-induced block and 120–150 times greater than required for reversal of gantacurium-induced block are associated with acute neurotoxicity [71, 72]. Toxicologic studies in dogs demonstrate that a single 200-mg/kg dose of L-cysteine caused no mortality, morbidity, or weight loss during the observed period and no difference in hematologic, coagulation, and serum chemistry values 2 or 14 days after administration, when compared to control dogs. Animals that received repeated doses of L-cysteine, 10, 20, 50, and 100 mg/kg, during a 4-week period for definition of the dose response relationship for reversal of CW002, maintained normal activity and behavior and had no change in appetite, weight loss, or morbid events.

Conclusion

Ongoing work related to the development of nondepolarizing neuromuscular blocking agents has allowed for the identification of an entirely new series of compounds. These compounds are potent nondepolarizing neuromuscular blockers that are inactivated at different rates, depending on their structure. Inactivation of these fumarates occurs through an entirely unique mechanism, that of cysteine adduction. Because of this, their effect can be reversed very rapidly through the administration of L-cysteine. Whether or not gantacurium or CW002 are introduced into clinical practice, they are likely the predecessors of similar compounds with even more favorable pharmacodynamic, kinetic and adverse effect profiles that will warrant study.

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