Forum Article

Novel drug development for neuromuscular blockade

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Abstract

Pharmacological advances in anesthesia in recent decades have resulted in safer practice and better outcomes. These advances include improvement in anesthesia drugs with regard to efficacy and safety profiles. Although neuromuscular blockers were first introduced over a half century ago, few new neuromuscular blockers and reversal agents have come to market and even fewer have remained as common clinically employed medications. In recent years, newer agents have been studied and are presented in this review. With regard to nondepolarizer neuromuscular blocker agents, the enantiomers Gantacurium and CW002, which are olefinic isoquinolinium diester fumarates, have shown potential for clinical application. Advantages include ultra rapid reversal of neuromuscular blockade via cysteine adduction and minimal systemic hemodynamic effects with administration.

Key words: Anesthesia, CW002, gantacurium, neuromuscular blocker, nondepolorizer blocker

Introduction

The utilization of multiple pharmacologic agents is an essential component of modern day anesthetic practice. While there have been numerous advancements in recent years in both analgesic and amnestic medications available for an anesthesiologist to use in clinical practice, the cadre of neuromuscular blocking agents available in the United States has been stagnant. The ideal neuromuscular blocking agent is one that is rapidly acting, has minimal to no adverse effects, is independent of end organ metabolism, and allows for rapid and complete reversal of neuromuscular blockade. Advancements in this pharmacologic area are particularly important for several reasons. First, the deleterious effects of residual neuromuscular blockade in the postanesthetic care unit have been well studied and are clinically relevant.[1-3] Emphasis on operative efficiency and patient discharge has also been widely identified as an area for potential cost saving measures in modern healthcare settings.

Novel drug development has been proven to be a difficult and timely process as it has been over 20 years since a new nondepolarizing muscle relaxant has been introduced for clinical use. This paper will highlight some of the latest pharmacological advancements in the area of neuromuscular blockade.

Fumarates

The enantiomers gantacurium and CW002 are two of the most recent neuromuscular blocking agents that have shown potential for clinical application. These molecules are classified

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as olefinic isoquinolinium diester fumarates. The appeal of these molecules is the ultra-rapid reversal of neuromuscular blockade via cysteine adduction and minimal systemic hemodynamic alterations with administration.[4-6]

Gantacurium is an asymmetric alpha-chlorofumarate and is classified as an ultra-short acting nondepolarizing neuromuscular blocker.[1,4,6,7] Its structure can be seen in Figure 1. Its pharmacologic properties have been established using both animal and human models with its ED95 found to be 0.19 mg/kg.[7,8] Maximum neuromuscular blockade using gantacurium was found to be within 90 s following administration of 1.5 × ED95 with even faster onset at higher doses.[7] Duration of action has been found to be approximately 10 min.[9,10] This pharmacologic profile is comparable to that of succylincholine and could eventually serve as a replacement for a rapid depolarizing muscle relaxant.

CW002 differs in structure from gantacurium by being symmetrical and lacking a chlorine at the fumarate double bond. Its chemical structure can be seen in Figure 2. These properties give CW002 a greater potency than gantacurium and an intermediate duration of action of approximately 30 min. Using both animal and human models, its ED95 has been found to be 0.05 mg/kg.[11,12] As with gantacurium, CW002 has minimal to no hemodynamic effects at administered doses well above its documented ED95.

Inactivation of both fumarates occurs via two unique pathways. The first is a slow pH-sensitive hydrolysis at the ester linkages of the molecules.[9] This results in a t½ of 56 min and 495 min for gantacurium and CW002, respectively. The second pathway for inactivation is much more rapid and has the greatest clinical implications. This pathway utilizes L-cysteine adduction and allows for organ-independent metabolism. L-cysteine adduction results in a byproduct of extremely low potency that also subsequently undergoes hydrolysis to form inactive molecules.[13] L-cysteine dosed at 10 mg/kg facilitates complete resolution of neuromuscular blockade within 3 min.[14,15] Furthermore, of importance is that unlike conventional neuromuscular blockers, this pathway allows for complete reversal at any time after bolus administration of neuromuscular blockers. L-cysteine adduction terminates the relaxants action via inactivation and not by overcoming competitive inhibition.

Conclusion

Advancements in neuromuscular blocking agents have the potential to have significant impact on anesthetic care in the United States. The ability to rapidly and reliably induce and reverse favorable conditions for tracheal intubation and surgery can profoundly impact anesthetic care in ambulatory, inpatient, and emergent settings. All anesthesia providers will need to consider some of the advantages and potentially disadvantages of these new drugs in their practice in the future. This paper details some of the promising medications on the horizon for clinical use. Continued research is needed in the most important area of neuromuscular modulation in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

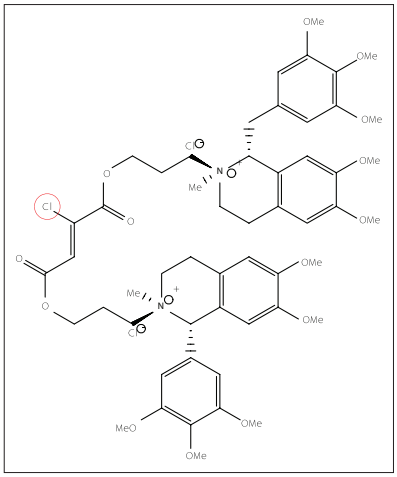

Figure 1: Gantacurium chemical structure

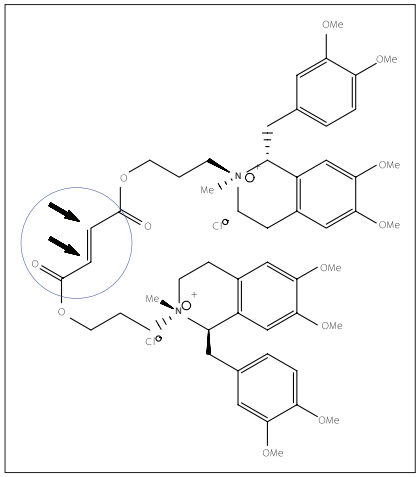

Figure 2: CW002 chemical structure

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