Commentary

Cardiovascular adverse effects of sugammadex

Sugammadex is a synthetic γ-cyclodextrin, designed to selectively bind amino-steroid neuromuscular (NM) blockers (rocuronium and vecuronium). It reverses NM blockade by encapsulating rocuronium, thereby preventing the NM blocker from binding to acetylcholine receptors on the motor endplate.[1] Sugammadex has a hydrophobic cavity, which traps the NM blocker, and has a hydrophilic polar body. The water-soluble guest-host complex formed remains stable until it is eliminated from the body, as it has a high binding rate and a low dissociation rate. Its use is associated with a fast and predictable reversal of any degree of the block, and it reduces the risk of postoperative residual NM blockade. However, cost and regulatory constraints have hindered the widespread use of sugammadex.

Sugammadex has no effect on the NM junction or any receptor system in the body. Its use eliminates the need for anticholinergic drugs, which have undesirable adverse effects. Clinical studies have reported mild adverse effects of sugammadex, and these are limited in duration.

The reported cardiovascular adverse effects of sugammadex include QTc prolongation, atrioventricular block, hypotension,

atrial fibrillation, and even asystole.[2-6] The company package insert notes a 1% incidence of bradycardia with its use, and a recent meta-analysis reported an incidence of 2%.[7] Most cases of bradycardia respond to the administration of anticholinergics, but in some cases, the administration of adrenaline is required to reverse the bradycardia. As sugammadex lacks muscarinic effects and bradycardia may not respond to atropine, some authors suggest the primary use of low-dose adrenaline to treat bradycardia, instead of anticholinergics.[8,9]

Trent Sims *et al*. report a high incidence of bradycardia (7%) after sugammadex administration.[10] The higher incidence, compared to the earlier studies, can be attributed to higher heart rate criteria used by them. The authors also suggest that the bradycardia may be dose-related, with those receiving higher initial doses more likely to experience it. A similar high incidence of 8% has been reported in children, with an increased incidence of bradycardia in the presence of a comorbid cardiac condition. However, other studies did not find an association between dose and incidence of bradycardia.[11] The cardiovascular effects might be associated with the amount of free sugammadex plasma molecules.[9]

In 2008, sugammadex use for NM blockade reversal was approved in Europe. However, the United States Food and Drug Administration (FDA) granted its approval only at the end of 2015, due to safety concerns such as the risk of anaphylaxis and bradycardia.[12] Recent case reports have elucidated more serious cardiovascular adverse effects, which include hypotension, third-degree atrioventricular block, and persistent bradycardia.[4-6,13,14] Cardiac arrest after sugammadex administration has been reported, which were triggered by coronary vasospasm in patients.[15,16] One cardiac arrest victim had normal coronaries[16] while the other had nonobstructive coronary lesions.[15]

Multiple reports of adverse effects warrant further studies to examine its safety. The significant incidence of bradycardia and cardiac arrest after sugammadex highlights the need for extreme vigilance in patients, especially those with slow recovery times.[12,17] No definitive mechanism for the cause of bradycardia has yet been postulated. Although the occurrence of serious cardiac adverse effects after sugammadex administration is well recognized, no pharmacologic or physiologic mechanism has been proven nor postulated.[11]

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Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/joacp.JOACP_132_20

How to cite this article: Kapoor MC. Cardiovascular adverse effects of sugammadex. J Anaesthesiol Clin Pharmacol 2020;36:469-70.

Submitted: 21-Mar-2020 **Accepted:** 23-Mar-2020
Published: 29-Sep-2020