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Is there a role for sugammadex in the reversal of neuromuscular blockade? A systematic review

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Background

Sugammadex is a recently developed agent for the reversal of neuromuscular blockade (NMB). Different doses of sugammadex are available:

Indication	Dose of sugammadex
Reversal of Moderate Block	2 mg kg^{-1}
Reversal of Profound Block	4 mg kg^{-1}
Immediate/Rapid reversal of high dose rocuronium-induced NMB	16 mg kg^{-1}

Potential clinical benefits from the use of sugammadex in routine surgery include the ability to reverse neuromuscular blockade more quickly and predictably from any level of blockade, and therefore increase patient safety, improve surgical conditions and reduce incidence of residual blockade on recovery. However, sugammadex is substantially more expensive than alternatives and can only be used with specific and relatively expensive neuromuscular blocking agents (in particular rocuronium).

For patients requiring rapid sequence induction (RSI) of anaesthesia, tracheal intubation and the onset of neuromuscular block must be as rapid as possible. The standard drug used for this is succinylcholine, which has a rapid onset of action and no reversal agent is required. However, it is associated with adverse effects. High dose rocuronium can achieve a similarly rapid onset of action but for safety reasons it must be possible to reverse the block immediately. High dose rocuronium + sugammadex for immediate reversal may provide an onset of effect and rapid reversal at least equal to succinylcholine, but with a better safety profile.

Objectives and Methods

To determine the clinical effectiveness of sugammadex for the reversal of muscle relaxation in UK practice we conducted a comprehensive systematic review of RCTs assessing all the indications and doses of sugammadex. We searched bibliographic databases, conference proceedings, internet sites and clinical trials registers to identify published and unpublished studies. We also searched the manufacturer's submission to the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) assessment report for sugammadex.

Comparators for moderate or profound (routine) reversal were rocuronium with placebo reversal agent, or standard UK NMB/reversal agent combinations. Comparators for rapid reversal following RSI were spontaneous recovery from succinylcholine-induced blockade. Outcomes were measures of time to recovery from blockade, using monitoring of neuromuscular activity (time to train of four (TOF) 0.9). Full details are reported in the HTA report by Chambers *et al* (in press).[1]

Results

Meta-analyses across all studies were not appropriate and data were therefore presented as a narrative synthesis, retaining the original summary statistics.

Routine reversal

Four placebo-controlled trials indicated that recovery was significantly faster with sugammadex 2 mg kg^{-1}, although the magnitude of the difference varied between studies: median recovery times were 1.3 to 2.9 minutes with sugammadex compared with 21.0 to 86.2 minutes with placebo. Similarly, both placebo-controlled trials showed that reversal after 15 minutes of rocuronium block with sugammadex 4 mg kg^{-1} was clearly faster than placebo (medians of 1.5 and 5.6 minutes vs. 30.6 and 94.2 minutes, respectively).

Two trials indicated that sugammadex 2 mg kg^{-1} produces statistically and clinically significantly more rapid recovery from moderate blockade than neostigmine/glycopyrrolate (Table 1). One trial indicated that sugammadex 4 mg kg^{-1} produces significantly more rapid recovery from profound neuromuscular blockade (Table 1). No patients showed clinical evidence of recurrence of blockade or residual blockade.

Table 1: Summary of time (min) from start of administration of sugammadex or neostigmine/glycopyrrolate to recovery of TOF ratio 0.9 in trials of sugammadex for reversal of moderate or profound neuromuscular blockade

Moderate NMB		
Blobner 2007	**Rocuronium + Sugammadex (2 mg kg^{-1}) (n=48)**	**Rocuronium + neostigmine/glycopyrrolate (0.05 mg kg^{-1}) (n=48)**
Geometric mean (95% CI)	1.5 (1.3 to 1.7)	18.5 (14.3 to 23.9)
Median (range)	1.4 (0.9 to 5.4)	17.6 (3.7 to 106.9)
Flockton 2008	**Rocuronium + Sugammadex (2 mg kg^{-1}) (n=34)**	**Cisatracurium + neostigmine/glycopyrrolate (0.05 mg kg^{-1}) (n=39)**
Geometric mean (95% CI)	1.9 (1.6 to 2.2)	9.0 (7.5 to 10.8)
Median (range)	1.9 (0.7 to 6.4)	7.3 (4.2 to 28.2)
Profound NMB		
Jones 2008	**Rocuronium + sugammadex (4 mg kg^{-1}) (n=37)**	**Rocuronium + neostigmine/glycopyrrolate (n=37)**
Geometric Mean (95% CI)	2.9 (2.5 to 3.4)	50.4 (43.5 to 58.4)
Median (range)	2.7 (1.2 to 16.1)	49.0 (13.3 to 145.7)

Rapid reversal

Three trials indicated that sugammadex 16 mg kg^{-1}, administered 3 or 5 minutes after rocuronium, produced markedly faster recovery than placebo or spontaneous recovery from succinylcholine-induced blockade (Table 2). Overall rates of adverse events were similar between sugammadex and comparators.

Table 2: Time to recovery in trials of sugammadex for rapid reversal of rocuronium-induced neuromuscular blockade

Placebo controlled trials (time to recovery of the TOF ratio 0.9, 5 or 3 minutes after rocuronium, respectively)		
De Boer 2007	**Rocuronium + sugammadex (16 mg kg^{-1}) (n=7)**	**Rocuronium + placebo (n=4)**
Median (range)	1.3 (0.7 to 6.9)	126.1 (96.8 to 139.4)
Puhringer 2008	**Rocuronium + sugammadex (16 mg kg^{-1}) (n=11)**	**Rocuronium + placebo (n=5)**
Median (range)	1.3 (0.8 to 2.3)	124.3 (87.3 to 156.1)
Active control trials (time to recovery (T1 of 90%) 3 minutes after rocuronium)		
Lee 2009	**Rocuronium + sugammadex (16 mg kg^{-1}) (n=55)**	**Succinylcholine (n=55)**
Median (range)	5.7 (4.2 to 13.6)	10.7 (5.0 to 16.2)

Conclusions and implications

The evidence base for use of sugammadex in UK clinical practice is limited. However, sugammadex appears to produce a more rapid recovery from neuromuscular block compared with commonly used agents. The availability of sugammadex 16 mg kg^{-1} to reverse high dose rocuronium means that rocuronium plus sugammadex could be considered as a replacement for succinylcholine in rapid sequence induction. The benefit of sugammadex requires further evaluation in routine practice.

See HTA report by Chambers *et al* (in press) for full details.[1]

References

1. Chambers D, Paulden M, Paton F, Heirs M, Duffy S, Craig D, *et al.* Sugammadex for the reversal of muscle relaxation in general anaesthesia: systematic review and economic assessment. *Health Technol* Assess 2010;**14**(in press). http://www.hta.ac.uk/project/1780.asp

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