Special Article

Reversal agents in anaesthesia and critical care

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ABSTRACT

Despite the advent of short and ultra-short acting drugs, an in-depth knowledge of the reversal agents used is a necessity for any anaesthesiologist. Reversal agents are defined as any drug used to reverse the effects of anaesthetics, narcotics or potentially toxic agents. The controversy on the routine reversal of neuromuscular blockade still exists. The advent of newer reversal agents like sugammadex have made the use of steroidal neuromuscular blockers like rocuronium feasible in rapid sequence induction situations. We made a review of the older reversal agents and those still under investigation for drugs that are regularly used in our anaesthesia practice.

Key words: Flumazenil, naloxone, platelet factor 4, sugammadex

INTRODUCTION

Balanced anaesthesia practice involves the use of potent sedatives, opioids, neuromuscular blocking agents (NMBA) and local anaesthetics (LA). Despite the advent of short and ultra-short acting drugs, an in-depth knowledge of the reversal agents used is a necessity for any anaesthesiologist. Reversal agents are defined as any drug used to reverse the effects of anaesthetics, narcotics or potentially toxic agents.[1] Routine reversal of neuromuscular blockade is common in many countries after surgery under general anaesthesia, in order to prevent recurarisation.[2] However, the use of reversal for opioids, LA and benzodiazepines (BZDs) is limited to overdose.

Moreover, the introduction of newer drugs such as dexmedetomidine, rocuronium and gantacurium make it important for us to update our knowledge on the newer reversal agents. Hence, we conducted literature search using the search words reversal agents, sugammadex, naloxone in Google Scholar, Medline, PubMed for the period after 2000, for research and review articles. Reversal agents, in general, fall into two categories: Receptor-specific antagonists and non-specific analeptic agents.[3] Antagonists are defined as agents which have a high affinity for a receptor and no intrinsic activity. For example anticholinesterases, naloxone, flumazenil, etc. Analeptics are defined as stimulants. For example theophylline, doxapram, caffeine, etc.

AGENTS REVERSING NEUROMUSCULAR BLOCKADE

Routine reversal of neuromuscular blockade is more common in the United States but is not used in the European countries. However, the risk of residual neuromuscular blockade makes it necessary to reverse NMBAs.[2] NMBAs may be reversed either by increasing the concentration of acetylcholine in the synaptic junction or aid the elimination of the drug or its metabolism.[2,4] Benzyl isoquinolinium compounds such as atracurium and cisatracurium under metabolism by Hoffmann elimination and non-specific esterases.

ANTICHOLINESTERASES

These drugs exert their effect primarily by inhibiting acetylcholinesterase and butyrylcholinesterase,

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prolonging the existence of acetylcholine at the motor end-plate.[5] In addition, anticholinesterases may have a direct agonistic effect by increasing the release of acetylcholine from presynaptic nerve terminals.[4] For neostigmine, the maximum effective dose is 60–80 μg/kg and for edrophonium, it is 1.0–1.5 mg/kg.[4] The addition of two antagonists is avoided as they are not additive and inadequate reversal can occur. It is not advisable to administer additional anticholinesterase if maximal doses of edrophonium (1.5 mg/kg), neostigmine (70 μg/kg), or pyridostigmine (350 μg/kg) fail to antagonize the residual blockade and may in turn increase the weakness.[4] They are combined with atropine or glycopyrrolate in order to neutralize the muscarinic side-effects of these drugs. The combination of glycopyrrolate to neostigmine and pyridostigmine and atropine for edrophonium is matched to their duration of action. Glycopyrrolate may be preferable to atropine in case of cardiac arrhythmias and the anticholinesterases and anticholinergics should be administered more slowly (e.g., 2–5 min) to reduce the incidence and severity of disordered rhythm. Neostigmine is the most potent and the preferred drug.[4] High-dose neostigmine or unwarranted use of neostigmine may translate to increased post-operative respiratory morbidity.[6] Recent guidelines specify the use of reversal with neostigmine based on the train of four (TOF) monitoring with the neuromuscular monitor. Neostigmine can be given for reversal in patients who were receiving drugs which augment the action of NMBAs (inhalational agents) if TOF count is 4, in patients receiving anaesthetic drugs which do not augment the blockade by NMBAs (intravenous anaesthetics) if TOF count is 2 and if TOF ratio is more than 0.9 then reversal should not be given.[7] Furthermore, the guidelines also specify that if the TOF count is <2 reversal should be delayed, if TOF count is 4 and no fade is perceived or if TOF ratio is 0.4:0.9 on qualitative neuromuscular monitoring neostigmine at a lower dose of 20 μg/kg should be considered.[7]

SUGAMMADEX

Development of this cyclodextrin is said to be the first pharmacological breakthrough in the past 60 years. It was discovered by Anton 'Ton' Bom a pharmaceutical chemist and presented in the 7th International Neuromuscular Meeting in Belfast.[8] Sugammadex (modified γ-cyclodextrin) [Figure 1] is a selective relaxant binding agent (su refers to sugar, whereas gammadex emphasizes to the structural molecule gamma-cyclo*dex*trin). Sugammadex complexes with steroidal NMBAs in a 1:1 ratio (rocuronium > vecuronium ≫ pancuronium) by forming a guest-host complex, which helps in rapid removal of free rocuronium molecules from plasma. It completely encapsulates the molecule of steroidal NMBAs and is excreted via the kidney unchanged [Figure 2].[9] The dose of sugammadex is dependent on the dose of muscle relaxant used. The recommended doses are between 2 and 16 mg/kg body weight.[4] Studies have found the incidence of inadequate reversal with 0.5 mg/kg.[10] One case report has reported recurarisation in an obese individual with a dose of 1.74 mg/kg.[11] The use of this molecule is also very important in cardiac surgery[12] as the arrhythmogenic potential of standard neostigmine and glycopyrrolate limits their use. Sugammadex can also be used as an acute therapeutic option in the event of an allergic reaction against rocuronium.[13] Use of sugammadex makes the use of rocuronium possible in patients with neuromuscular disorders.[14] Controversy on the dose to be administered in morbidly obese patients still continues. The present recommendation is to administer sugammadex based on the actual body weight, but one study has compared the use of doses based on lean body weight, lean body weight +20% and lean body weight +40% and found the administration of lean body weight +40% to be better.[15] The disadvantage is that it cannot reverse the action of benzylisoquinolinium compounds.[4]

CYSTEINE

A new class of NMBAs fumarates (gantacurium) undergo spontaneous elimination by cysteine adduction. This adduction reaction replaces chlorine and saturates the fumarate double bond. The compound formed is

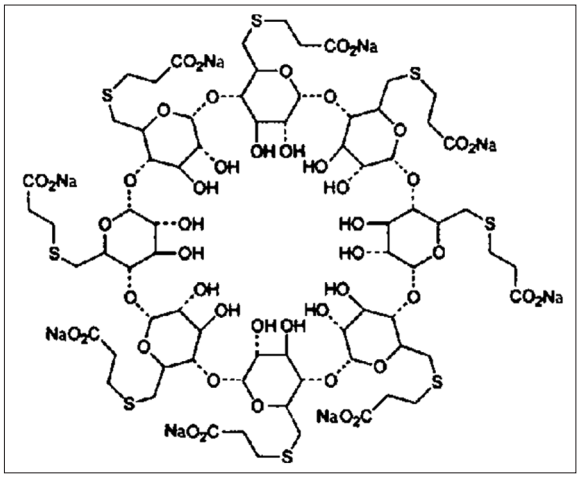

Figure 1: Structure of Sugammadex

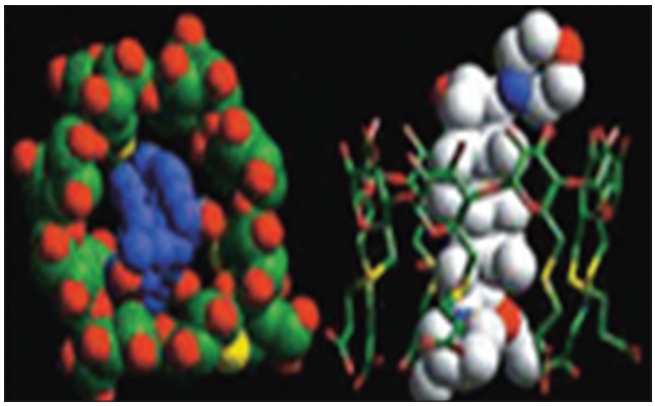

Figure 2: Sugammadex encapsulating rocuronium

structurally different from gantacurium and cannot cause neuromuscular blockade.[2] Administration of cysteine will usually hasten the recovery from gantacurium induced blockade.[2,4] Doses of 10 mg/kg have been known to reverse the effect of 8 times the ED_{95} of gantacurium within 1–2 min.[16]

OTHER AGENTS

Four aminopyridine is a tertiary compound and a potassium channel antagonist which acts by increasing the concentration of acetylcholine. It has been used regularly in countries like Bulgaria in combination with anticholinesterases. However, its use is limited by its stimulant effect on the central nervous system (CNS).[17,18]

Galanthamine is another tertiary compound like 4 aminopyridine whose inconsistency in reversal and stimulant effect on the CNS has unpopularised it.[17]

Suramin is an anti-trypanosomal drug used in African sleeping sickness. Its mechanism of NMBA reversal is yet unexplained. It may be due to P_2 purinoceptor blockade, post-synaptic action, the release of adenosine triphosphate, etc. Its main disadvantage is its very short duration of action, but similar synthetic agents may be of use in the future.[18]

OPIOID ANTAGONISTS

Naloxone

Naloxone is chemically N-alylnor-oxymorphone and it possesses the ability to antagonise all types of opioid receptors. However, it shows high affinity for μ receptors. Naloxone shows high first pass metabolism. The drug is metabolised in the liver primarily by conjugation with glucuronic acid. The half-life of naloxone is about 1 h. It acts in 1–2 min when it is given intravenously (IV). Intravenous naloxone (0.4–0.8 mg) promptly antagonises all actions of morphine. In patients with respiratory depression, an increase in respiratory rate is seen within 1 or 2 min. At a dose of 10-15 mg, it also can antagonise the actions of nalorphine and pentazocine (dysphoric effects). Rebound release of catecholamines may cause hypertension, tachycardia, ventricular arrhythmias and pulmonary oedema. Primary indications are to reverse respiratory depression due to intraoperative opioid overdose (0.1–0.2 mg IV). It is used as an agent to decrease neonatal respiratory depression secondary to the intravenous or intramuscular administration of opioids to the mother. In the neonate, the initial dose is 10 μg/kg given IV, intramuscularly or subcutaneously.[19] To antagonize actions of buprenorphine naloxone, continuous infusion is required. Abrupt reversal of opioid depression with large doses of naloxone can precipitate sympathetic activity and hence nausea, vomiting, tachycardia, hypertension, tremors, sweating, seizures and cardiac arrest can occur. To prevent these, diluting the drug (0.4 mg) to 10 ml (0.04 mg/ml) and injecting 1–2 ml every 1–2 min is recommended.[5] At the end of 2014, the World Health Organization published a position paper recommending community access to naloxone in an effort to stem the tide of accidental deaths from opioids.[20]

OTHER OPIOID ANTAGONISTS

Nalmefene is effective for the reversal of opioid-induced CNS effects and may be administered orally or IV showing a dose-dependent duration of action 4–8 h following IV administration. The initial adult dose is 0.5 mg.[21] If there is an incomplete response or no response, additional doses can be given at 2–5 min interval. Nalmefene has a relatively slow onset of action, and no serious adverse reactions were noted in studies where 4 times the normal dose was given.[22] There is one case report in the literature of a healthy patient developing acute post-operative pulmonary oedema after a very low dose (75 μg) of nalmefene.[23] It is available in the oral and intravenous form. The dosage for opioid overdose is 1 ml (100 μg)/1 mg of opioid IV. For the reversal of post-operative respiratory depression, 25 μg increments are given every 2–4 min.[24] The principal advantage over naloxone is its considerably longer duration of antagonistic action. Naltrexone, primarily used for opioid detoxification is a potent, long-acting, pure opiate antagonist and effective orally. It has a longer duration of action lasting

up to 72 h. It is only available in oral form and its main indication for use is during opioid withdrawal and to maintain abstinence. The recommended dose range is from 50 to 300 mg/day/oral.[24]

REVERSAL AGENTS FOR SEDATIVES

Flumazenil

Flumazenil is 1,4-imidazobenzodiazepine and has got a structural resemblance to midazolam. Flumazenil is administered IV. It is used as a reversal agent for BZDs. In addition, it is a potential reversal agent after subcutaneous, sublingual, intramuscular, submucosal, intranasal,[25] rectal and endotracheal administration. On intravenous administration, flumazenil has a half-life of about 1 h and the duration of clinical effects usually is only 30–60 min. It is eliminated via liver to inactive products and excreted renally. Therefore, re-sedation is a possibility with longer acting BZDs and may occur within 1–2 h after administration, which requires subsequent doses. It is indicated for reversal of procedural sedation, a reversal of sedation in the Intensive Care Unit, management of BZD overdose, intra-operative wake-up testing in clinical practice. For this purpose in adults 0.2 mg/dose, to a total of 3 mg, over 30 s followed by 0.3 and 0.5 mg at 1 min intervals to a maximum dose of 3 mg can be given. In children 0.01 mg/kg IV per dose, to a total of 0.05 mg/kg or 1 mg[26] is administered. A total of 1 mg flumazenil given over 1–3 min usually is sufficient to abolish the effects of therapeutic doses of BZDs such as the sedative, anxiolytic, anticonvulsant, ataxic, anaesthetic and muscle relaxant effects of BZDs. The sublingual approach would allow convenient and better treatment availability for patients with hepatic encephalopathy as well as for reversing the residual hypnotic effect after a surgical procedure.[27] Adverse effects could be dizziness, facial erythema, anxiety and headache which are often mild and disappear within several minutes. Additionally, flumazenil has been noted to precipitate seizures in epileptic patients who are on BZDs for seizure control. It should also be avoided in patients who have consumed a combination of Tricyclic anti-depressants and BZDs.[28] Recent literature on flumazenil investigate the reversal of the sedative effect of sevoflurane with its administration. Karakosta *et al*. have concluded that recovery from sevoflurane/remifentanil anaesthesia is faster in patients administered 0.3 mg flumazenil.[29] In another study, Liang *et al*. have concluded that 0.006 mg/kg of flumazenil may only partially reverse the hypnotic effect without changing the time to recovery or extubation.[30]

Atipamezole

Use of dexmedetomidine a specific alpha 2 agonist has become common in anaesthesia practice. Use of atipamezole a specific alpha 2 antagonist to reverse the psychomotor effects of dexmedetomidine is being investigated in human volunteers way back as 1991.[31] They have been found to have sympathomimetic effects.[32] Dose range of 40:1–100:1 has been found to be effective for the rapid reversal of the effects of dexmedetomidine. [30] However, its regular use has not been approved by the Food and Drug Administration yet.

ANALEPTIC AGENTS

Conventionally, the use of doxapram has been reserved in patients with chronic obstructive pulmonary disease receiving oxygen therapy and because controlled ventilation and supportive therapy can manage drug-induced coma, it is not to be used for this indication.[33] Side effects could be panic attacks, palpitation, tremors, sweating and convulsions. Hence, it is relatively contraindicated in coronary artery disease and epileptic patients. In a recent study, however, doxapram has been found to hasten the recovery from dexmedetomidine–propofol-remifentanil anaesthesia in patients undergoing uvulopalatopharyngoplasty and may benefit patients with obstructive sleep apnoea.[34]

REVERSAL OF ANTICOAGULANTS

Heparin is the commonly used anticoagulant in anaesthesia practice in patients undergoing cardiac or major vessel surgery. Effect of unfractionated heparin can be reversed with protamine sulphate a component of salmon sperm. The problems are histamine release, pulmonary hypertension and allergic reactions.[35] Platelet factor 4(PF4) is a protein found in platelet alpha granules and has been found to reverse the anticoagulant effect of heparin within dose ranges of 0.5–5 mg/kg over 3 min.[36,37] Demma *et al*. in a case series have commented that PF4 in a dose of 5 mg/kg reversed the effect of heparin in 10 min.[37] However, this is currently not being developed for clinical use.[38] *In vitro* studies have been done on heparinase 1 but, *in vivo* study has been done only on dogs and not on humans.[39] This study shows a promising result, but further extensive studies are required even though the *in vitro* and *in vivo* studies confirm lesser side effects in comparison to protamine. Heparin removal devices are being investigated. These involve veno-venous

Table 1: Reversal agents for common drug overdoses in toxicology

Drug	Reversal agent	Dose
Calcium channel blockers	Calcium chloride	10 ml IV in adults 0.2-0.25 ml/kg in paediatric patients
Insulin	Dextrose	1 g/kg IV in adult 0.5 g/kg in paediatric
Digoxin	Digoxin Fab	5-10 vials in adults if acute, 3-6 vials if chronic 1-2 vials IV in paediatric age group, for both acute and chronic toxicity
IV bupivacaine	IV lipid emulsion 20%	1.5 ml/kg bolus over 1 min followed by 0.25 ml/kg infusion
Anticoagulant rodenticides/warfarin	Vitamin K	20 mg/day PO in adults 1-5 mg/day PO in paediatric

IV – Intravenous; IM: – Intramuscular

extracorporeal circulation with adsorption of the heparin using a polycation.[40]

REVERSAL AGENTS IN CRITICAL CARE AND TOXICOLOGY

Naloxone and flumazenil are used in patients with opioid and BZD in the critical care setting too. Other reversal agents used in toxicology are listed in Table 1.[41]

SUMMARY

The introduction of newer reversal agents such as sugammadex has revolutionised anaesthesia practice. However, much needs to be done in terms of reversal agents in critical care and toxicology.

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Conflicts of interest

There are no conflicts of interest.

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