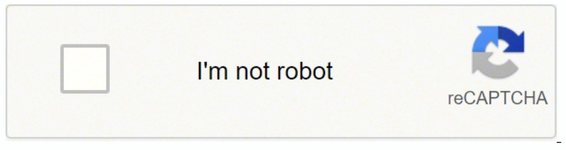

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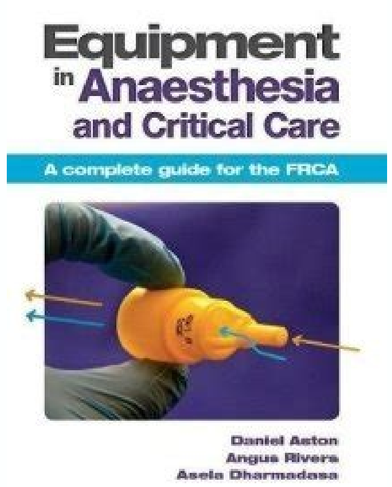

Special Article

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.[1] 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.[1] 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.[1] 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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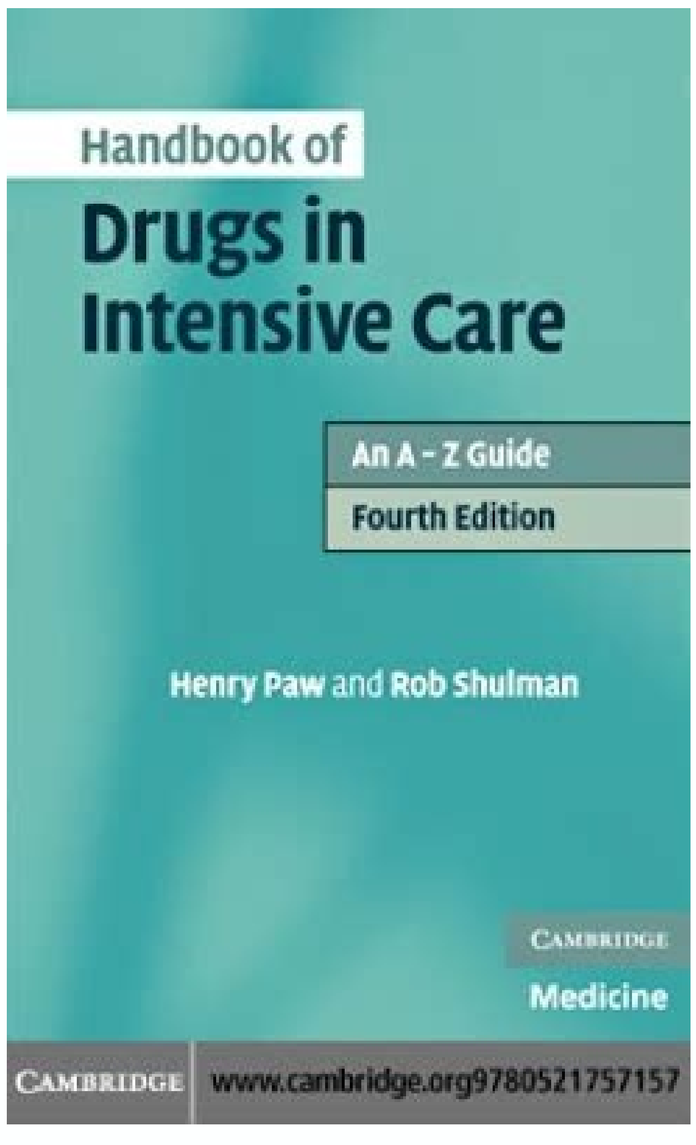

respectively. Hyposecretion causes **adrenocortical insufficiency**.

The adrenal medulla is thought to be derived from a sympathetic ganglion in which the postganglionic neurones have lost their axons, and secrete **catecholamines** into the bloodstream. Hypersecretion results in **phaeochromocytoma**.
See also, Sympathetic nervous system

Adrenaline (Epinephrine). **Catecholamine**, acting as a hormone and **neurotransmitter** in the **sympathetic nervous system** and brainstem pathways. Synthesised and released from the **adrenal gland** medulla and central adrenergic neurones (*for structure, synthesis and metabolism, see Catecholamines*). Called epinephrine in the USA because the name adrenaline, used in other countries, was too similar to the US-registered trade name Adrenalin that referred to a specific product (both adrenaline (Latin) and epinephrine (Greek) referring to the location of the adrenal gland "on the kidney").

Stimulates both α- and β-**adrenergic receptors**; displays predominantly β-effects at low doses, α- at higher doses. Low dose infusion may lower BP by causing vasodilatation in muscle via β_2-receptors, despite increased cardiac output via β_1-receptors. Higher doses cause α-mediated vasoconstriction and increased systolic BP, although diastolic pressure may still decrease.

- Clinical uses:
  - with **local anaesthetic agents**, as a vasoconstrictor.
  - in **anaphylactic reaction**, **cardiac arrest**, **bronchospasm**.
  - as an **inotropic drug**.
  - in **glaucoma** (reduces aqueous humour production).
  - in **croup**.

Adrenaline may cause cardiac **arrhythmias**, especially in the presence of hypercapnia, hypoxia and certain drugs, e.g. **halothane**, **cyclopropane** and **cocaine**. During halothane anaesthesia, suggested maximal dosage of adrenaline is 10 ml 1:100 000 solution (100 μg) in 10 min, or 30 ml (300 μg) in 1 h. More dilute solutions should be used if possible. Adrenaline should not be used for ring blocks of digits or for penile nerve blocks, because of possible ischaemia to distal tissues.

- Dosage:
  - anaphylaxis: 0.1 mg iv (1 ml 1:10 000 solution), repeated as required. The recommended initial route in general medical guidelines is usually im (0.5–1.0 ml 1:1000 solution), reflecting the risks of iv administration without appropriate monitoring.
  - cardiac arrest: 1 mg (10 ml 1:10 000) iv.
  - by infusion: 0.01–0.15 μg/kg/min initially, increasing as required.
  - croup: 0.4 ml/kg nebulised up to 5 ml maximum, repeated after 30 min if required.

  Subcutaneous injection in shocked patients results in unreliable absorption. Adrenaline may be administered via a tracheal tube in 2–3 times the iv dose.

See also, Tracheal administration of drugs

α-Adrenergic receptor agonists. Naturally occurring **agonists** include **adrenaline** and **noradrenaline** which stimulate both α_1- and α_2-**adrenergic receptors**.

Methoxamine and **phenylephrine** are synthetic α_1-receptor agonists, used to cause vasoconstriction, *e.g.* to correct hypotension in **spinal anaesthesia**.

Clonidine acts on central α_2-receptors. Clonidine and other α_2-receptor agonists (e.g. **dexmedetomidine**) have been shown to reduce pain sensation and reduce requirements for general anaesthetics and have also been used for **sedation** in ICU. Other α_2-receptor agonists (e.g. xylazine, detomidine and medetomidine) have been used in veterinary practice as anaesthetic agents for many years.

β-Adrenergic receptor agonists. Agonists include adrenaline and **isoprenaline** which stimulate both β_1- and β_2-**adrenergic receptors**. **Dopamine** and **dobutamine** act mainly at β_1-receptors.

Salbutamol and **terbutaline** predominantly affect β_2-receptors, and are used clinically to cause bronchodilatation in **asthma**, and as **tocolytic drugs** in premature labour. Formoterol and salmeterol are longer acting agents given by inhalation for chronic asthma. **Ritodrine** is also used as a tocolytic drug. Some β_1-receptor effects are seen at high doses, e.g. tachycardia. They have been used in the treatment of **cardiac failure** and **cardiogenic shock**; stimulation of vascular β_2-receptors causes vasodilatation and reduces afterload.

α-Adrenergic receptor antagonists (α-Blockers). Usually refer to **antagonists** which act exclusively at α-**adrenergic receptors**.

- Drugs may be:
  - selective:
    - α_1-receptors, e.g. **prazosin**, **doxazosin**, **terazosin**, indoramin, **phenoxybenzamine**. Tamsulosin acts specifically at α_{1A}-receptors and is used in benign prostatic hypertrophy.
    - α_2-receptors: yohimbine.
  - non-selective, e.g. **phentolamine**.

Labetalol and carvedilol (a drug with similar effects) are antagonists at both α- and β-receptors. Other drugs may also act at α-receptors as part of a range of effects, *e.g.* **chlorpromazine**, **droperidol**.

Antagonism may be competitive, *e.g.* phentolamine, or non-competitive and therefore longer-lasting, e.g. phenoxybenzamine.

Used to lower BP and reduce **afterload** by causing vasodilatation. Compensatory tachycardia may occur.

- Side effects: postural hypotension, dizziness, tachycardia (less so with the selective α_1-antagonists, possibly because the negative feedback of noradrenaline at α_2-receptors is unaffected). **Tachyphylaxis** may occur.

β-Adrenergic receptor antagonists (β-Blockers). Competitive **antagonists** at β-**adrenergic receptors**.

- Actions:
  - reduce heart rate, force of contraction and myocardial O_2 consumption.
  - increase **coronary blood flow** by increasing diastolic filling time.
  - antiarrhythmic action results from β-receptor antagonism and possibly a membrane-stabilising effect at high doses.
  - antihypertensive action (not fully understood but may involve reductions in cardiac output, central sympathetic activity, and renin levels).
  - some have partial agonist activity (**intrinsic sympathomimetic activity**), e.g. pindolol, acebutolol, celiprolol and oxprenolol.
  - practolol, **atenolol**, **metoprolol**, betaxolol, bisoprolol, nebivolol and acebutolol are relatively cardioselective, but all will block β_2-receptors at high doses. Celiprolol has β_1-receptor antagonist and β_2-receptor agonist properties, thus causing peripheral vasodilatation in addition to cardiac effects.
  - labetalol and carvedilol have α- and β-receptor blocking properties. The former is available for iv administration and is widely used for acute reduction in BP.

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