Comment on Zhang M, Liu H, Han X, Guo J, Ge Y. Reversing the triad of anaesthesia in a cannot intubate, cannot oxygenate emergency. Br J Anaesth. 2024 Jul;133(1):190-192. doi: 10.1016/j.bja.2024.04.020. Epub 2024 May 16. PMID: 38760265.

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Keywords - Opioid; Reversal; Antagonist; Naloxone; Fentanyl; Nitazene;

We read with interest the recent pieces in this journal on using remimazolam-sufentanil-rocuronium for a rapid sequence induction followed by flumazenil-naloxone-sugammadex if rapid reversal is required.[1,2] Reversibility is clearly central to the triad of anaesthesia. Pharmacological antagonism can take many forms which has significant clinical implications and is not simply of academic interest. We provide some cautionary notes around generalisation of the idea of "reversal agents" particularly focusing on opiates. This has never been more relevant than with the growing problem of nitazenes abuse[3] although nitazenes are not used by anaesthetists they may find themselves called upon to assist with these patients. We first discuss the concept of antagonism of neuromuscular blockade which is illustrative of the rich pharmacology of reversal as a case study of reversal pharmacology before turning our focus to opiate reversal.

Antagonism can take the form of direct competition at the orthosteric binding site, negative allosteric modulators or chemical antagonism. Rocuronium is a competitive antagonist at the nicotinic acetylcholine receptor (nAChR). It can be chemically antagonised by sequestration by the γ-cyclodextrin sugammadex or biochemically by neostigmine (an acetylcholinesterase inhibitor) to increase the levels of acetylcholine in the neuromuscular junction, allowing acetylcholine to out compete the rocuronium. High doses of neostigmine can cause phase II blockade recapitulating suxamethonium (a short lived nAChR agonist) induced blockade whereas high doses of sugammadex can reverse even deep neuromuscular blockade when caused by an aminosteroid neuromuscular blocker. Some effects of neostigmine must be antagonised using glycopyrrolate (competitive antagonist) to prevent the action on muscarinic receptors. This pharmacology is likely familiar to any practicing anaesthetist and illustrates the richness of

pharmacological antagonism. It is therefore surprising therefore that naloxone is viewed as the universal opioid antagonist.

It is commonly assumed that a competitive antagonist will be equally effective against all agonists acting at a given receptor. This would imply that naloxone is equally efficacious in reversing morphine and fentanyl, however this is not experimentally correct. The fentanyl series compounds (including fentanyl and related compounds such as alfentanil, sufentanil and remifentanil) show considerable different pharmacology to the morphinan ligands such as morphine and oxycodone.[4] Clinically relevant anomalies include the greater propensity to cause respiratory depression and to cause skeletal muscle rigidity.[4,5] Whilst Zhang et al were successful in reversing the triad of anaesthesia with naloxone, one cannot assume that naloxone can reverse the effects of opiates particularly with the growth of nitazenes, ultra-potent opiates, which are currently a drug of abuse but not used therapeutically and are difficult to reverse with naloxone.[6]

Competitive antagonists classically bind to the orthosteric binding site of the receptor when unoccupied which is agonist independent. Naloxone is commonly considered to be a competitive antagonist at the mu-opioid receptor (MOP) but more recently has been shown to be pseudo-competitive.[7] Some fentanyl analogues and nitazenes appear to have slow dissociation kinetics at the MOP and this correlates with the requirement for higher doses of naloxone to reverse their effects.[7] Murine studies suggest that naloxone is less potent in reversing the respiratory depression induced by fentanyl than by morphine,[8] fentanyl also induces incomplete cross tolerance.[8] This lower potency may be overcome by use of higher doses of naloxone but there is

concern that naloxone may cause non-cardiogenic pulmonary oedema in a dose dependent fashion.[9]

Zhang et al. should be applauded for their swift action in a potentially life-threatening situation which was successful in treating an unanticipated difficult airway. However, clinicians need to consider that naloxone may be less effective against some fentanyl analogues and nitazenes and although high doses of naloxone have been found to be effective in some circumstances, this approach may be associated with higher incidence of non-cardiogenic pulmonary oedema. Efforts are underway to develop novel opiate antagonists[8,10] which might provide methods to reverse the clinical effects of high potency lipophilic opioid receptor agonists such as fentanyl analogues and nitazenes.

Acknowledgement of funding

Huw Garland was supported by the University of Southampton National Institute of Health Research Academic Clinical Fellowship Scheme (ACF-2022-02-005). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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