ISSN: 0975-833X

Available online at http://www. journalcra. com

International Journal of Current Research
Vol. 9, Issue, 11, pp.60717-60722, November, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

REVIEW ARTICLE

REVERSAL FROM NEUROMUSCULAR BLOCKADE

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ARTICLE INFO

Article History:
Received 28th August, 2017
Received in revised form
19th September, 2017
Accepted 04th October, 2017
Published online 30th November, 2017

Key words:
Nondepolarising Muscle Relaxants,
Reversal Agents.
Conflicts of Intrest,
None to Mention.

ABSTRACT

Recovery from the effects of non-depolarising relaxants can occur spontaneously by elimination of the agent either unchanged or after metabolism in general anaesthesia. However, this process may be slow, of variable time and cannot be reliably predicted. It may result in residual curarization. Also, surgical procedures can be of unpredictable duration and may require intense relaxation until near the completion of surgery. Pharmacological antagonism or reversal of NM block is therefore indicated in clinical practice. This can be accomplished with a variety of drugs called as reversal agents**.**

Citation: Dr. Sanjay P. Gadre and Dr. Vineet Mishra, 2017. "Reversal from neuromuscular blockade", *International Journal of Current Research*, 9, (11), 60717-60722.

INTRODUCTION

Recovery from the effects of non-depolarising relaxants can occur spontaneously by elimination of the agent either unchanged or after metabolism in general anaesthesia. However, this process may be slow, of variable time and cannot be reliably predicted. It may result in residual curarization. Also, surgical procedures can be of unpredictable duration and may require intense relaxation until near the completion of surgery. Pharmacological antagonism or reversal of NM block is therefore indicated in clinical practice. This can be accomplished with a variety of drugs called as reversal agents**.**

The qualities of an ideal reversal agent

It should have a fast onset.

- It should be efficient at any time, even soon after curarization of the patient.
- It should be able to provide complete reversal either for light or profound block.
- It should have a longer half life than the NM blocking agent.
- It should be free of any side effects.
- It should be able to restore sustained neuromuscular function rapidly even when NM blockade is profound at the time of administration.

Clinical guidelines for reversal of non-depolarising neuromuscular blockade (Harper, 1995)

- A peripheral nerve stimulator should be used whenever a muscle relaxant drug is given.
- It is unadvisable to reverse the blockade until at least one twitch of the train of four has returned.
- Always give a reversible agent unless NM function has recovered spontaneously to the extent that there is absolutely no fade in the response to double burst stimulation i.e. full recovery of NM activity is confirmed.
- Choose a dose of antagonist drug which is commensurate with the extent of NM blockade and give this dose as a single bolus. A divided dose, separated by a few minutes, may result in a less satisfactory reversal than a single dose of the same total amount.
- Long acting muscle relaxants reverse more slowly than intermediate or short acting drugs; therefore allow more time for antagonism to take place before discontinuing general an aesthesia.
- Antagonism of NM blockade is a less rapid process than is actually believed.
- Reversal should be omitted only when absence of any residual block has been clearly demonstrated.

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- Because small degree of blockade is difficult to access clinically, reversal agents are generally given to all patients.
- Choice of reversal drug and dose should be made according to the intensity of the block to be reversed.

Aims of reversal

In some cases NM blockade is allowed to persist into the post operative period (e.g.: to assist mech-ventilatory support). However, usually the patient should leave the OT with unimpaired muscle strength. The extent of permissible residual paresis is an important issue. Adequacy of recovery of NM function has usually been defined in terms of the patient's ability to maintain satisfactory ventilator function and a patent airway.

The clinical criteria for adequate reversal includes

- TOF ratio of 0.9 or greater is predictive of recovery of pharyngeal muscles, masseter muscle and striated muscles of upper oesophagus. At TOF <0.9 there may be a substantial risk of aspiration.TOF ratio of 0.6-0.7 of adductor pollicis indicates ventilator adequacy.
- Inspiratory force (maximum negative pressure that could be generated against an occluded airway) between -20 to -30 cm water pressure indicates sufficient ventilator reserve to allow safe return of patient to PACU.
- Ability to sustain a 5 sec head lift. This indicates sufficient strength in normal patients to protect the airway against obstruction & aspiration of oral contents. It corresponds to TOF ratio of 0.75.
- Grip strength (absence of a firm & sustained handgrip): More sensitive indicator of residual weakness than head lift. It requires the use of a dynamometer & pre-op control values. So, it is less useful as a clinical tool. At TOF of 0.9 the grip strength will be 70-100% of control.
- Sustained leg lift for 5 sec: It is a valuable sign of adequate reversal in children as old as 12 weeks of age & it indicates adequate airway control and ventilatory function. It usually corresponds to TOF ratio of 0.75.
- Absence of double vision over 2 hrs.
- No double burst fade.
- Masseter strength –ability to prevent a wooden tongue depressor clenched between two incisors from being pulled out by even a vigorous effort.
- Difficulty in speaking, swallowing if TOF <0.75.

Factors which influence the effectiveness of reversal (Taberner, 1996; Cecil Gray, 1971)

- **Method of measurement of nm function –** the optimum index of returning NM function is the TOF ratio.
- **Intensity of block –** the depth of NM blockade at the time of administration of reversal agents has a profound influence on the speed & efficacy of reversal. Reversal of a profound blockade proceeds more slowly than reversal of less intense block.
- **Choice of relaxant –** The speed of reversal is related to the inherent duration of action & rate of spontaneous recovery from the effects of the relaxant. Intermediate acting drugs are therefore easier & faster to reverse then are long acting relaxants. Reversal following single bolus doses of the relaxant is easier than after relaxant infusion.
- **Choice of reversal agent** - Neostigmine has been found to be a more reliable antagonist than edrophonium for antagonism of deep blocks. Sugammadex can reverse very deep NM blockade induced by Rocuronium without muscle weakness.
- **Dose of reversal agent –** when given at 10% spontaneous T1 recovery anticholinesterases like neostigmine & other drugs like sugammadex produce larger effects when the dose is increased. Anticholinesterases like neostigmine, edrophonium & pyridostigmine have a ceiling effect. The effect of these drugs is dose dependent until a plateau is reached at which point an increase in dose does not produce further reversal of NM blockade. This is known as the 'ceiling effect'. This plateau corresponds to a TOF ratio of approx 0.6.
- **Plasma concentration of relaxant –** the concentration gradient of muscle relaxant from NM junction to plasma does influence the rapidity of spontaneous recovery of NM function to some extent. Under conditions of equilibrium, the degree of NM blockade & the plasma concentration are closely correlated. However, a situation of equilibrium rarely exists in clinical practice, unless the relaxant is infused continuously. If a repeated bolus technique is used, the direction of gradient is continuously changing. After a prolonged continuous infusion or after numerous boluses, the plasma concentration associated with a given level of NM blockade might be expected to be greater than after a single bolus during the offset of blockade. Hence the recovery after a single bolus dose of relaxant is more rapid compared with a prolonged continuous infusion.
- **Anaesthetic agent –** Potent volatile agents result in slower recovery following pharmacologic muscle relaxant reversal if their use is continued during reversal eg: sevoflurane, enflurane, isoflurane
- **Renal failure-** anticholinesterases like neostigmine are actively secreted into the renal tubules & their plasma clearance is reduced in renal failure. The plasma clearance decreases for neostigmine by 2 folds & edrophonium by 3 folds. The elimination of muscle relaxants eg: vecuronium is also delayed in renal failure. Hence, the rate of reversal may be unaffected or decreased. The rate & extent of recovery from pancuronium after administration of neostigmine is not impaired in renal failure, & recurarization does not occur.
- **Age –** the plasma clearance of anticholinesterases is reduced in the elderly in common with plasma clearance of NDPR because of age related decrease in hepatic metabolism & renal clearance. It is unnecessary to increase the dose of neostigmine in the elderly. The dose can be decreased because this group of patients exhibits a left shift in the dose-response relationship. The speed & extent of recovery is no different between young & old if the reversal agent is given at the same level of NM blockade. Atracurium, because of metabolism by Hoffman elimination & enzyme hydrolysis is not affected. Spontaneous recovery from NM blocking drugs is more rapid in children aged 1-10 yrs than in adults. Recovery in infants is slower than in children for pancuronium, atracurium & vecuronium. Reversal occurs more rapidly & the dose of reversal

agent required to produce equivalent effects is less in infants & children than in adults.

- **Drug interactions –** any drug which potentiates NM blocking drugs will impede the reversal of NM blockade. Eg: doxapram, anti-arrhythmic agents like lidocaine & verapamil, aminoglycosides antibiotics, hypotensive drugs, immunosuppressants & anti-cancer drugs, mag sulphate, Ca channel blockers.
- **Electrolyte & Acidbase disorders –** respiratory acidosis, metabolic alkalosis & hypokalemia impede/delay reversal of NM block. The degradation of atracurium is partially pH dependant (hoffman elimination) but there is no evidence that acidosis impedes its antagonism by neostigmine in the clinical situation.
- **Pre existing medical conditons – dm**, underlying neurological diseases & obesity. Here, reversal of NM block is less predictable.
- **Hypothermia –** it can prolong the spontaneous recovery from NDPR & delay reversal.

Residual neuromuscular block – (RNMB)

This is commonly observed in the PACU when NMBDs are administered intra operatively.

Factors contributing to residual nm block

- Use of long acting muscle relaxants
- Many anaesthesiologists do not routinely use quantitative NM function monitor to ensure adequate recovery to a TOF ratio of 0.9 or more. Although they are fast to adopt new monitoring technologies, such as capnography, pulse oximetry & BIS monitoring, the same is not true for NM function monitoring.
- Neostigmine has a ceiling effect & when administered at a deep level of NM blockade, it can result in an inadequate recovery of NM function.
- Failure to pharmacologically reverse the block.

Incidence of RNMB – It is less frequent in outpatients than in inpatients, probably because of use of shorter acting NMBD. Despite the applications of techniques proven to limit the degree of residual paralysis, upto 33%-44% of patients have evidence of inadequate NM recovery on arrival to PACU.

Signs of residual curarization:

- Typical my as thenicfacies = ptosis, lack of expression & loss of tone in masseter.
- Inability to raise head from pillow & hold it up for atleast 5 sec.
- Loss of firm sustained head grip.
- Tracheal tug, any paradoxical indrawing of intercostals muscles during inspiration in the absence of any CNS, CVS or RS problems, RR > 20 breaths/min.
- TOF ratio < 0.7.
- Presence of double burst fade
- Lack of sustained leg lift for 5 sec.
- Poor massetter strength by tongue depressor test.
- Presence of diplopia, blurred vision.
- Difficulty in speaking, swallowing.
- Hypoxaemia (SpO2, 90% on room air).
- Inability to breathe deeply when asked by PACU nurse.

Prevention of residual neuromuscular block

- Avoid using long acting muscle relaxants.
- Routine use of intra-op quantitative NM monitoring
- Do not give reversal agents at deep levels of block.
- Use of newer agents like sugammadex which can reverse even deeper levels of rocuronium / vecuronium block.
- Return of TOF ratio of 0.9 should be one goal before shifting to PACU.
- Titrate muscle relaxants & their reversal agents to effect.

Consequences of residual neuromuscular blockade

- Impairment of respiratory response to hypoxaemia.
- Pharynx dysfunction & dysfunction of upper oesophagus- risk of aspiration.
- Upper airway obstruction.
- Inadequate return of pulmonary function

The different pharmacological reversal drugs are classified as

Older drugs

- Traditional & currently in clinical use = neostigmine (widely in use) , edrophonium , pyrido stigmine.
- Currently not much in clinical use = ambenonium, 4-aminopyridine,suramine,gallanthamine, germinediacetate, tetraethyl ammonium, congo red, chlorasol fast pink, evans blue, purified human plasma cholinesterase for mivacurium block.

Newer agents

- Sugammadex (Org 25969)
- Cysteine.

Anticholinesterases: (AchE)

- Mechanism of action for reversal : mainly by inhibition of acetylcholinesterase which results in increased concentration of Ach thus allowing Ach to be present at the NMJ for a longer time, so that each molecule could bind repeatedly with the receptor.
- Presynaptic effect: AchE generate action potentials in the nerve terminal and these action potentials spread dromically. They enhance presynaptic liberation of Ach.
- Direct stimulating effect on the receptor , facilitating NM transmission
- Modification of depolarisation of motor nerve terminals

Complications of Anticholinesterases (Gaurav Kuthiala, 2009; Rosemary, 2009)

- Long lasting muscle weakness in patients with myasthenia gravis/ myotonic dystrophy.
- **CVS –** produced vagal muscarinic effects leading to bradycardia/ other brady arrhythmias like nodal/ & ventricular escape beats & asystole may occur. Onset of bradycardia is rapid for edrophonium, slower for neostigmine & slowest for pyridostigmine.
- **Alimentary effects –** Muscarinic: increased salivation & increased oesophago gastric bowel motility (proximal bowel more than distal). There are reports of increase of

Table 1. Pharmacology of Acetylcholinsterase inhibitors and Anticholinergics

Drug	Dose & Route of admn. (mg/kg) IV	Dura-tion of action	Onset of action	Concurrent Antichol. of choice	Peak effect in min	Vd (mg/kg)	Cl (ml/kg/ min)	Elim. Half life(min)	Cinical application
Neostigmine	0.035-0.05	0.5-1 hrs	7-11 min	Glycopyrrolate	4-10	700	9	80	Reversal of block.
Edrophonium	0.5-1.0	10 min	1-2 min	Atropine	2-4	1100	9.6	112	Diagnosis of M.gravis
Pyridostigmine	0.2-0.25	3-6 hrs	15 min	Propanthelene/Atropine	10-15	1100	8.6	110	Chr. Treatment of M.gravis

Table 2. Doses and interactions of sugmamadex with, muscle relaxants

Muscle relaxant	Dose of Sugammadex (mg/kg)	Depth of block at which Sugammadex given	Median time taken to return to TOF ratio 0.9 (minutes)
Rocuronium	2	shallow	1.9
Vecuronium	2	Moderate	2.3
Rocuronium	2	Shallow	1.3
Rocuronium	4	Deep	1.6-2.3
Vecuronium	4	Deep	3.3

Table 3. Comparison of Sugammadex with Neostigmine

	Sugammadex	Neostigmine
Recovery time	faster	Longer
Technique of anesthesia – eg volatile agents	Efficacy not effected	Efficacy effected
Profound / deep block	Can be given	Cannot be given
Side-effects	Common, no anticholinergic side-effects	Anticholinergic to be coadministered & hence undesirable side-effects of anticholinergic occur
Biological activity	-	+
Chances of residual block	Less if correct dose used	More

bowel anastomotic leakage & anastomotic breakdown when neostigmine was used to reverse NM blockade. This is due to potentiation of Ach released from parasympathetic ganglia present in Auerbach's plexus & at the postganglionic endings on the smooth muscle fibres. Regurgitation of gastric contents may occur at high doses.

Neostigmine block

If administered in large doses more than used clinically in the absence of muscle relaxants, it may produce fasciculations/ depolarising block. This mechanism is likely to be indirect via the accumulation of a large concentration of Ach in the synaptic cleft which itself produces this agonist type of block. Scoline can enhance this block. It is more likely to occur if two divided doses of 2.5mg are given, separated by 2 to 5 mins rather than a single dose of 5 mg. Halothane enhances noestig blockade. It can be partially reversed by NDPR. It can be demonstrated using TOF technique.

- Respiratory effects – increase in airway resistance & broncho-constriction because of cholinergic stimulation of bronchi.
- Increase incidence of PONV with neostigmine.

Prevention of complications of anticholinesterases

- Avoid giving neostigmine in 2 divided doses of 2.5mg,2-3 min apart to prevent neostigmine block.
- Avoid large doses in patients with NM disorders.
- To counteract the unwanted muscarinic alimentary respiratory & CVS effects of acetylcholinesterases, co-administer them with anticholinergic drugs like atropine/ glycopyrolate.

Atropine has a rapid onset of action (approx 1 min) &duration of 30-60 min. It also crosses the BBB & is associated with increased memory deficits after anaesthesia. The simultaneous administration of atropine & neostigmine leads to an initial tachycardia because of the more rapid action of atropine, followed 10-20 min later by a bradycardia. The dose of atropine required with neostigmine is 20 microgram/kg for 40 microgram/kg of neostigmine. Atropine dose for edrophonium is much lesser i.e. 7 microgram/kg for edrophonium 0.5mg/kg & it is the preferred agent with edrophonium because of their similar speed of action. Glycopyrolate has a slower onset (2-3 min), duration around 30-60 min, better anti-sialaogogue action & does not crosses BBB. The time course of glycopyrolate (10 microgram/kg) matches that of neostigmine more closely & simultaneous administration of both drugs results in stable heart rates over time.

Sugammadex (Mirakhur, 2009; Pramila Bajaj, 2009; Sorin J Brull, 2009; Thomas, 2010; Francois Gijsenbergh, 2005; Naguib, 2007)

It was previously known as ORG 25969. It was discovered at the Newhouse Research site in Scotland. The first phase/ study of sugammdex in human voluntaries was published in 2005. It is the first compound in a new class of neuromuscular reversal drugs called Selective Reversal Binding Agents (SRBA), a novel & unique compound which was originally specifically designed to reverse the steroidal NMB drug rocuronium.

Chemistry- It is a synthetic modified γ-cyclodextrin. Sugammadex refers to sugar & γ -dex refers to the structural molecule γ-cyclodextrin. Unmodified γ -cyclodextrin has a 3 dimensional structure which resembles the doughnut. Hydrophobic interactions trap the drug molecule (rocuronium/ vecuronium) into the doughnut hole resulting in the formation of water-soluble guesthost complex. The stability of the rocuronium-sugammadex complex is the end result of interplay of intermolecular Van der waals forces.

Pharmacokinetics & dynamics - It has a plasma clearance at approaching the GFR (120ml/min). With upto 80% of the dose eliminated unchanged in urine within 24 hrs. Its clearance is

decreased in patients with creatinine clearance below 30ml/min by 17 fold. Hepatic impairment does not influence its excretion. Doses of 0.1-8.0mg/kg sugammadex have a clearance of rate of 88ml/min, elimination half-life of 1.8 hrs & a volume of distribution of 11-14 litres.

Mechanism of action- It exerts its effect by forming very tight water soluble complexes at 1:1 ratio with steroidal NMB drugs (rocuronium>vercuronium>pancuronium). The I.V. administration of sugammadex results in rapid removal of free rocuronium molecules from plasma. This creates a concentration gradient favoring the movement of remaining rocuronium molecules from the NM junction back into the plasma where they are encapsulated by free sugammadex molecule thus resulting in fast recovery of NM function. The rocuronium-sugammadex complex has a very low dissociation rate & hence chances of residual muscle weakness are very low. Only 1 out of every 25 million sugammadex-rocuronium complexes dissociates. It has no effect on acetylcholinesterase or any receptor system in the body.

Role of sugammadex in clinical NM antagonism (Pramila Bajaj, 2009)- Sugammadex has been evaluated in clinical practice in different scenarios & in different doses mainly related to the depth of the block & the time at which sugammadex has been given relative to administration of NMB. Doses of sugammadex of 2-4mg/kg can reverse rocuronium/ vecuronium induced NM blockade within 3 minutes. The reversal of vecuronium block with neostigmine is marginally slower than reversal with rocuronium block. Sugammadex can be used for immediate reversal of high dose rocuronium block. 12-16mg/kg sugammadex can adequately reverse 1-2mg/kg rocuronium induced NM block even when reversal is carried out 3minutes after relaxant administration. This may encourage the replacement of scoline by high dose rocuronium-sugammadex combination for rapid sequence induction.

Drug interactions of Sugammadex

- Displacement reactions: Drugs like Termifene, antibiotics like flucloxacillin & fucidic acid can bind with sugammadex & displace rocuronium & vercuronium lead to delay in recovery/ recurarization.
- Capturing reaction- Sugammadex can encapsulate other drugs like Progestogen/ OCPills & lead to decrease in efficiency of the drug.

Safety of Sugammadex

It is a well tolerated drug & has a good safety profile even when administered in doses upto 6 times higher than clinically recommended doses. There is limited data & lack of available evidence regarding its safety in patients with respiratory disease, renal disease, extremes of age especially children <2yrs. Obesity has been shown to have very little effect on action of sugammadex. Sugammadex provides reliable & fast reversal of NM blockade without any important side effects in high-risk cardiac patients with no prolongation of QTc interval. The reported side effects of sugammadex (1-10% incidence) include- transient hypotension, cough, dysgeusia, movement before the end of anesthesia, drymouth, nausea, vomiting, sensation of changed temperature, parosmia, abnormal levels of N-acetyl-glucosaminidase in urine, allergic & hypersensitivity reactions.

Potential impact of sugammadex on current NM blockade practice

- Deep NM block can be maintained upto end of surgery. Eg Ophthalmic, thoracic, neurosurgery, endoscopic surgeries
- Greater use of aminosteroid relaxants like recuronium/vercuronium
- Possible elimination of problem of residual block.
- Minimal or no use of scoline even for rapid sequence induction. Eg trauma, obstetric patients.
- Anesthesiologist will be capable of maintaining the desired depth of NM block at anytime, thereby assuring optimum surgical conditions.
- Combining the rapid onset of a drug like rocuronium with the fast reversal & stable profile of sugammadex we can achieve rapid onset & rapid offset & reliable NM block.
- Morbidity associated with "cannot ventilate or cannot intubate" clinical scenario can be avoided.

Current status of sugammadex (Naguib Mohamed, 2009)- In January 2008, the Schering Plough Company which manufactured sugammadex submitted a drug application to the US FDA for approval of sugammadex but the FDA rejected it in August 2008 by issuing a "not approval" letter citing concerns about hypersensitivity & allergic reactions. It was approved for use in the European Union on July 29th, 2008 under the trade name 'Bridion'. Additional clinical & safety data will soon become available from the European Union & this may influence the US FDA to approve sugammadex.

Cysteine (John J Savarese, 2010)

Chemistry - It is a semi-essential aminoacid. It can be synthezised from the essential aminoacid methionine & the non-essential aminoacid serine. It has 2 sterio-iosomers- the L & D enantiomers. D-cysteine is toxic & deleterious. The L-cysteine acts as a precursor aminoacid for the synthesis of several proteins like coenzyme-A. L-cysteine & Cysteine are rate limiting precursors in the synthesis of glutathione. Cysteine is stored in the body as glutathione which can be hydrolysed to generate cysteine if needed. L-cysteine is a sulfate donor in detoxification reactions. It interferes with entry of injurious heavy metal ions across BBB. L-cysteine thus has neuroprotective effects but in high concentrations it can be neurotoxic by multiple putative mechanisms.

Animal data regarding Cysteine pharmacology

- L-cysteine when exogenously administered has excitatory & neurotoxic effects. This neurotoxicity is also linked to hypoglycemia. Eg- it can cause central neural damage.
- Excess exogenous L-cysteine can cause lethal metabolic acidosis. L-cysteine interacts with catecholamines (dopamine, epinephrine, norepinephrine) & forms neurodestructive cysteinylcatechols which inhibit mitochondrial respiration.
- Half life of Cysteine 1-2hrs.

Cysteine for antagonism of NM block

Gantacurium & its 2 new analogues CW002 & CW011 are olifinic (double-bonded) diester NMBAs that are naturally

degraded chemically to inactive derivatives called as adducts by condensation (adduction) of endogenous L-cysteine to the double-bond. This is known as cysteine adduction pathway. Exogenous administration of cysteine accelerates this natural chemical degradation of gantacurium & its 2 new analogues CW002 & CW011 by the cysteine adduction pathway. This is followed by nonenzymatic alkaline hydrolysis to fragments that are less than the adducts. This chemical antagonism causes immediate clearance of the active drug. L-cysteine thus antagonizes NM blockade in a chemical fashion by inactivation of the NMBA in an organic reaction requiring no enzymatic catalyst & taking place under physiological condition of pH 7.4 & 37degree Celsius.

Animal data regarding Cysteine for NM block antagonism

In Rhesus monkeys, cysteine 10mg/kg results in decrease of duration of NM block after doses of gantacurium 8 times greater than the ED95 from 14 minutes to 1-2 minutes. Cysteine 50mg/kg can decrease the duration of NM block of AV002 from 30 minutes to 2-3 minutes. Doses ranging from 20-50mg/kg cysteine result in minimal changes in mean arterial blood pressure & heart rate. 100 mg/kg cysteine resulted in 14.6% increase in MAP & 5.2% decrease in heart rate (<10% effects). Adult rhesus monkeys, rats & dogs have received iv cysteine (50-200mg/kg) every 4-6weeks for over 3years. There have been no reports of organ damage / HP changes, hematological changes, serum chemistry changes, body weight changes.

Current status of cysteine in NM pharmacology

- It is still in experimental phase in animals.
- It provides a novel method of facile chemical antagonism of NM blockade superior to anticholinesterase reversal because
- L-csyteine antagonism inactivates NMBA much more rapidly.
- The antagonism is effective & complete at any point during the block at any depth of blockade.
- The undesirable side-effects of anticholinesterase are avoided.
- The degradation mechanism assumes that residual weakness will not occur after L-cysteine reversal of NM block.

  L-cysteine will promote clinical development of the new ultra-shorting NDPR: gantacurium & its analogues CW002 & CW011.

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