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Interactions of Muscle Relaxant

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Drug interactions in general, should be shortly reviewed before the lecture on the main subject. Polypharmacy is ubiquitous. Incidence of adverse reaction is 7% if patient receive 6-10 drugs, it's come to 40% if patient receive 10-20 drugs. Especially elderly patient are the greatest consumers of medications.

Drug interactions can be beneficial e. g. muscle relaxing properties of isoflurane to reduce the dose of pancuronium. Or they can be hazardous e.g. chronic cocaine abuse enhancing cardiac irritability of halothane.

Predicting a drug interaction is not easy since multiple factors come into play. Not only must one consider the drugs that have been administered, but also the duration of exposure to each drug, and the patient's underlying disease, age, weight, cardiac output, genetic make-up, level of enzyme induction, diet, etc.

Mechanism of drug interaction ;

1. Pharmaceutic interactions : chemical & physical factors

e. g. barbiturates & NDR (non-depolarizing relaxant) form a precipitate.

2. Pharmacokinetic interactions : when one drug alters the absorption, distribution, metabolism or excretion of another

A. Interaction at the site of absorption

e. g. epinephrine reduces uptake of local anesthetic

B. Distribution phenomena

e. g. contrast media displaces barbiturates from protein

C. Altered biotransformation

e. g. phenobarbital therapy increases metabolism of multiple other drugs

e. g. echothiophate reduces succinylcholine (SCh : DR=depolarizing relaxant) metabolism

D. Altered excretion

e. g. bicarbonate enhances phenobarbital excretion

3. Pharmacodynamic interactions

due to interactions at effector sites, one drug may have an enhancing effect, or an inhibitory effect on another

e. g. Antagonism of opioids with

naloxone

e. g. Additive effect of magnesium & NDR

4. Unknown mechanisms

e. g. Pancuronium reduces halothane MAC

In reality, it is likely that a specific drug interactions may involve more than one mechanisms simultaneously.

e. g. Halothane may enhance the action of NDR by altering both pharmacokinetic (uptake & distribution) and pharmacodynamic (receptor site) factors.

Why anesthesiologists use muscle relaxants ?
Because muscle relaxants are an adjunct to modern anesthesia practice today.

Muscle relaxants as a primary anesthetic indications are ;

1. To produce relaxation of skeletal muscles
2. To reduce the amount of an inhalation agent required for a given procedure
3. To facilitate intubation
4. To overcome laryngospasm

Introduction of muscle relaxants has greatly contributed to the modern anesthesia practice.

Since d-tubocurarine (dTc) was introduced in 1942, there have been so many muscle relaxants routinely used today in general anesthesia.

What should be prepared whenever using the muscle relaxant ?

Of course, artificial respiration is absolutely necessary.

Why should anesthesiologists monitor the neuromuscular (N-M) blockade ?

Because there are so many factors affecting N-M blockade.

I) Drug interactions

II) Patient disease

III) Age

IV) CNS effect

V) Body temperature

VI) Acid-Base & electrolyte abnormalities

VII) Individual & species differences

I) In drug interactions, there are more than 250 drugs which may affect the N-M blockers.

Among inhalational agents enflurane, isoflurane & halothane may increase the action of dTc & pancuronium. Blocking action of vecuronium is also increased by enflurane, halothane & isoflurane. Isoflurane & N₂O increase the blocking action of SCh. Halothane & isoflurane increase the blocking action of atracurium infusion in children.

Intravenous anesthetics diazepam did not alter the magnitude or duration of block & thiopental has minimal effect.

Ketamine+SCh, ketamine+dTc ; increase the duration of N-M block.

Propanidid may increase the duration of N-M blockers but has limited clinical importance.

Procaine : inhibit caffeine-induced contraction of skeletal muscle e.g. Augment SCh block.

Ester type of local anesthetics can prolong N-M block.

Lidocaine, procaine, other anesthetic agents may prolong the N-M blockade.

Lidocaine with gentamicin increases the action of dTc.

DR (SCh)

Complications of SCh

1. Cardiovascular ; ventricular arrhythmias (cardiac arrest)
2. Fasciculation
3. Hyperkalemia
4. Muscle pain
5. Intra gastric, intraocular & intracranial

pressure elevation

6. Prolonged paralysis
7. Generalized muscle contraction
8. Masseter muscle rigidity
9. Malignant hyperthermia

In 1993, the F.D.A. declared that the routine use of SCh, a mainstay of relaxant administration, was contraindicated in children and adolescents.

Combination of NDR having additive effect :

- e. g. dTc + metocurine
- pancuronium + vecuronium
- mivacurium + pancuronium
- mivacurium + rocuronium
- atracurium + mivacurium

Other combination also has potentiation

- e. g. pancuronium + metocurine

*Little clinical importance was reported by combination of NDR.

Potentiation is perhaps mainly postsynaptic origin.

Combination of NDR + DR has mutually antagonistic.

- e. g. dTc + SCh prevent fasciculation & muscle pain
but SCh is less potent.
- e. g. pancuronium + SCh action prolonged due to inhibit plasma cholinesterase by pancuronium.
- e. g. atracurium + SCh, mivacurium + SCh ;
antagonistic action
- e. g. conversely potency of NDR is enhanced when they are administered after SCh.

*SCh effect is potentiated after the anticholinesterase administration.

Neomycin & streptomycin depress the N-M function.

Those effects are potentiated by magnesium & antagonized by calcium.

Most potent of all antibiotics is polymixins.

Lincomycin, clindamycin ; pre & postjunctional effect

*Block cannot be reversed with calcium or anticholinesterases.

Calcium channel blockers ; nifedipine, nicardipine does not affect vecuronium.

Phenytoin ; resistant to pancuronium, metocurine, vecuronium but not to atracurium.

Propranolol ; potentiates DR & NDR

Diuretics, corticosteroids, immunosuppressants, hypotensive agents, several psychotropic drugs ; *Abnormal response

Cimetidine ; prolongs vecuronium block

Dantrolene ; depress skeletal muscle directly & also blocks excitation-contraction coupling although it does not block N-M transmission, the mechanical response will be depressed without demonstrating any effect on the EMG.

- e. g. NDR enhanced by dantrolene

Altered responses to N-M blockers :

In ICU ; residual weakness

sometimes recovery was prolonged

*Asthmatics by pancuronium, vecuronium, atracurium

*Complex syndrome of "critical illness neuropathy" in sepsis &/or MODS

- *Other predisposing conditions ;
- electrolyte abnormality
- acid-base disturbance
- aminoglycoside antibiotics
- cyclosporine

*Commonly overdose but not confirmed

*Transmission failure from pre & postjunctional

ctional mechanism

II) Myasthenia gravis ;

functional reduction of acetylcholine receptors

Dx : EMG

regional curare test

final Dx : circulating Ach antibody

DR ; slightly resistant, phase II block

slow recovery

NDR ; sensitive

Anesthesia—>inhalational anesthesia with/without regional anesthesia

*N-M monitor

Choice of N-M blockers—>atracurium or mivacurium without anticholinesterase

Myotonia ;

DR—>dose related contracture

NDR—>normal response

Anesthesia : avoid DR

caution with resp. depressants

Muscular dystrophy (DMD) ;

DR & NDR—>normal response

“SCh induced hyperkalemic cardiac arrest”

*difficult to treat

malignant hyperthermia (MH) susceptibility—>controversy

unrecognized DMD in young males (less than 10 ys old)

Upper motor neuron lesions ;

hemiplegia or quadriplegia

DR & NDR—>abnormal response

*Avoid SCh

NDR—>resistant in hemiplegic patient

Miscellaneous ;

Denervated muscle —>K release with SCh

resistant to

NDR

Amyotrophic lateral sclerosis	}contractures by SCh
Myotonia	
Multiple sclerosis	

*Avoid SCh—>neurologic disease

e. g. Friedrich's ataxia

Hyperkalemic polyneuritis

Parkinson's disease

III) There are significant age-related differences in the potency of some N-M blockers.

In children one should be aware of this variability and the effects of bolus become more predictable.

Recent studies regardless of the use of potent inhalation anesthetics, found infants to be more sensitive & have smaller ED₅₀ than children. The relative sensitivity of the infant less than 12 months old also has been documented for several N-M blockers of intermediate duration of action.

The major factors influencing spontaneous recovery rate are rate of drug clearance, ED₅₀ & volume of distribution. e.g. A bolus of 0.1 mg/kg of vecuronium may produce <90% block for almost an hour in infant, but less than 20 minutes in children & less than 40 minutes in adolescent. e.g. After a bolus of rocuronium 0.6 mg/kg, <75% block lasted 25 to 30 minutes in healthy children during halothane anesthesia. Rate of recovery is slower & more variable after the same dose in mg/kg in infants than children.

Pancuronium, metocurine, dTc, vecuronium & rocuronium all show prolonged pharmacodynamics & pharmacokinetics in the elderly patient due to decreased clearance depend on kidney & / or liver for their metabolism & elimination.

IV) NDR pass into the CSF.

e. g. Gallamine increase the seizure threshold to lidocaine in dogs.

*Whether the CNS effects of muscle relaxants contribute to the morbidity & mortality of critical care patient is unknown.

V) The force of contraction of adductor pollicis decreases by 10 to 16%/°C decrease in muscle temperature below 35°C.

e. g. mild hypothermia—>prolong vecuronium & atracurium.

VI) Respiratory acidosis enhances dTc & pancuronium induced N-M blockade.

VII) Other factors as individual & species differences.

Conclusion :

1. Nondepolarizing muscle relaxant should be used.
2. Choice of neuromuscular blockers are important.
3. Basic monitorings are blood pressure, ECG, SpO₂, E_TCO₂, body temperature and peripheral nerve stimulator.
4. Dantrolene should be always at hand.

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