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PHARMACY COMMITTEE ... NOTES

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Prolonged Paralysis and Muscle Weakness following Administration of Neuromuscular Blocking Agents

Introduction

Neuromuscular blocking agents are currently used in the intensive care unit (ICU) to facilitate respiratory support, lower metabolic demands, prevent shivering, lower intracranial pressure, and improve chest compliance in patients with adult respiratory distress syndrome. Additionally, these agents are used to improve ventilation in patients with status epilepticus uncontrolled by anticonvulsants, status asthmaticus patients, patients with strychnine and methaqualone poisoning or tetanus.

Recently the literature has described numerous reports of prolonged blockade and muscle weakness following use of neuromuscular blocking agents in the ICU, particularly associated with pancuronium and vecuronium.[1,2,3,4,5,6,7] Additionally, the Food and Drug Administration held a special advisory committee meeting to discuss the issue of prolonged blockade following vecuronium use in the ICU. This newsletter will address the problem of prolonged paralysis and muscle weakness in the ICU, which will be defined as paralysis >6 hours after discontinuation of the neuromuscular blocking agent.

Pharmacology

Non-depolarizing neuromuscular blocking agents (NMBs) act by competitive inhibition of acetylcholine at receptors found on the post-synaptic motor endplates of muscle tissue. Thus, the degree of blockade is dependent on the relative concentrations of acetylcholine and NMBs at the neuromuscular junction.

Another important point about NMBs is that they have no effect on sedation, relief of pain or anxiety. Therefore, neuromuscular blocking agents must be used in combination with drugs that have sedative, anxiolytic and analgesic properties.

Metabolism & Active Metabolites

Pancuronium and vecuronium are chemically related to corticosteroids and dependent on renal and hepatic organ systems for elimination. When these elimination systems are dysfunctional, accumulation of pancuronium and vecuronium is likely, especially when administered for an extended time period.[8] Additionally, the elimination of the active metabolite 3-desacetylvecuronium is highly dependent on renal function.[9] In man, the 3-OH pancuronium metabolite is approximately half as potent as pancuronium as a neuromuscular blocking drug.[10] The potency of the 3-desacetyl metabolite of vecuronium is unknown in humans; however, studies in cats suggest that it possesses 50%-70% of the potency of vecuronium.[3,4]

Atracurium is a benzylisoquinolinium ester chemically unrelated to corticosteroids and is not dependent on organ elimination. Elimination is through Hofmann elimination (spontaneous degradation at physiologic pH and temperature) and nonspecific esterases.[11] Atracurium has no metabolites which possess neuromuscular blocking activity.

Prolonged Blockade and/or Muscle Weakness

In some cases of prolonged paralysis associated with pancuronium and vecuronium, the investigators have postulated that accumulations of the active metabolites 3-OH pancuronium and 3-desacetylvecuronium may be a primary cause of the observed prolonged paralysis.[1,2] Segredo reported persistent high levels of 3-desacetylvecuronium in 7 ICU patients with renal failure who experienced prolonged blockade following vecuronium administration.[1]

Currently, there is only one report of prolonged blockade in an ICU patient who received atracurium, however, the authors attributed the prolonged recovery to hypophosphatemia and not to the atracurium infusion.[12]

In 1932, Cushing reported an association between corticosteroid excess and muscle weakness.[13] Corticosteroid-induced myopathy is characterized by the subacute onset of proximal muscle weakness, which may involve respiratory muscles, and is followed by the gradual spread to limb muscles. Myopathy rarely occurs less than three weeks after initiating corticosteroid therapy. Muscle biopsy reveals atrophy of primarily type 2B fibers. Serum CPK levels are usually normal without myoglobinuria. Corticosteroid-induced myopathy has been described following intravenous administration of methylprednisolone, hydrocortisone, dexamethasone, and betamethasone.

(continued on next page)

A slightly different type of myopathy has recently been described in ventilated patients receiving high-dose corticosteriods concomitantly with pancuronium or vecuronium. This myopathy is characterized by proximal and distal muscle weakness, elevated CPK levels, and on muscle biopsy, significant atrophy of type 1 and 2 muscle fibers. Based on the association of corticosteroids with myopathy and the steroidal structure of pancuronium and vecuronium, it is hypothesized that corticosteroids enhance the potential for the development of myopathy when administered with a steroidal neuromuscular blocking agent.[5,6,7,14,15] The manufacturer of pancuronium and vecuronium is aware of reports of muscle weakness and myopathy in association with these agents alone and in combination with corticosteroids.[15]

There are no published or spontaneous reports describing muscle weakness or myopathy attributable to atracurium alone in the ICU.[16] However, one published report describes quadriparesis in an ICU patient who received high-dose corticosteroids, pancuronium, vecuronium, and atracurium.[17] There are a few spontaneous reports of muscle weakness or myopathy in ICU patients who received corticosteroids and atracurium or corticosteroids, vecuronium, and atracurium.[16]

Conclusion

Prolonged paralysis following pancuronium and vecuronium administration has been reported, including severe tetraparesis and diffuse muscle atrophy persisting for weeks to months after discontinuation of these drugs. Case reports of prolonged blockade and muscle weakness after pancuronium and vecuronium use have implicated the accumulation of pancuronium and vecuronium, the accumulation of their active metabolites, and the steroidal structure of pancuronium and vecuronium. In addition, patient age, pregnancy, metabolic disturbances, concurrent disease (i.e., myasthenia gravis or muscular dystrophy), renal failure, hepatic failure, and concomitant drug therapy (i.e., aminoglycosides, corticosteroids, diuretics) may be contributing variables to prolonged blockade and muscle weakness. The etiology of prolonged blockade and muscle weakness following the use of pancuronium and vecuronium is not well defined in most cases. Currently, there is no known single explanation for pancuronium- or vecuronium-induced prlonged blockade and muscle weakness in these patients. However, the accumulation of active metabolites, in addition to the steroidal structure of pancuronium and vecuronium have been implicated as potential causes in many of the reported cases. Dosing of NMBs should be monitored pharmacodynamically. Doses should be adjusted based on the assessment of the degree of blockade. The most reliable method to assess the degree of blockade is with a peripheral nerve stimulator. Maintaining the appropriate degree of blockade may help prevent NMB overdose and potential prolonged blockade.

Bob Lee, Pharm.D.

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Benzodiazepine Receptor Antagonist

Flumazenil (Mazicon® - Roche) is the first commercially available benzodiazepine antagonist which could prove to be essential for all emergency rooms and intensive care units; however, its exact role in the outpatient setting is still uncertain.

Pharmacology

Flumazenil is a competitive antagonist at the benzodiazepine receptor. At pharmacologic doses it has minimal intrinsic activity and has no effect on systemic benzodiazepine serum levels.[1] Inhibition of the benzodiazepine receptors produces antisedative and antiamnesic actions from the point of administration and no retrograde antiamnesic effect is produced. Flumazenil reverses some components of midazolam induced ventilatory depression and may improve resting ventilation.[2] Onset of reversal is within 1 - 2 minutes and the peak effect usually occurs in 6 - 8 minutes. The duration of antagonism can range from 15 minutes to 2.5 hours and is dose dependent. Repeated low dose injections, high doses, or continuous infusion can extend the duration of effect.[1,2,3,4]

Pharmacokinetics

Absorption following oral administration is extensive; however, due to high first-pass metabolism, systemic bioavailability is less than 20 percent.[2,3] Flumazenil is extensively metabolized to an inactive metabolite by the liver and its clearance is dependent on hepatic flow. Only 0.12 percent of the drug is excreted unchanged in the liver.[1,2,3,5,6] Clearance can be reduced by 40 percent to 60 percent with moderate hepatic dysfunction and as much as 75 percent with severe dysfunction.

Comparative Efficacy

Benzodiazepine Anesthesia

The use of benzodiazepines alone or in combination with other agents to induce or maintain anesthesia is a common practice. The subsequent use of flumazenil has been advocated to improve patient alertness following the procedure to provide easier assessment of neurologic status and potential complications.[7]

Skielboe et al.[8] studied forty (40) patients anesthetized with diazepam, alfentanil, nitrous oxide, and paralyzed with atracurium. After reversal of neuromuscular blockade, patients were given either flumazenil or placebo. Patient assessments were made at 0, 5, 30, 120, and 240 minutes after administration. The median dose for flumazenil was 0.35 mg. The following chart outlines the results of the study.

% Fully Awake				
	5 min	30 min	120 min	240 min
Flumazenil	100%	100%	100%	100%
Placebo	60%	90%	95%	100%

Philip et al.[9] studied forty-one (41) elective GYN surgery cases who were anesthetized with fentanyl, midazolam, nitrous oxide, succinylcholine, and isoflurane. Post operative psychodiagnostic tests were performed on patients given flumazenil or placebo. During a 5 - 60 minute post operative period, the flumazenil group performed better; however, at 120 and 180 minutes, no difference was found. Improvement in pulse oxygen saturation and end expired carbon dioxide tension was seen 15 minutes after active drug but not placebo.

Benzodiazepine Sedation

Andrews et al.[10] studied fifty (50) patients receiving outpatient upper gastrointestinal endoscopy who had received midazolam to produce sleep but continue to respond to commands. Patients were randomized to receive flumazenil or placebo and were evaluated for reaction times, critical flicker fusion frequency, paired word association, linear analogue sedation, and pain scales. The battery of baseline tests were repeated at 30 minutes and 3.5 hours post baseline. Assessment at 30 minutes showed the placebo group compromised with respect to coordination, psychomotor performance, and short term memory; however, neither group had performance return to baseline later than 3.5 hours. No difference between the groups was noted at any time using the linear analogue pain scale. The linear sedation scale showed the flumazenil group was subjectly more alert at 3.5 hours, but this was not borne out with any objective assessment.

Sanders et al.[11] performed a similar double blind study to assess the effectiveness in 120 patients receiving diazepam or midazolam sedation prior to outpatient gastroscopy. Psychomotor performance was assessed at 20, 90, and 180 minutes. Flumazenil was effective in reversing the sedation induced by both diazepam and midazolam. No cases of resedation were reported; however, the psychometric test showed that all patients had some degree of impairment at the time of discharge. Based on these results, it does not appear that flumazenil would hasten the safe discharge of patients receiving benzodiazepines prior to outpatient gastroscopy.

Benzodiazepine Overdose

A double blind, randomized, placebo-controlled study was conducted with 60 patients who had overdosed with benzodiazepines alone or in combination with alcohol, tricyclic antidepressants, opiates, barbiturates, phenothiazines or acetaminophen. Patients were assigned to either placebo or flumazenil therapy. Flumazenil proved to be safe and effective in reversing coma and excessive sedation produced by benzodiazepines. In cases where barbiturates or tricyclics antidepressants were the only agent, flumazenil had no effect.[12]

Adverse Reactions

Common adverse reactions include nausea, vomiting, agitation, dizziness, pain at the injection site, increased sweating, headache, blurred vision, anxiety, and sensation of being cold. Others have reported panic attacks and withdrawal syndrome.[1,2,13] Seizures tend to occur in patients who have been on benzodiazepines for long term sedation, physically dependant on benzodiazepines, or mixed overdoses involving tricyclic antidepressants.[1]

Dosing

The dose is dependent on the condition being treated. It should be infused over 15 - 30 seconds via a freely running intravenous infusion into a large vein to minimize injection site pain. Repeat doses may be required depending on the duration of sedation or anesthesia and the dose of the benzodiazepine used or ingested. If improvement is not seen after a dose of 5 mg, the situation may not be the result of benzodiazepine effect alone, and other types of intoxicants should be considered.[9]

For reversal of conscientious sedation, the recommended initial dose is 0.2 mg. If an inadequate response is achieved, an additional 0.2 mg can be administered after 45 seconds, and repeated at 60 second intervals up to a total dose of 1 mg.[1]

For management of suspected benzodiazepine overdose, the initial dose should be 0.2 mg followed by 0.3 mg in 30 seconds, if no response is observed. If additional doses are required, the dose should be increased to 0.5 mg and given every 60 seconds up to a maximum dose of 1 mg.[1] The duration of a single dose of flumazenil is less than 1 hour; therefore, repeat doses may be required in situations where long half-life drugs are involved.[3]

Conclusion

Flumazenil is the first benzodiazepine antagonist to become available for use in the United States. In cases of coma of unknown etiology or suspected benzodiazepine overdose, the diagnostic value of flumazenil is similar to naloxone. However, since flumazenil does not consistently reverse benzodiazepine induced respiratory depression, routine airway management, lavage and charcoal must still be the gold standard in drug overdose management.

The short duration of action of flumazenil discourages the routine use of this agent to quicken recovery following conscious sedation or anesthesia with benzodiazepines. Routine use of flumazenil to reduce the length of the recovery period may result in the premature discharge which can result in resedation in a setting where the patient cannot be closely monitored.

The Pharmacy Committee reviewed flumazenil and felt it provided a significant advance in the treatment of benzodiazepine overdose; however, it should not be routinely used to reverse conscience sedation and reduce recovery observation time. It was also concluded that any use of flumazenil should be accompanied by an adverse drug reaction (ADR) report reflecting either an overdose or excessive sedation with a benzodiazepine.

David Wheeler, R.Ph.

References available upon request.

The Hospital Medication Formulary

Who decides what goes on the formulary? Who approves it? How does medication get placed on formulary? Why can't I have the medications that I want on formulary? These are commonly asked questions among physicians, as well as other hospital personnel.

In an effort to limit inventory, minimize costs, and optimize patients' pharmaceutical care, the Medical Board has authorized the Pharmacy Departments at The Moses H. Cone Memorial Hospital and The Women's Hospital of Greensboro to substitute pharmaceutical products which are chemically equivalent (generics), as well as therapeutically equivalent (as approved by the Pharmacy Committee). The focus of the Pharmacy Committee is to assure the best value, taking into consideration product cost, indirect expenses, quality, and therapeutic outcome. Through an educational and research role in evaluating therapeutic interchanges, pharmacists present their findings to the Medical/Dental Staff members of the Pharmacy Committee. With the help of the other interdisplinary members of the Pharmacy Committee which include pharmacists, nurses, and hospital administration, the Medical/Dental Staff members make the final decision to either admit or delete a product to the formulary. It is important to realize there may be patients who do not meet the interchange policy criteria. In such instances, the physician may order any brand product he desires by writing "Dispense as written" or "Do not subsitute" by the order and the Pharmacy Department will obtain the product as quickly as possible.

Opponents of the therapeutic interchange have implied there may be medicolegal implications when FDA-approved indications differ for similar drugs considered for interchange. This liability potential is minimized because legal review begins with measuring standards of care. As long as the institutions' conduct is similar to other facilities and Pharmacy Committee decisions are based on relevant literature and not solely on economics, the law provides that the standard is "reasonable care." It is also important for regular reviews of therapeutic interchanges within a class to occur to ensure that the original criteria and policy still reflect the standard of care.

Communication of therapeutic interchanges is handled formally through the pharmacy newsletter, PHARMACY COMMITTEE NOTES. Physicians who most often prescribe the drug being interchanged are also notified verbally by a pharmacist or by other physicians through staff meetings.

Selection of products reviewed often evolves from recently approved medications or FDA-approved indication changes, but may also emerge from drug use evaluations or adverse drug reaction monitoring. Any member of the Medical or Dental Staff may request inclusion of a drug or dosage form simply by writing to the Secretary of the Pharmacy Committee, Judith Crouch, R.Ph., Director of Pharmacy at Moses Cone. A form for such request may be obtained from either Pharmacy Department at both institutions.

B. Campbell, R.Ph.
Director of Pharmacy
The Women's Hospital of Greensboro

1992 Top Twenty Pharmacy Items

1992 Product	Cost	%	1991	Cost
1 Dobutamine	$297,128.00	4.19%	3	$187,438.00
2 Ondansetron	$293,570.00	4.14%	2	$196,863.00
3 G-CSF (Neupogen)	$241,074.00	3.40%	8	$125,828.00
4 Ceftriaxone	$186,077.68	2.63%	4	$147,298.52
5 Enteral Products	$183,247.37	2.59%	1	$312,438.50
6 Diabetic Supplies	$180,442.18	2.55%	7	$136,132.35
7 Immune Globulin IV	$179,543.00	2.53%	17	$107,952.00
8 Ranitidine	$168,550.00	2.38%	5	$144,977.00
9 Albumin	$163,202.00	2.30%	N/A	
10 Midazolam	$155,535.00	2.20%	9	$107,927.00
11 Lorazepam	$154,441.00	2.18%	14	$113,439.00
12 Etopside	$153,694.00	2.17%	11	$123,111.00
13 Sufenta	$138,651.00	1.96%	N/A	
14 Vecuronium	$133,114.00	1.88%	N/A	
15 Timentin	$126,914.00	1.79%	10	$125,112.00
16 Hetastarch	$125,053.00	1.76%	20	$101,664.00
17 Ceftazidime	$119,560.00	1.69%	18	$107,507.00
18 Vancomycin	$111,651.00	1.58%	13	$118,241.00
19 Imipenem-Cilastatin	$111,395.00	1.57%	N/A	
20 Cipro	$105,057.00	1.48%	N/A	
Total Top 20	$3,327,899.23	46.97%	Of Total Purchases	
Total Other	$3,757,396.68	53.03%	Of Total Purchases	
Total Pharmacy 1992	$7,085,295.91	100.00%		

% Of Total Pharmacy Purchases
NA – These Did Not Rank In Top 20 In 1991

1/15/93