Editorial:
Anistreplase Added to UH Formulary - Why Another Thrombolytic Agent?

Thrombolytic therapy is a major advance in the treatment of acute myocardial infarction (AMI). Several large controlled trials have now documented that the hospital mortality of AMI can be markedly decreased with the early administration of a thrombolytic agent. Despite this progress, however, several major issues related to thrombolytic therapy continue to be debated, least of which is the superiority of one specific thrombolytic agent over another. Recent studies, particularly the GISSI-2 trial in over 12,000 patients published this last month in The Lancet, have suggested no difference in the outcome indicators for streptokinase and t-PA, yet t-PA costs almost 200 times the price. Given today's cost conscious environment, many institutions have abandoned the more expensive t-PA from their formularies, in preference to streptokinase. The addition of another very expensive thrombolytic to the formulary at UH seems a little out of step. So why was it done? Here are the reasons:

1) While the evidence that all thrombolytics are equal is very suggestive, it is not conclusive. We will have to wait for the results of the GISSI-III and TEAM-3 trials to be convinced of the superiority (or lack of it) of any thrombolytic therapy. While current cardiologists are skeptical of the superiority of any one agent, they are not convinced.

2) While thrombolytic use at UH is low (because many patients receive it prior to arrival, and because of new laser angiography techniques), t-PA is the only thrombolytic used for cardiac indications. This is because t-PA was heavily investigated here at UH as part of the TIMI trials. Streptokinase was not. The current group of cardiologists are comfortable with t-PA, but not streptokinase.

3) Anistreplase offers some theoretical advantages over both t-PA and streptokinase as a result of its short administration time. Because of this physicians may be inclined to use anistreplase over t-PA to see for themselves if these advantages truly exist. Having anistreplase on the formulary allows this. In addition, any use of anistreplase (which costs less than t-PA) will save the institution (and the patient) money.

4) If physicians feel more comfortable with anistreplase, they may be more comfortable with streptokinase, since the side effect profiles are the same. Thus, they may be more inclined to use streptokinase.

These were the arguments presented for the addition of anistreplase to the UH Formulary. Given the current use of thrombolytics at UH, the addition of anistreplase to the UH Formulary seems reasonable and physicians are encouraged to use the drug. In light of the current evidence, taking t-PA off the formulary (or restricting the agent) and limiting thrombolytic therapy to streptokinase, as some hospitals are doing, would not be wise at UH. Giving physicians the opportunity to gradually discover what the optimal and cost effective therapy is may eventually lead to the same result, but with much more satisfied customers (both patients and physicians).

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Published by The University Hospital, Department of Pharmacy, 75 E. Newton Street, Boston, MA 02118
P&T Committee News:
Human Insulins to be Used Exclusively at UH

At the August meeting of the Pharmacy and Therapeutics Committee of the Medical Staff, it was decided to eliminate all forms of insulin from the UH Formulary except human insulin (Regular, NPH, Lente and Ultralente) and animal-source Protamine Zinc (no human form is currently available). This decision was based on the clinical superiority of human insulin over animal forms yet similar pricing. Having only human forms of insulin available will reduce stock levels and waste, saving UH money.

Human regular and NPH insulins will continue to be floor stock items and can be obtained by the nursing unit via a yellow requisition. Lente, Ultralente and Protamine Zinc Insulin will be dispensed from the pharmacy as a patient charge item. Other forms of insulin will no longer be stocked by the Pharmacy. If necessary, they can be obtained by physician request through the non-formulary drug process within 24-72 hours. This change will officially take place on September 10, 1990.

Pharmacy News
Automated Unit-Dose Packaging Machine to Begin Operation:
Implications for Nursing

After months of delay due to computer interface problems, the automated unit-dose packaging machine (Baxter ATC-212) is now in operation in the Pharmacy. The top 87% of all unit-dose medications will now be purchased in bulk and packaged in special labelled packages by this automated device, reducing the labor needs of the department. The medications will require more careful attention by nurses (in selecting the right product from the patient bin) since the packages for most oral solid dosing forms will look alike, however the packages will be significantly easier to open than commercial unit-dose packaging. Initial trial implementation began on August 21st for nursing unit F2, expanding to F5 on August 28th. Pharmacy staff training will commence after Labor Day, with hospital-wide implementation occurring on the night shift Wednesday, September 12, 1990.

Reports of reduced theft of certain Schedule III and IV substances as a result of strip packaging by this machine has prompted the pharmacy to investigate the possibility of removing oral acetaminophen w/codeine #3, alprazolam, lorazepam, and triazolam from the narcotic system and placing them in the ATC machine. This will reduce both nursing and pharmacy workload considerably. This trial will continue for 3 months. The pharmacy will closely monitor usage of these products. If increased usage and diversion is suggested, the products will be placed back in the narcotic system.

Policy and Procedure:
Unique Restriction System in the OR

Currently, three anesthesia medication are on “restricted” status - Atracurium (Tracrium), Propofol (Diprivan) and Sufentanil (Sufenta). This drugs will not be stocked in any area of the OR and can only be obtained from the OR Pharmacy Satellite (or from the Main Pharmacy afterhours). The following summarized the restriction policies and reasons for them:

Atracurium (Tracrium) - This drug was the most recent put on restriction because of increasing usage and high cost. The literature has demonstrated clear inferiority of atracurium over vecuronium as a result of a higher allergic potential (especially in asthmatic patients), higher incidence of cardiovascular side effects and higher cost. The only clear indication for the use of atracurium over vecuronium is in hepatic failure patients.

Propofol (Diprivan) - This drug was recently added to the Formulary as a restricted agent. There is concern that propofol will be used universally over thiopental. Propofol is only superior to thiopental in patients undergoing outpatient surgery and in patients with a history of intractable nausea and vomiting on thiopental.

To receive atracurium (in any case) or propofol (for other than outpatient cases), a special form will need to be filled out and signed by the attending anesthesiologist PRIOR TO DISPENSING the drug. A reason for why the less expensive alternative could not be used will be required to be documented on the form. The completed forms will be reviewed by the Pharmacy and Therapeutics Committee and Chief of Anesthesiology.

Sufentanil (Sufenta). Despite vast claims of superiority of sufentanil in cardiac surgery in the literature of the 70’s, studies in the 80’s have cast serious doubt on the advantages of sufentanil over fentanyl. With sufentanil’s cost approaching 100 times that of fentanyl, the restriction policy was implemented. More definite guidelines for appropriate sufentanil usage are being developed in conjunction with attending anesthesiologists. To acquire sufentanil, an attending anesthesiologists signature is needed on the narcotic order form. The signature must be obtained prior to dispensing in all but cardiac cases.

None of these three drugs will be dispensed in areas other than the Operating Room without completion of the same paperwork and prior approval only by an attending physician with administrative responsibilities for the service involved.
Drug Review:

Anistreplase (Eminase®)

By: The Drug Information Service, Department of Pharmacy Services, The University Hospital, Boston, MA

Description: Anistreplase (Eminase® by SmithKline Beecham Laboratories and comarketed by The Upjohn Company), previously known as anisoylated plasminogen-streptokinase activator complex or APSAC, is a new thrombolytic agent approved for the treatment of acute myocardial infarction (AMI). It is in the same therapeutic class as streptokinase, urokinase and alteplase (t-PA). Anistreplase is a modified congener of streptokinase, which was designed to provide functional advantages over streptokinase, particularly simpler administration, longer half-life and enhanced fibrin (thrombus) affinity. A prolonged state of fibrinolytic activity as a result of its increased half-life has been demonstrated over streptokinase. The major advantage of anistreplase is that it can be administered over 5min (vs. 1 hour for streptokinase and 3 hours for t-PA). This savings in time may be critical to optimizing outcome from thrombolytic therapy, whose prompt initiation after presentation is encouraged. This may be particularly true near the end of the 6 hour window. Anistreplase has a rate of reperfusion and fibrin clot affinity greater than IV streptokinase and equal to t-PA. The clinical significance of this is unknown at present. It is less costly than t-PA but significantly more costly than streptokinase. Its prolonged half-life should make it better than t-PA or streptokinase in preventing early reocclusion although this has not been proven. Its major drawback to t-PA is the chance of allergic reaction, which is similar to streptokinase at an incidence of 1.9%, with serious reactions in 0.2% of patients. Alteplase (t-PA) is preferred if the patient was treated with anistreplase, streptokinase or had a streptococcal infection between 5-180 days prior. Anistreplase is preferred in situations where quick or easy administration (ER or ambulance) is needed. Additionally, its use over t-PA is encouraged because of its lower cost and potential for improved outcome.

Mechanism of Action: Anistreplase is a prodrug of the streptokinase-plasminogen activator complex which is formed after administration of streptokinase in humans. Anistreplase is prepared in vitro by acylating human plasma-derived Lys-plasminogen and streptokinase. Initially this complex is inactive, as it contains an anisoyl group which blocks the active site. However, deacylation of the annisoyl group occurs once the drug is administered and the complex is converted to the active form, which results in the subsequent generation of plasmin (the proteolytic enzyme responsible for clot lysis) both in the blood stream and within the thrombus (fibrin). As with other thrombolytics, the lysis of clots in the coronary artery within 6 hours restores blood flow to the heart muscle and minimizes the damage from the AMI, reducing mortality significantly.

Clinical Trials: The important end points of thrombolytic therapy are patency or reperfusion rate, left ventricular function, reduced infarct size and mortality. Well controlled trials have shown that IV streptokinase, alteplase (t-PA) and anistreplase all significantly improve these endpoints over placebo-heparin therapy. Two major studies and 5 smaller studies show an average reperfusion rate for anistreplase of 55.4% at 90 min. This increases to 60% in patients at 4 hours, which is the same as t-PA. Patency rates for anistreplase averaged 73.3% at 90 min and 80% at 1-14 days (t-PA=81-83%). Left ventricular ejection fraction is greater than heparin therapy alone, regional wall motion is greater and there is a 31-33% reduction in infarct size, which is similar to streptokinase and t-PA. Based on trials in large numbers of patients, the 30 day mortality rate is 6.4% for anistreplase, vs. 8.7% for streptokinase and 7.2% for t-PA. However, such comparisons across different studies are merely suggestive, not
conclusive. Randomized multi-center trials in several hundred patients comparing anistreplase with IV streptokinase found the two drugs comparable in effectiveness (reperfusion, reocclusion and late patency rates) and adverse effects (CVA, hemorrhage, hypotension and allergic reactions). The only comparative trial between anistreplase (30mg over 5 min) vs. t-PA (100mg over 3 hours) was conducted in 180 AMI patients (J. Am. Coll. Cardiol. 1990; 15:214A). Coronary angiography demonstrated a patency rate of 72% for anistreplase and 75% for t-PA (not a statistically significant difference). There was also no difference between the treatments in regard to infarct size, ejection fraction or mortality. Ongoing multi-center studies (TEAM-3 and ISIS-III) will conclusively demonstrate if any differences in thrombolytic therapy exist. However, data-to-date suggest that anistreplase is equally effective to IV streptokinase and t-PA as thrombolytic therapy after an AMI.

**Pharmacokinetics:**
The drug, like other thrombolytics, can only be administered injectably. Its half-life averages 88 min. with a range of 70-114 min. (vs. 9 min for t-PA and 18-23 min for streptokinase). The drug undergoes acylation by first order kinetics. Very little is known about its other pharmacokinetic characteristics.

**Adverse Reactions:**
Adverse reaction, both in type and incidence are similar to other thrombolytics except for the absence of an allergic potential with t-PA. The incidence of bleeding is between 4-47% (average 17.1%) but severe in only 1.6% of patients. The incidence of hemorrhagic stroke is 0.34% (vs. 0.5% for t-PA). Mild and transient hypotension has been reported in 10-25% of cases. Arrhythmias occur in 38% of patients, but also in 46% of control (post-AMI) patients. Allergic type reactions are similar to streptokinase: rash (0.9%), erythema (0.2%), bronchoconstriction (0.5%) & anaphylactic reactions (0.2%).

**Pregnancy Category:**
C (unknown effect on fetus)

**Drug Interactions:**
Interactions with other drugs have not been studied. Prior administration of heparin, warfarin, aspirin and dipyridamole may increase the risk of bleeding.

**Contraindications:**
Contraindications to the use of anistreplase are the same as for other thrombolytics. Active internal bleeding, a history of cerebral vascular accidents, recent (within 2 months) intracranial neoplasm, arteriovenous malformation or aneurysm, severe and uncontrolled hypertension, and known bleeding diathesis are absolute contraindications.

**Dosage and Administration:**
Anistreplase is available in 30unit vials as a sterile, white, lyophilized powder that must be kept refrigerated (36-46°F). The product should be reconstituted with 5ml of sterile water for injection and must be administered within 30 min. The solution must not be mixed with any infusion fluid or other medications. It should be give as an IV bolus over 2-5 minutes.

**Acquisition Cost:**
Anistreplase (Eminase®) 30unit = $1,680.00
Alteplase, recombinant or t-PA (Activase®) 100mg = $2,244.00
Streptokinase 1.5 million IU = $80.18
Urokinase (Abbokinase®) 750,000 IU = $599.85

**Status at UH:**
Anistreplase (Eminase®) was recently added to the UH Formulary. Its use is restricted to Cardiology Service approval. It will be distributed by the same procedure as t-PA. Limited floor stock is allowed in the cardiac catherization lab and ER only. The pharmacy guarantees 10 min delivery to other areas.

(Reference Citations Available Upon Request)
Pharmacy News (Continued from page 2)
Anesthesia Kit System Temporarily Put On-Hold in OR.

The past system of anesthesia drug kits has been placed on hold due to complaints of high waste and increased workload with the system for both anesthesiologists and pharmacy personnel. The pharmacy is working towards development of a revised kit system with pre-filled medication syringes. In the interim, the medications will be stocked in the Anesthesia Workroom. A special charge sheet will be used, however, for charging patients for medications used. Medications used and not charged to the patient will be charged to the Anesthesiology Department.

Pharmacy Hires its first Clinical Specialist (for Antibiotic Therapy)

The pharmacy hired its first full-time Pharmacy Clinical Specialist, Elizabeth Buonpane, Pharm.D., who will be assigned to the area of Antibiotic Therapy. This individual will be responsible for concurrent monitoring of antibiotic usage at UH as well as changing microbiological sensitivity patterns to antibiotics and will work closely with the Section on Infectious Diseases. She will also have educational responsibilities and some staff development responsibilities in the pharmacy, but will have no dispensing responsibilities. Liz received her Doctor of Pharmacy degree from the University of California, San Francisco. She completed a Residency in Clinical Pharmacy at the University of Illinois Medical Center in Chicago and a Fellowship at the University of Washington (Harborview) Hospital in Seattle. She has served as a Clinical Pharmacist at Hartford Hospital in the SICU the past 3 years, working with past UH physician Neil Yeston. She has numerous publications in the area of parenteral nutrition and antibiotic therapy. Liz starts September 10th.

New Evening Charge Pharmacist

Amy Levy, R.Ph. has recently been promoted to permanent Evening Charge Pharmacist, a position which has been vacant for almost 2 years. This allows nurses to contact a charge pharmacist or supervisor on each shift during the weekdays. To recap:

Pharmacy Supervisor (Day Shift M-F) - Yu Choi, R.Ph., M.B.A.  
Charge Pharmacist (Evening Shift M-F) - Amy Levy, R.Ph.  
Charge Pharmacist (Night Shift) - Micky Reed, R.Ph.  
alternating every other week with Mark Williams, M.S., R.Ph.  
Charge Pharmacist (Weekends - Day/Evening Shifts) -  
continue to rotate among full-time day-shift pharmacists.

The charge pharmacist can be reached at Extension 6784. Nurses who cannot resolve problems with the pharmacist on-duty and cannot wait to discuss it with their liaison pharmacist are encouraged to contact the appropriate charge pharmacist.

P&T Committee News (Continued from page 2)
P&T Committee Approves the Use of High Dose Methylprednisolone in Spinal Cord Trauma.

Based on evidence presented in a recent article of the New England Journal of Medicine, the use of high dose methylprednisolone in patients with cervical spinal cord trauma was endorsed by the Pharmacy and Therapeutic Committee at its last meeting after submission of a request for such a ruling by the Department of Neurosurgery. Doses as high as 155mg/kg/day may be used in spinal cord patients without question from the pharmacy or nursing. Such high doses in other types of patients may prompt a call from a pharmacist.

Chemical Peritonitis in Chronic Peritoneal Dialysis Patients Resulting From Intraperitoneal Generic Vancomycin Discussed by P&T Committee

Concerns were recently raised by nurses in the Home Dialysis Unit in response to a FDA Safety Alert regarding the use of generic vancomycin in peritoneal dialysis fluid as a cause of chemical peritonitis. A review of the literature and facts involved, the Pharmacy and Therapeutics Committee agreed that there is presently a lack of sufficient evidence to document generic vancomycin as a cause of chemical peritonitis in home dialysis patients as well as insufficient evidence of a lack of a problem by the trade brand. Considering the tremendous cost impact to the institution and the lack of evidence of a problem, a change in brands is not warranted at the present time. The Committee further noted that physical cloudiness caused by the drug does not mean that a true incompatibility or that a clinical problem exists. The Pharmacy and Therapeutic Committee will continue to monitor this issue in the literature. Physicians and nurse are asked to immediately report any cases of peritonitis that develop in UH patients to the Pharmacy. However, for the present, the current brands will continue to be used at UH in all patients.

Antibiotic Order Sheet Under Review - Comments Welcomed

The Antibiotic Order Sheet is currently being reviewed by the Antibiotic Subcommittee of the Pharmacy and Therapeutics Committee for revision. Comments about the current sheet should be given to Kimberly Mu-Chow, Pharm.D., (Ext. 6790). A revised form will be approved by October 1990.
Pharmacy News
(Continued from page 5)

Other Pharmacist Changes at UH.

Recently hired in the past few months was Peter Lutz, R.Ph., a graduate of Northeastern University and a practicing pharmacist for 2 years. Peter has been assigned to the Evans Satellite.

We regret to announce the resignation of UH past resident and staff pharmacist for a year, Lorena Scanlin, R.Ph. Lorena has decided to pursue her career elsewhere. The pharmacy is currently looking for a replacement for Lorena.

New Pharmacy Resident

This year's Pharmacy Resident is Marisel Segarra, R.Ph. Marisel recently graduated (Magna Cum Laude) from the Massachusetts College of Pharmacy with a Bachelor's Degree in Pharmacy and a B.S. degree in Chemistry and passed her Board Exams this past month to become a licensed pharmacist. Marisel starts her clinical rotations on the floors in October.

P&T Committee Actions
August 1990

Additions to the Formulary
Anistreplase (Eminase) **Restricted**
30mg vial

Propofol (Diprivan) **Restricted to the OR for Use in Outpatient Surgical Procedures or with Attending Anesthesiologist Approval in Inpatient Procedures with Documented Prior Intractable Nausea and Vomiting to Thiopental**
2% (200mg) 30ml vial

Leuprolide Acetate Depot (Lupron Depot)
**Restricted to Medical Oncology**
7.5mg vial

Deletions
All forms of insulin except human insulin (Regular, NPH, Lente, Ultralente) and Protamine Zinc.

Miscellaneous
Guidelines for the Use of High Dose Methylprednisolone in Cervical Spinal Cord Trauma Approved.
Generic Equivalence of Vancomycin for Intraperitoneal Use in Home Dialysis Reestablished.