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BOSTON UNIVERSITY MEDICAL CENTER

The University Hospital

PHARMACY UPDATE

A Newsletter of Current Topics from the Pharmacy

Volume 4, Number 2 March/April 1989

Clinical Investigational Drugs Studies at UH:

What investigators need to know about pharmacy services.

According to Medical Staff policy, JCAHO standards and state regulations, all drugs, including investigational drugs, used on inpatients at the University Hospital must be dispensed by the pharmacy. In addition, many pharmaceutical companies now demand pharmacy participation and even have standards of their own related to the level of services the pharmacy must provide for their investigational product.

The Department of Pharmacy has always supported the tri-mission of the hospital towards patient care, research and education, with patient care being the pharmacy's top priority. Until recently, the pharmacy has helped in its role in the distribution of investigational drug products as part of its overall services, without budgeted personnel resources committed to this function. Specifically, the clinical coordinator, as part of her overall responsibilities to the pharmacy, was allocated a maximum of 8 hours per week towards coordinating the pharmacy's participation in clinical investigational drug studies. However, the number of clinical investigational drug studies went from 10 in 1987 to 38 in 1988, with even more studies anticipated for 1989. This has placed an unbearable strain on this individual.

As a result, the Department of Pharmacy has reorganized. Two pharmacy managers and the clinical coordinator position were consolidated into two manager positions. With support from hospital administration, a new staff pharmacist position was created from this consolidation to exclusively deal with clinical investigational drug studies and the drug information service. While this will increase the manpower dedicated to clinical investigational drug studies on the part of the pharmacy, it will not totally solve all the problems associated with the increased number of studies being conducted at UH.

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FDA issues Warnings on Use of Encainide, Flecainide & Sucralfate

Encainide (Enkaid) and flecainide (Tambocor), a new class (IC)of antiarrhythmic agents, have been used in the treatment of serious arrhythmias such as frequent premature ventricular contractions (PVC's), symptomatic non-sustained ventricular tachycardia, and the non-approved treatment of other types of arrhythmias. Recent results from multi-center studies linking the drugs to a higher incidence of mortality, has prompted the FDA to issue warnings against using the drugs for anything but the treatment of documented life-threatening arrhythmias, such as sustained ventricular tachycardia. Both drugs should be taken as high-risk, potentially dangerous drugs. The UH status of both drugs remains the same - "formulary but restricted to cardiology service approval".

The FDA also requested Marion Laboratories to clarify misconceptions resulting from their promotion of their drug sucralfate (Carafate). Sucralfate is indicated only for short term (up to 8 weeks) treatment of duodenal ulcers.

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Clinical Investigational Drugs

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There are some important points that need to be known by investigators about the pharmacy services provided before considering starting a study:

1) When writing the grant proposal or negotiating finances associated with a proposed study, be sure to include a cost component for the pharmacy services provided. Contact the pharmacy's clinical investigational drug coordinator (Ext. 6790) for an estimate. Almost all drug companies will accept the cost of pharmacy services provided since they are aware that the record keeping and additional labor needed to set up and maintain study drugs is costly. In today's era of cost containment, continuation of a pharmacy position dedicated to clinical investigational drug studies will only occur with the financial grant support of all UH investigators.

   It is important to note that the pharmacy will not assume the cost of any supplies needed in the dispensing of investigational drugs or the cost of the drug(s)(unless it is a formulary drug). Funds for these must be provided by the investigator. In general, the P&T Committee will not approve drugs to the formulary strictly for the purpose of studying them.

2) The pharmacy can provide a wide range of services to investigators besides mere dispensing of the product. These include protocol design; assistance in writing for grants, informed consent forms, and drug information summaries; randomized blinding of study drug; special packaging and formulation; among others. Some services, such as the development of a unique drug delivery device, may not be possible because of a lack of resources. To be sure which services the pharmacy can and cannot provide, contact the investigational drug coordinator in the pharmacy beforehand. This will save a lot of wasted effort in advance.

3) Be sure to contact the pharmacy's clinical investigational drug coordinator **at least one month in advance** of the planned start of the study to work out the exact details of the pharmacy's handling of the drug. Contacting the pharmacy with less advance notice, may result in delay in the initiation of the study. The pharmacy will work on a first-come, first-served basis with investigators. Currently, there is a two month backlog of new studies the pharmacy is working on setting up for distribution. This is due to a large number of investigators wishing to start their studies at the same time. Even under the best of circumstances, a week is needed for the pharmacy to properly set up a study for drug distribution.

4) Because of the large number of studies underway and the fact that all pharmacists rotate work shifts on the evenings and weekends, the pharmacy's clinical investigational drug coordinator can only meet with investigators or drug company representatives by appointment only. This can sometimes only be accommodated on certain days. Appointments with the clinical investigational drug coordinator can be made with the pharmacy's administrative secretary at extension 6790. This is also true of drug companies wishing to inspect the pharmacy or their drug supply. The state is required to give notice of inspections, we expect no less of the drug companies. We also expect the primary investigators to support us in our policy of meeting with drug company study monitors by appointment only.

Kimberly Mu-Chow, who helped to coordinate investigational drug studies in the past, with her recent promotion is no longer responsible for this activity. The new position of clinical investigational drug coordinator/drug information pharmacist is vacant and is currently being recruited for. In the interim, Kim will continue to help coordinate studies in addition to her other duties. Patience and understanding (and extra lead time in setting up studies) is needed until the new position is filled.

Through mutual cooperation and understanding, the pharmacy can work with investigators in many ways to help them in their research goals. With the increase in the number of investigational drug studies at UH, better planning on the part of the investigators is needed, especially when it comes to pharmacy services provided. For more information on anything discussed in this article or on how the pharmacy can help you better plan your investigational drug study, contact Darryl Rich, Director of Pharmacy Services at Extension 6790.□

Errata

In the September/October 1988 *Pharmacy Update* in an article entitled : "Policies and Procedures: Handling Investigational Drugs", it was indicated that nurses are not allowed to administer investigational drugs unless, as 1 of 4 criteria, the protocol for the drug is readily available in the patient's chart. This is in error. Only the completed UH Investigational Drug Sheet from the approved protocol and signed informed consent form are necessary. A complete copy of the protocol will be kept on file in the pharmacy, from which nurses can obtain further drug information. Also that same article indicated incorrectly, that an emergency use of an investigational drug outside an approved protocol for a specific patient, had to be approved by the IRB within 48 hours. The IRB does not give "approval" to the emergency use of an IND drug, but the first use of such drug must be reported to the IRB in writing within 5 working days. Subsequent use requires IRB approval.

Drug Review:

Lovastatin (Mevacor®)

By: Darryl S. Rich, Pharm.D., Department of Pharmacy, The University Hospital

Description: Lovastatin (Mevacor) is a relatively new (released by Merck, Sharp and Dohme in September of1987) oral hypocholesterolemic agent that inhibits cholesterol synthesis. The product is only indicated for the reduction of elevated total and LDL cholesterol levels in familial or primary hypercholesteremia (Types IIa and IIb)as an adjunct to diet, and in patients with nonfamilial hypercholesteremia when diet and other nonpharmacological measures have been inadequate in reducing cholesterol levels. The product is only available as an oral tablet in 20mg and 40mg strengths.

Mechanism of Action: Lovastatin, an inactive lactone, is hydrolyzed to the corresponding beta-hydroxyacid form which is a metabolite and inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the rate-limiting step in early cholesterol synthesis. Lovastatin also increases elimination of circulating low-density lipoproteins (LDL) and may potentially decrease production of LDL. The overall effect on plasma lipoproteins is to lower LDL concentrations, with a resulting decrease in total plasma cholesterol, while high-density lipoproteins (HDL) concentrations increase or remain the same.

Clinical Trials: In combined studies of diet-treated patients with both familial and non-familial hypercholesteremia lovastatin 20mg/day resulted in lowering LDL cholesterol and average of 27% and total plasma cholesterol 21%. The LDL/HDL ratio decreased 30%. Doubling the dose to 20mg twice daily achieves an additional 7% decrease in the respective levels, with 40mg twice daily achieving another 7% respectively. Plasma triglyceride levels decreased an average 8% to 27%. Both 20mg and 40mg of lovastatin twice daily were shown to be more effective in lowering elevated total and LDL cholesterol than either cholestyramine (Questran) 12grams twice daily or probucol (Lorelco) 500mg twice daily. In addition, probucol decreased HDL levels 23%, whereas lovastatin increased HDL levels 6-12%.

Concurrent use of lovastatin with bile acid sequestrants can lower LDL-cholesterol further than lovastatin alone. Adding 10 grams twice daily of colestipol (Colestid), decreased LDL levels 26% more than lovastatin alone, to an average reduction of 48-52%. Use of neomycin (1gm bid) with lovastatin had no effect on lowering LDL levels beyond that of lovastatin alone but did, unwantingly, reduce HDL levels 19%. The combination of lovastatin and neomycin cannot be recommended. Niacin (3 grams/day) has been reported to have an additive effect in reducing cholesterol levels when added to lovastatin therapy.

Once the drug is discontinued, all cholesterol concentrations return to pretreatment levels. Hence, the drug must be given continuously for life. The effectiveness of lovastatin in preventing or reversing atherosclerosis or on cardiovascular morbidity or mortality has not been established.

Pharmacokinetics: Because the drug requires activation in the stomach to the beta-hydroxyacid form in order to be effective, only oral forms of the drug are effective. Only 5% of the drug reaches the plasma as the active metabolite from a single dose. Thus, it takes 4-6 weeks of the initiation of therapy to reach maximal and stable cholesterol reduction, as well as 4-6 weeks to return to baseline after discontinuation. Twice daily dosing appears to be the most effective schedule, with daily evening dosing being slightly less effective and daily morning dosing

being the least effective. The difference is explained by the fact that cholesterol synthesis is maximal from midnight to 4AM. In patients with non-familial hypercholesteremia who do not require a dramatic reduction in cholesterol, a single evening dose of 20mg may be appropriate, otherwise 20-40mg twice daily is probably the most effective regimen.

Adverse Reactions: To date, lovastatin has been shown to be the best tolerated hypocholesterolemic agent available, however it is not devoid of adverse effects. Gastrointestinal effects, including flatus (6.4%), abdominal pain/cramps (5.7%), diarrhea (5.5%), constipation (4.9%), nausea (4.7%), dyspepsia (3.9%) and heartburn (1.6%) are the most common. Myalgia (2.4%), headache (9.3%), rash (5.2%), dizziness (2%), muscle cramps (1.1%) and tiredness and malaise have also been reported. These are typically mild to moderate in intensity and transient. Drug-related elevations in hepatic enzymes have been reported especially after heavy alcohol use. Myositis with CPK elevations has also occurred. Severe myositis, rhabdomyolysis, and acute renal failure have been reported, particularly in patients receiving gemfibrozil (Lopid) or cyclosporine (Sandimune) or patients with impaired hepatic function. Past concerns about cataract formation related to lovastatin have recently diminished. Concerns have been expressed about the unknown long term effects of interfering with the synthesis of cholesterol, an important component of the cell membrane. The drug is teratogenic in mice and hence is not recommended in pregnancy. It is also not recommended for nursing mothers, and children, where little data on its use is available.

Drug Interactions: Alcohol, gemfibrozil (Lopid), cyclosporine (Sandimmune) *(see above under adverse effects).* Lovastatin can also cause an increased PT time in patients taking warfarin.

Dosage and Administration: It is recommended that lovastatin be started at a dose of 20mg per day (at bedtime), raised to a maximum dose of 40mg twice daily. Taking lovastatin with food or milk is recommended because food enhances the absorption of the drug. If further reductions are necessary, the addition of colestipol (10g bid) or niacin (3g qd) is recommended. A maximum dose of 20mg per day is recommended for patients taking immunosuppressive drugs (e.g. cyclosporine). Dosage adjustments should be made based on cholesterol levels at 4-6 week intervals. Because of the unknown long term effects, it must be emphasized that the drug should be taken only after diet have been shown to be ineffective.

Cost: $1.77 for each 20mg dose including indirect labor costs.

Status at UH: Lovastatin was recently added to the UH Formulary. It is stocked only in the 20mg strength.

P&T Committee Actions
March/April 1989

Additions to the Formulary

Flutamide (Eulexin)
125mg capsule

Lovastatin (Mevacor)
20mg tablet

Nicardipine (Cardene)
20mg, 30mg capsule

Diltiazem Sustained-Release (Cardizem SR)
60mg, 90mg, 120mg sustained-release capsule

Requested Additions to the Formulary Denied

Powdered Cellulose (Unifiber)

Deletions from the Formulary Approved

Aminogluthimide (Cytadren)
Amitriptyline/Perphenazine (Triavil)
Ammonia Inhaler
Ammonium Chloride
Amobarbitral (Amytal)
Benzylpenicilloyl Polylysine (Pre-pen)
Betamethasone (Celestone)
Boric Acid Ointment
Calcium Lactate
Carbachol Ophthalmic (Isopto-Carbachol)
Clove Oil
Cycloserine (Seromycin)
D-amphetamine (Dexedrine)
Desoxycorticosterone Pivalate (Percorten)
Diazoxide (Hyperstat)
Dibucaine HCL Cream (Nupercainal)
Dihydroergotamine mesylate (DHE)
Diphenhydramine Cream (Benadryl)
Epinephrine Ophthalmic (Epifrin)
Ergonovine maleate (Ergotrate)
Fentanyl/Droperidol (Innovar)
Floxuridine (FUDR)
Fluorescein Sodium Ophthalmic (AK-Fluor)
Fluorescein Sodium Strips (Fluor-i-strip)
Fluorescein Sodium/Benoxinate Ophth. (Fluress)
Flurandrenolide Tape (Cordran)
Gentamicin Sulfate Cream
Gentian Violet
Gluconic Acid / Citric Acid (Renecidin)
Glycerin Ophthalmic (Ophthalgan)
Gonadotropin Chorionic (APL)
Guaifenesin/Codeine (Robitussin AC)
Guaifenesin/Pseudoephedrine (Robitussin PE)
Histamine Phosphate
Homatropine HBr Ophthalmic
Hydrocodone/Pyrilamine/Homatropine (Hycodan)
Hydrocortisone Sodium Phosphate(Hydrocortone)
Indocyanine Green (Cardiogreen)
Isosorbide (Ismotic)
Lomustine (CEENU)
Maprotiline (Ludiomil)
Mercaptopurine (Purinethol)
Methylprednisolone (Medrol) 2mg, 4mg Tablets
Methylprednisolone Acetate (Depo-Medrol)
Miconazole (Monistat IV)
Mitotane (Lysodren)
Nalidixic Acid (NegGram)
Naphazoline (Albalon)
Pectin/CME/Cellulose Gel (Orabase)
Penicillin G Sodium
Pentagastrin (Peptavlon)
Potassium Iodide (SSKI)
Potassium Phosphate
Pramoxine/Hydrocortisone Acetate (Proctofoam)
Procyclidine (Kemadrin)
Progesterone
Reserpine (Serpasil)
Sodium Chloride Ophthalmic (Muro-128)
Sodium Chloride/Phenol/Parafin (P&S)
Streptomycin
Tetracycline HCl Cream
Tolnaftate (Tinactin) Cream, Powder, Solution
Tranylcypromine sulfate (Parnate)
Triamcinolone/Nystatin Cream (Mycolog)
Tripelennamine (PBZ)
Vitamin A&D Ointment

Miscellaneous

- Request for addition of alfentanyl to the formulary was tabled until more information could be made available.
- Requests to lift the restriction classification for ticarcillin/clavulanic acid (Timentin) and imipenem/cilastatin (Primaxin) were denied pending results of microbiological studies under investigation.
- Approved 3 Nursing & 3 Pharmacy Policies & Procedures.

New Administative Structure in Pharmacy

Darryl S. Rich, Pharm.D., M.B.A., *Director*
Daniel B. Dobson, M.S., *Pharmacy Manager for Operations*
Kimberly J. Mu-Chow, Pharm.D., *Pharmacy Manager for Clinical Services*
Yu Cheung Choi, R.Ph., *Central Pharmacy Supervisor*
Gail M. Chazanovitz, R.Ph., *Pharmacy Systems/Billing Coordinator (Part-time)*
Lorena Scanlin, R.Ph., *Resident in Hospital Pharmacy*
L. Joseph Fleming, *Pharmacy Purchasing and Inventory Supervisor*
Mary Beth Dorus, *Administrative Secretary.*

FDA Warnings on Encainide, Flecainide & Sucralfate

(continued from page 1)

Sucralfate is not indicated for the prevention and/or treatment of gastric ulcers, gastritis, esopharitis, or stress ulcers. Sucralfate has also not been approved for the prevention of duodenal ulcers related to administration of non-steroidal anti-inflammatory drugs (NSAIDs), or for concomitant administration with NSAIDs for the treatment of NSAID-related duodenal ulcers. Also, no dosage form or regimen of sucralfate other than a single gram tablet given four times a day has been approved by the FDA. □

New Pharmacy Window Hours

The pharmacy window hours for the pick-up of departmental requisitions will change from 9:00AM to 10:30AM and 3:30PM to 5PM Monday through Friday to its new hours of 9:00AM to 11:00AM only, Monday through Friday, starting June 1, 1989. The reason for the change was to improve efficiency. A low volume of orders were being picked up in the afternoon, during a time that inpatient workload in the pharmacy was at its peak. As before, in an emergency, orders can be picked up by calling Ext 6784 and ask for the pharmacy supervisor or charge pharmacist (eves and weekends) prior to coming to the main pharmacy. □

Pharmacy's Employee of the Month

The pharmacy initiated an employee of the month program this year to recognize pharmacy employees who display behavior which project the image that the Department wishes to achieve. Criteria include the display of a courteous personality to the staff, management, patients, and visitors to the hospital; exhibition of a high degree of helpfulness to other departments as well as within the pharmacy; and the performance above and beyond the normal and expected duties of the position as well as exhibiting an overall exemplary work attitude. Recipients receive a bonus and have their picture, along with a brief description of the basis for which the award was given, in a new display case outside the main entrance to the central pharmacy. People outside of the department of pharmacy are encouraged to nominate pharmacy personnel for the award, by writing or calling (X6790) Pharmacy Manager, Dan Dobson. Past recipients for 1989 have included:

January	*Susan Lynch*
February	*Mohamed Saab*
March	*Brenda Waning, R.Ph.*
April	*Tina Pateras*

This coming month's recipient will be Pharmacy Secretary, Mary Beth Dorus.

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