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BOSTON UNIVERSITY MEDICAL CENTER

The University Hospital

A Newsletter of Current Topics from the Pharmacy

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# Drug Review: Use of AZT in the Treatment of AIDS and AIDS Related Complex

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Zidovudine (Retrovir®), formerly called azidothymidine or AZT, is a recently released antiretroviral drug indicated for the management of certain adult patients with symptomatic HIV infection (AIDS and advanced ARC) who have a history of cytologically confirmed *Pneumocystis carinii* pneumonia (PCP) or an absolute CD4 (T4 helper/inducer) lymphocyte count of < $200/mm^2$ in the peripheral blood before therapy is begun. Patients meeting these criteria must be enrolled (by a physician) and approved (by the manufacturer) for a special RETROVIR distribution program before he/she can receive the drug. Currently, the only form of the drug is a 100mg oral capsule. The drug is non-formulary at The University Hospital, because of the requirements of the special distribution program (see related article this page).

### Clinical Pharmacology

Zidovudine is a thymidine analogue (the 3' -hydroxy group is replaced by an azido group), which is converted by a series of enzymatic steps to zidovudine triphosphate. This latter compound interferes with the HIV (also known as HTLVIII, LAV or ARV) viral RNA dependent DNA polymerase (reverse transcriptase) and thus inhibits viral replication. Zidovudine triphospohate also inhibits cellular alpha- DNA polymerase, but at concentrations 100-fold higher than those required to inhibit reverse transcriptase.

## Policy & Procedure: Acquiring AZT: Mfgr's Stringent Rules that Physicians & Nurses Must Follow

Zidovudine (Retrovir®), formerly called AZT, is unique in the way it is being distributed by the manufacturer, Burroughs Wellcome Co. The University Hospital Pharmacy cannot acquire the drug to stock in the pharmacy like most drugs. The following rules must be followed in order to acquire the drug:

### A. Prescribing The Drug For the First Time

Patients must be enrolled in the manufacturer's RETROVIR distribution program. To do so patients must meet the following criteria:

- have a history of cytologically-confirmed *Pneumocystis carnii* pneumonia (PCP). or
- an absolute CD4 (T4 helper/inducer) lymphocyte count of < $200/mm^3$ in the peripheral blood prior to therapy.

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## Use of AZT in the Treatment of AIDS and AIDS Related Complex *(Continued from page 1)*

Zidovudine is believed to signficantly decrease mortality and prolong life during the initial treatment period (<24 weeks). Patients also show improved performance level, neuropsychiatric function, maintenance of body weight, and number and severity of symptoms associated with HIV infection. Long term effects of zidovudine on mortality and morbidity are unknown at present. The drug does not reduce the potential for transmitting the disease to others.

#### Pharmacokinetics

After oral dosing, zidovudine was rapidly absorbed from the gastrointestinal tract with peak serum concentrations occuring within 0.5 to 1.5 hours. The CSF/plasma concentration ratio was found to average 0.15. The bioavailability of the oral capsule averages 65% (range 52-75%) due to first pass metabolism. Zidovudine is rapidly metabolized to GAZT through glucuronidation in the liver. Following oral administration, urinary recoveries of zidovudine and GAZT accounted for 14% and 74% of the dose respectively. The mean zidovudine half-life is approximately 1.1 hours (range 0.48 to 2.86 hrs). It is unknown if patients with hepatic or renal insufficiency are at greater risk of toxicity from zidovudine.

#### Adverse Reactions

The most common adverse reactions to zidovudine are severe anemia and granulocytopenia, occuring in 45-55% in patients receiving the drug. The effects are directly related to dose and duration of drug use. Patients usually develop signs of anemia or granulocytopenia within 4-6 weeks of therapy. Frequent (every 2 weeks) blood counts are recommended for all patients on zidovudine. Treatment of the adverse effects usually requires dose modification (see below) and/or blood transfusions. It is believed that the need and frequency of blood transfusions are the most costly aspect of zidovudine therapy. Other side effects that occur in 5% or more of patients include: severe headache, nausea, insomnia, and myalgia.

#### Precautions/Drug Interactions

The drug should be administered with extreme caution in patients with compromised bone marrow evidenced by granulocyte count $<1000mm^3$ or hemoglobin <9.5 g/dl. An increased risk of toxicity may result from administration of zidovudine with drugs that are nephrotoxic, cytotoxic, or which interfere with the number or function of RBCs/WBCs (e.g. dapsone, pentamidine, amphotericin B, flucytosine, vincristine, vinblastine, adriamycin, or interferon) or glucuronidation (e.g. acetaminophen, aspirin, indomethacin, or probenecid). Use of these other drugs should be avoided. Some experimental nucleoside analogues may inactivate zidovudine and coadministration should be avoided. Zidovudine and acyclovir may increase the risk of neurotoxicity if administered together. No drug interactions have been found with cotrimoxazole or pyrimethamine.

Little is known about the drug's safety in terms of its carcinogenesic or mutagenesic potential, impairment of fertility, use in pregnancy, breast feeding, or in pediatrics.

#### Dosage and Administration

The recommended dosage regimen of zidovudine is 200mg PO q4h round the clock. No loading dose is necessary. Significant anemia (hemoglobulin < 7.5 g/dl or reduction >25% from baseline) and/or significant granulocytopenia (granulocyte count $<750/mm^3$ or reduction >50% from baseline) may require a dose interruption until some evidence of marrow recovery is observed. For less severe anemia or granulocytopenia, a reduction in daily dose may be adequate, with gradually increasing doses following marrow recovery (depending on hematologic indices and patient tolerance).

#### Summary

Currently, zidovudine is the only effective therapy for the treatment of AIDS or AIDS related complex. It does not eradicate HIV infection, but it doesprolong and improve the quality of life of patients with AIDS or ARC. It is an extremely toxic substance, causing severe anemia and granulocytopenia in half of patients receiving the drug. Dose modification and/or frequent blood transfusions are often needed for patients who develop these side effects. Currently, the only form of therapy that is available is oral capsules given 200mg q4h. The cost of therapy is expensive (over $2 per 100mg capsule). Very few studies have been done with the drug, which was released by the FDA much sooner than normal. The most unique feature of the products is its distribution from the manufacturer (see related article) in which the patient must be enrolled and approved to use the drug. For the manufacturer package insert information, contact the pharmacy at Ext 8790.

## Acquiring AZT: Mfgr's Stringent Rules that Physicians & Nurses Must Follow *(continued from page 1)*

Physicians must complete an application form (available from the UH Pharmacy or mfgr. representative) for each eligible patient. The application will be reviewed by a panel of experts at the RETROVIR center. The physician will be notified if the patient(s) were accepted. If accepted, an enrollment number will be given which must be placed on all prescriptions or it cannot be filled. *(Please note: The University Hospital Pharmacy does not dispense outpatient prescriptions. The Pharmacy will help in finding a suitable outpatient pharmacy to fill prescriptions for RETROVIR)*

The patient's pharmacy upon receipt of the prescription must contact the RETROVIR Sales Department with the enrollment number to acquire the drug. A one-month supply of the drug will be sent within a few days. The manufacturer will not allow pharmacies, including UH, to stock the drug. With each prescription or refill request, only a one-month supply will be issued by the manufacturer. No additional RETROVIR can be ordered under a particular patient enrollment number until the following month. Loss or sharing of medication will result in interruption of the patient's drug therapy.

Because of the time needed for this application process, the patient must be enrolled in the distribution program prior to admission. The UH pharmacy cannot acquire the drug for inpatients not previously enrolled in the program. The program, as designed, precludes starting patients on the drug as an inpatient. Because pharmacies cannot stock the drug, it cannot be obtained by other means than from the manufacturer through this program.

**B. Patients Already on the Medication**

If a patient on zidovudine (RETROVIR) is admitted to the hospital, he/she must bring their existing supply of RETROVIR with them. The patient was informed of this when they first received the drug. The physician must write an order that the patient should take their own supply of the medication, the dosage regimen and an order that nursing should notify the physician 3-4 days before the medication runs out. If the patient's medication supply is within 3-4 days of being used up before the patient leaves the hospital, the physician must write a new prescription for the patient with the patient's enrollment number on it. This must be on an outpatient prescription form. The pharmacy will order the drug, fill and appropriately label it. The entire month's supply will be sent to the patient's floor. It is important that the drug not be borrowed from other patients or lost. The patient from whom the drug is borrowed or lost will be deprived of therapy with severe liability problems potentially arising as a result of any patient harm. Any remaining drug must be taken by the patient when he/she leaves the hospital.

It is important to note the following:

1. The patient must use their own supply. Even if a patient forgets to bring in their medication or loses it, the manufacturer will not allow the pharmacy to obtain more for the patient until 1 month from the last filling of their prescription. For the same reason, the patient must take any remaining supply of drug with them at discharge, as they will not be able to obtain a replacement supply.

2. The Pharmacy cannot stock the drug, but must acquire it through the manufacturer. The Pharmacy cannot acquire the drug unless the patient enrollment number is known, hence it must be on the prescription.

3. Because the product can **only** be obtained from the manufacturer in this program, it takes 3-4 days to receive the drug (holidays and weekends excluded). The drug must be ordered before the patient runs out. It cannot be obtained on a STAT basis.

4. The drug cannot be borrowed from another patient, as that patient from whom the drug was borrowed will not be able to receive a replacement supply and will hence be deprived of sustained therapy.

Generally, the pharmacy has be able to skirt internal drug distribution procedures when the interest of the patient is at stake. It should be made perfectly clear that the manufacturer, Burroughs Wellcome, (because of short supplies of the drug), has developed a distribution system that is so rigid the Pharmacy will not be able to accommodate physicians or nurses who do not follow the rules, even if patient harm could result. This is because the manufacturer distributes the drug directly to and for a specific patient, rather than the usual procedure of pharmacy acquiring and stocking drugs for the institution's need. All physicians and nurses should be advised of these rules for acquiring RETROVIR.

# News Tibits from the Pharmacy

A. *Unit Dose Drug Distribution*
The implementation of the unit dose system continues to expand. Currently all floors in the Evans and F Buildings are on this new drug distribution system. Modifications to improved response time through filling of all initial doses on the satellites, decrease transit time for picking up orders in nursing station by using more technicians for this function, incorporation of continuous IV drugs in the unit dose bins in lieu of a total floor stock replacement system, and use of punch clocks to document and monitor new order response time have been implemented to improve the system. Expansion to the B&C buildings is expected to start in mid May to be completed by the end of June. Each unit dose floor has been assigned a specific pharmacist to assist nurses with UD concerns. Listings of these pharmacists and new cart delivery times for each unit are available from Greg Aldridge X8790.

B. *IV Wastage Reduction Program Started.*
The pharmacy recently implemented an IV wastage reduction program to increase the recycling of prepared IV drugs (minibags). Preparation cycles were increased from 2 to 3 per day. Unused doses are picked up by technicians for use in other patients. Nurses are asked to assist in the waste reduction program through the following steps:

## P&T Committee Actions March/April 1987

**Additions to The Formulary:**
Ipratropium Bromide (Atrovent)
Amino Acids 15% (Novamine)
Terfenadine (Seldane)

**Deletions from The Formulary:**
Protamine Zinc Insulin
Oxycodone/Aspirin (Percodan)
Secobarbital (Seconal)

1. Keep all minibags refrigerated.
2. Check the labels of all minibags and used the drug with the shortest expiration date first.3.
Make sure all drugs are sent with the patient, when transfered to a new unit.
4. Make sure the pharmacy knows of all d/c'd IV orders as soon as possible.

Nursing cooperation with Pharmacy can help tremendously in keeping drug waste costs down.

C. *Pharmacy now prepares all cardioplegia solutions.*
The pharmacy began the preparation of all cardioplegia solutions for use in the OR starting in April.Preparation of these solution in sterile environments with stringent aseptic technique should reduce the potential for infection in patients undergoing cardiothoracic surgery.

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