AMERICAN HEALTH CONSULTANTS

DRUG UTILIZATION REVIEW

Pharmaceutical Care Across the Continuum

IN THIS ISSUE

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Can you break the 10-minute barrier for tPA delivery to stroke patients?

Top stroke hospitals get the patient in the door and the drug to the patient

Recent results of a study performed by the HCIA-Sachs Institute (formerly Health Care Investment Analysts) reveal that U.S. hospitals can save as much as $117 million annually just by managing Medicare stroke patients in a manner similar to leading stroke hospitals. The HCIA-Sachs study, *100 Top Hospitals: Stroke Benchmarks for Success*, identified the hospitals setting benchmarks in stroke treatment. Results of the study show that there are significant opportunities for hospital pharmacists to improve treatment of stroke patients while at the same time reducing costs.

This particular top-100 hospitals study reviewed the number, severity, lengths of stay, costs, and outcomes of stroke patients. St. Luke's Hospital in Kansas City, MO, is among those listed.

St. Luke's is involved in a study sponsored by the National Institutes of Health. "We're enrolling patients in this study for the interventional management of stroke," says **Debbie Summers**, RN, MSN, stroke clinical program coordinator at St. Luke's Hospital. "The primary investigators are a team at the University of Cincinnati.

"Timing is everything," Summers tells *Drug Utilization Review*. "If a patient reaches us within a three-hour window of the onset of the stroke, he's a candidate for IV tPA. That's one option. There are studies looking at intra-arterial tPA for the cerebral arteries, but again, the timing must be right. The patient must get to the hospital, then be evaluated to determine what type of stroke is occurring, then treatment begun — all within a rather narrow window of time."

Information from the American Heart Association (AHA) confirms Summers' sense of urgency in getting patients treated. The AHA advises readers at its web site to take immediate action when a stroke occurs. It lists the following as actions people should take when they suspect either they or someone around them is suffering from a stroke:[1]

• Don't ignore signs of stroke — not all of the warning signs occur with each stroke, so don't ignore individual signs, even if they go away.

• Check the time — make note of the time the first warning sign started; physicians will need this piece of information later.

• Don't delay — if one or more stroke symptoms are present, call for help immediately; patients should be instructed to call 911 immediately.

• If you're with someone who is displaying stroke symptoms, call 911 immediately, despite their requests not to; patient denial is common; don't take no for an answer; insist on prompt action.

Part of getting a stroke patient to the hospital quickly is being able to recognize the signs and symptoms of stroke. Several symptoms manifest during and leading up to a stroke. These signs and symptoms include:[1]

• sudden numbness or weakness of the face, arm, or leg, especially on one side of the body;

• sudden confusion, trouble speaking or understanding;

• sudden trouble seeing in one or both eyes;

• sudden trouble walking, dizziness, loss of balance or coordination;

• sudden, severe headache with no known cause.

A transient ischemic attack (TIA) should not be taken lightly, according to the AHA. Any of the above-listed signs and symptoms may be temporary and last only a few minutes. This is how a TIA can manifest. TIAs don't occur before most strokes, but they are definitely predictive of future strokes. In fact, among patients who have had one or more TIAs, more than 30% will later suffer a stroke.[1] Because they are so predictive of later stroke, TIAs should not be ignored and medical help should be sought immediately.

Where pharmacists fit in

"Pharmacists are an important part of the stroke team," Summers says. "Treatment of a stroke patient is acute. It's urgent. tPA is not stocked in the emergency department, so pharmacists are needed for emergent preparation of the drug.

"We're doing a quality review of our time frame. The national time frame for patients with neurological diseases and stroke is to get them from the moment they enter the emergency department to treatment within one hour's time. That includes the time needed for CT scans, labs — including PT/INR — to be drawn, assuming the stroke is not hemorrhagic. The pharmacist is part of the team. The minute the patient rolls in, the pharmacist is called and put on alert that we have a possible tPA patient. After we're sure by CT scan that the stroke is appropriate for tPA use, we call pharmacist with the go-ahead and the patient's weight. It's then up to the pharmacist to get the drug to the emergency department. Our goal is to have drug to the patient within 10 minutes. The faster the patient is treated, the better the patient outcomes."

Pharmacists can play an important role in helping the patient's family understand what's happening while they wait in the emergency department for a prognosis, according to Summers.

Review stroke basics with family

There are four main types of stroke. Two are caused by blood clots or other particles, and two are caused by hemorrhage. Cerebral thrombosis and cerebral embolism are the most common types of stroke, accounting for about 70% to 80% of all strokes. Cerebral and subarachnoid hemorrhages are caused by ruptured blood vessels. A subarachnoid hemorrhage occurs when a blood vessel on the brain's surface ruptures and bleeds into the space between the brain and the skull (but not into the brain itself). A cerebral hemorrhage occurs when a defective artery in the brain bursts, flooding the surrounding tissue with blood. Hemorrhagic strokes have a much higher fatality rate than ischemic strokes.[1]

Stroke is a cardiovascular disease that affects the blood vessels supplying blood to the brain. A stroke occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is blocked. Because of this rupture or blockage, part of the brain doesn't get the blood flow it needs. Deprived of oxygen, nerve cells in the affected area of the brain can't function and die within minutes. As a result, the part of the body controlled by these cells can't function either. When those cells die, the effect is permanent since they aren't replaced.[1]

As a cardiovascular disease, stroke treatment and prevention can mean treating the heart.

COMING IN FUTURE MONTHS

- Patient right to privacy
- Effects of growing PBMs
- Evaluating evidence-based medicine
- Pharmacoeconomics and you
- Medicare in the new administration

Damaged heart valves may require surgery or treatment with anticoagulants to reduce the chance of clot formation around them. Patients with atrial fibrillation are also at risk for clot formation and are thus treated with anticoagulants.

Push for anti-hypertensive compliance

Stroke prevention includes monitoring and controlling blood pressure. "Pharmacists play a role in secondary prevention of stroke," says Summers. "They help monitor patient blood pressure, for example. High blood pressure causes 80% of strokes. Pharmacists can educate patients about the importance of taking their blood pressure and other medications. Pharmacists know the importance of continuing to take blood pressure medicine, even when you feel good, and they can help pass that understanding along to patients."

Knowledge of various drug classes is important in knowing which drugs patients should take. "There is much data provided in the results of the HOPE trial," says **Cathy Carroll**, RPh, PhD, of the University of Missouri-Kansas City. "The American Heart Association published guidelines for high-risk cardiovascular patients to receive ramipril for the prevention of stroke. The HOPE trial demonstrated a 32% reduction in the incidence of stroke in high-risk cardiovascular patients receiving ramipril. Pharmacists can help patients by being aware of the patient's drug regimen upon discharge and making sure at-risk patients are on ACE inhibitors. Other data are showing us that patients who should be on an ACE inhibitor often are not."

Patient counseling is very important when warfarin is prescribed. "Nurses sometimes counsel these patients, but we've seen better results and better patient compliance when pharmacists provide the counseling," says Summers. "Every one of our patients who gets warfarin gets patient education."

Pharmacists can also develop and run anticoagulation clinics and smoking cessation programs, two services extremely useful to stroke and cardiac patients.

The days are gone when all pharmacists did was lick, stick, count, and pour. Today's pharmacists are relied upon for more cognitive services, including educating patients about the importance of taking their medications as directed.

"Pharmacists also educate patients about their disease states and different signs and symptoms to watch for that require further medical attention," says Carroll. "Stroke is one condition for which a pharmacist's counseling — and the patient's compliance with that counseling — is of the utmost importance."

How fast can you move?

Every pharmacy needs a protocol regarding its delivery time of tPA. Is it pushing toward the three-hour goal? Summers suggests a quality improvement study to determine the time taken at each institution from the moment the patient enters the door to the time the patient receives

More on tPA

The FDA approved the tissue plasminogen activator (tPA) for the treatment of stroke in 1996. This was a major advance in the treatment of stroke since tPA can be used to treat ischemic strokes caused by blood clots, which constitute 80% of all strokes. Thus far, tPA is the only drug that carries the indication of treating ischemic stroke. Studies have shown that tPA can significantly reduce the debilitating effects of stroke and minimize permanent disability, if administered promptly. For maximum benefit, the therapy must be started within three hours of the onset of stroke symptoms. Therefore, it's critical that caregivers, medical professionals, and the public recognize stroke as a medical emergency and respond immediately by calling 911 and getting the patient to the hospital.[1]

tPA carries a risk of bleeding in the brain, but its benefits outweigh the risks when used correctly by an experienced physician. Because of the risk for bleed, not every stroke patient, especially those suffering a hemorrhagic stroke, should receive treatment with tPA. ■

SOURCES

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- **Cathy Carroll**, RPh, PhD, University of Missouri-Kansas City, Assistant Professor, School of Pharmacy, 5005 Rockhill Road, Kansas City, MO 64110; (816) 235-1000.

treatment. Additionally, she suggests a time study to determine how long it takes from the time the pharmacy is notified of the definite need for tPA to delivery of the drug to the patient. "St. Luke's is not yet at the 10-minute mark, but we're close," Summers says.

(Editor's note: To see which hospitals in your area made the top 100 hospitals for the treatment of stroke, visit www.100tophospitals.com.)

Reference

1. American Heart Association. Web site: www.americanheart.org/Heart_and_Stroke_A_Z_Guide/strokews.html. ■

Med error reporting gets shot in the arm

MedMARx now in 300 hospitals

The U.S. Pharmacopeia (USP) has signed an agreement with the U.S. Department of Defense (DOD) to implement the USP's MedMARx program. MedMARx is an Internet-accessible, anonymous, national medication error reporting and prevention program for hospitals in the United States. The system allows hospitals to anonymously report, document, track, and analyze medication errors. The information generated by the MedMARx database identifies hospital system problems and helps form strategies for the prevention of medication errors.

The "Summary of 1999 Information Submitted to MedMARx: A National Database for Hospital Medication Error Reporting," appears on the USP's web site at www.usp.org. This report summarizes data submitted to MedMARx from 56 member hospitals.

In addition to other hospitals that have joined MedMARx since the 1999 report, the DOD agreement brings the total number of hospitals in the MedMARx program to more than 300. "MedMARx can be used in hospitals and other institutions to identify drugs and drug classes that are prone to medication errors," says **Diane Cousins**, RPh, vice president of USP's Practitioner and Product Experience Division.

Internal review of medication error data can help hospitals identify high-risk medications so that new employee orientation and staff competency programs can be designed to highlight those medications of concern. "It helps hospitals identify the source of medication error problems and develop strategies to prevent their recurrence," Cousins tells *Drug Utilization Review*. MedMARx participants can utilize national data about product error trends when making drug formulary selection decisions, in developing protocols, and in developing proactive safety measures for problematic products. "With MedMARx, hospitals have access to cutting-edge technology for reporting, tracking, and comparing medication errors. They also learn valuable lessons in medication error prevention and reduction from the strategies and recommendations of other hospitals nationwide," Cousins says.

MedMARx is strengthened by the USP's long history of experience in operating voluntary reporting programs for health care professionals. The USP launched MedMARx in 1998 to serve voluntary reporting needs of health care professionals. Since the first version was released, USP has continued to improve the software program with input from subscribing hospitals. MedMARx not only documents medication errors, but also focuses upon risk management solutions that ultimately will protect patients and consumers of health care services provided by the nation's 6,200 hospitals.

The USP demonstrated its MedMARx system at a congressional hearing on Feb. 9. Members of the House Commerce Committee and Veterans Affairs Committee were present. They heard Cousins testify on the importance of MedMARx as a national voluntary reporting system. The testimony included a background of USP's experience in promoting the quality and appropriate use of medicines.

Distracted pharmacists = more errors

"The response to the presentation was very favorable," Cousins says. "The data reported last December from 1999 MedMARx reports has been even more convincing. With this report, they're able to see what they've only been hearing about previously. For example, they can now see documentation that shows that distraction of pharmacists from their work load increases the numbers of medication errors. Congress also noted that if this is the kind of reporting that is generated without legal protection, just imagine what's possible with legal protection."

That type of legal protection would have to come at the federal level, since state policies vary too much, Cousins added.

"There are no patient identifiers in the database," Cousins says. "Where applicable, patient age is requested, but not the date of birth. Information is presented in aggregate form." This privacy and anonymity applies to the reporter and professionals involved in the medication error, too. "Those involved are identified only with information regarding their level of staff."

The USP has helped develop legislation to support the confidentiality of information submitted to national medication error reporting systems.

The absence of protection poses a major barrier to the reporting of medical errors. The Medication Error Prevention Act of 2000 was introduced by Rep. Connie Morella (R-MD) to provide for voluntary reporting of medication error information by health care providers by protecting this information. Morella prepared the legislation with the USP's assistance.

The USP continues to monitor congressional activity and meet with Senate and House staff members, administration officials, and national professional organizations to build support for the legislation and for MedMARx as the national voluntary reporting system.

Features of MedMARx as described on the USP web site include:

- Internet accessibility, which reduces the need for technical support;
- "point and click" technology and predefined drop-down boxes or pick lists with full on-line help for ease of use in creating individual medication error incident reports;
- the ability to hold reports for up to 60 days, at the facility's discretion, to facilitate the investigative process and/or update information;
- a hard copy of the medication error reporting form, which will make reporting easier and give increased access to health care professionals within the facility;
- a root-cause analysis (RCA) database update based on the latest Joint Commission on Accreditation of Healthcare Organizations' RCA framework;
- new user security access levels with a "write only" level added to give staff on patient units the ability to enter new medication error reports directly without accessing the entire database;
- a hyperlink from Notices to Update mode by clicking on record number, which allows faster access to reports that are about to be released.

When a user receives an electronic alert message from USP that a record will be released to the general database, the user can 1) click on the record number; 2) automatically hyperlink to the record in the update mode; and then, 3) check its accuracy and completeness prior to release.

"Reports generated by individual hospitals are visible only to the institution that generates them for the first 60 days they are in the system. This allows the hospital to make changes or updates to the report. You can think of it as being on a clipboard at this point," Cousins explains. "On the 60th day, the report is automatically transferred to the general database where other institutions can then access the report and include it in their searches.

"Recent enhancements to MedMARx have been primarily in infrastructure. In anticipation of becoming the national database for reporting medication errors, we have made changes to improve speed and capability," says Cousins.

Results of the data from the year 2000 will be published around the middle of 2001. During 1999, 6,224 medication errors were reported to MedMARx. Three percent (187) of these resulted in patient harm. Of these, 181 resulted in temporary harm, five in permanent harm, and one in death. The data do not compare the number of errors to the volume of medications dispensed; therefore the incidence is not known. The total volume of medication used per hospital is not captured by the MedMARx program.

The three drugs most frequently involved in medication errors were insulin (151), warfarin (155), and heparin (129). Cousins states that the frequency of errors reported for these agents is likely due to the protocols in which they are used. "Any deviation from these stringent protocols is considered an error and is therefore reported," she says.

Those interested in MedMARx can learn more about the program by calling (877) MedMARx. A free feature demo disk is available upon request, and a free on-line demo is available at www.usp.org/medmarx. ■

SOURCE

- **Diane Cousins**, RPh, Vice President, Practitioner and Product Experience, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852. Telephone: (800) 227-8772.

ISMP issues drug interaction warnings

Heparin, docetaxel, paclitaxel affected

The Institute for Safe Medication Practices (ISMP) has issued two medication safety alerts for pharmacists.

The first involves concomitant use of heparin products. Low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) products provide useful therapy in the treatment and prevention of deep vein thrombosis (DVT) and complications associated with unstable angina (UA) and non-Q-wave myocardial infarction. Since LMWH products have been made available, evidence has emerged that points to lack of safeguards (or lack of adherence) to avoid duplication of heparin products in patients. Three deaths were reported in the past year that support this statement.

In one case, a patient with UA died after receiving a dose of a LMWH in the emergency department, followed by IV heparin and a thrombolytic when he showed signs of having an acute myocardial infarct.

In the second case, a patient with an upper-extremity thrombosis died of intracranial hemorrhage after a physician accidentally prescribed a LMWH and then initiated a protocol for UFH.

A third death involved a hospitalized woman with a history of atrial fibrillation, hypertension, lethargy, and constipation. The consulting cardiologist ordered enoxaparin 60 mg every 12 hours subcutaneously. The next day, warfarin was added to the patient's regimen. Later that week, a gastroenterologist ordered a colonoscopy to rule out colorectal cancer. The warfarin was discontinued and heparin was ordered (5,000 unit bolus and 1,000 units/hour), but the enoxaparin continued to be administered every 12 hours. Additionally, the heparin order was never sent to the pharmacy. Instead, the nurse borrowed a vial of heparin and a premixed solution from another patient in order to give the new patient the heparin bolus and to begin the infusion. Hours later, the patient's aPTT was greater than 90 seconds. The heparin infusion was dropped to 900 units/hour. By morning, the patient's aPTT was still high, her hemoglobin and hematocrit had dropped, and there were signs of internal bleeding. Heparin and enoxaparin were both discontinued, but the patient still died, despite aggressive efforts by the health care team.

The ISMP reminds health care providers that thorough review of a patient's drug regimen is essential for the safe use of heparin products. Physicians, pharmacists, and nurses must consider current and recent pharmacological therapy before ordering, dispensing or administering heparin products. It's important to look back to medications administered in the emergency department for those patients just admitted to the hospital from the ED. One pharmacist reports stickers on the front of charts that state, "Patient on low-molecular-weight heparin" to alert others to this fact.

Computer alerts for duplicate therapy should not be suppressed. Nurses should be reminded of the risks of borrowing medications from another patient's supply. Another safeguard can be the requirement of an independent check by two individuals before administration of heparin products. An independent review of the patient's drug profile and recent lab results further strengthens a safety net. Pharmacists should always ask themselves whether or not it makes sense to give this specific drug to this particular patient. Verifying the drug and the dose without verifying its purpose doesn't help prevent errors.

With the many new drugs approved by the FDA and appearing on the market, including several forms of LMWH, it's often difficult for pharmacists to keep up. One step that pharmacy directors can take to help avoid errors due to unfamiliarity with new drugs is immediate education of pharmacy staff when a new drug is first purchased or added to the formulary. Some hospitals store their new drugs in a prominent place away from the normal stock until pharmacists are familiar with them. Pharmacy managers can also help by supporting pharmacist participation in journal clubs and educational programs. Physicians can help by writing the drug's intended purpose and including both the brand and generic name when ordering drugs new to the institution.

Red flags for Taxotere, Taxol

The second warning from the ISMP is an alert involving docetaxel (Taxotere) and paclitaxel (Taxol). The ISMP reports that the FDA's MedWatch program has identified three types of errors involving these two drugs.

First, look-alike and sound-alike similarities between the brand names have resulted in errors. In one instance, a physician ordered Taxotere 120 mg IV over one hour. The pharmacy dispensed Taxol 120 mg instead. After the dose was administered, a nurse noticed that the label read "paclitaxel" not "Taxotere." This error occurred despite the fact that at least three health care professionals checked the container.

The second type of error noted with these drugs involves reconstitution of Taxotere due to overfill in the drug vial and the enclosed diluent vial. The 20 mg vial of Taxotere actually contains 23.6 mg of drug; the 80 mg vial contains 94.4 mg due to overfill volumes. The final dose of drug in an infusion bag could be more than what was ordered if those reconstituting the drug in the pharmacy use the actual amounts of drug in the vials, rather than the amounts ordered.

Two dosages, same appearance

A third area for concern has been raised by physicians regarding the packaging and labeling of the 30 mg and 100 mg cartons of Taxol. The concern is for potential errors due to similarity in size and look of the two strengths. Formerly, the 30 mg cartons were smaller than the 100 mg cartons. Now, they are the same size and color.

To avoid confusion surrounding Taxotere and Taxol orders, ISMP recommends the following:

- Prescribers should print both the brand and generic names on their orders; the generic names do not look similar.
- Where confusion over handwritten prescriptions remains, pharmacists should confirm the desired drug with physicians.
- When confirmation is made verbally, the drug name should be spelled since the generic names sound similar.
- Prescribers can use preprinted order forms.
- Two pharmacists should independently check the drug before it is dispensed.
- Two nurses should independently verify that the right drug is going to the right patient before the drug is administered.
- To avoid choosing the wrong Taxol container, physically separate the storage of the two doses in the pharmacy.

For regular news from ISMP, visit its web site at www.ismp.org. ■

Product tampering alleged by Amgen

Amgen recently announced three incidents of product tampering. In a letter to health care providers, Amgen states that flip caps from the tops of eight vials from different lots of Epogen (Epoetin alfa) and Neupogen (filgrastim) were detached. The contents of the vials were then removed and replaced with varying amounts of an aqueous solution, then resealed.

None of these vials was used, either because crusty, white material was detected below the caps or because particulate matter was seen in solution. The lots involved were Epogen lots P000839, P000841, and Neupogen 300 mcg lots P000928 and P000698.

Amgen's plea to health care providers about this situation is good advice for pharmacists to

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heed for all injectables: "If you see any evidence of tampering of vials, e.g., vials that appear to have been opened, have white crusty deposits around the stopper, appear to contain discolored or cloudy fluid, particulate matter, volumes less or greater than expected, or if the labels appear worn, DO NOT USE the vials and call the manufacturer."

Amgen's letter to health care providers can be viewed at www.fda.gov/MedWatch/safety/2001/safety01.htm#epogen. ■

Feed your pocket brain

Cut out the attached list and paste it into your pocket brain for those times when patients or colleagues ask you what the criteria are for rheumatoid arthritis. The list below is adapted from the 1987 *Criteria for the Classification of Acute Arthritis of Rheumatoid Arthriti*s. Feel free to add your favorite bits of information to the pocket brain column of *Drug Utilization Review* by sending your information to the editor at ruthnoland@hotmail.com.

• **RA statistics:**

— Rheumatoid arthritis affects 2.1 million Americans, mostly women

— Onset is usually in middle-age, but often occurs in the 20s and 30s

— 1.5 million women have rheumatoid arthritis compared to 600,000 men

From: www.arthritis.org/answers/diseasecenter/ra.asp.

• **Criteria for rheumatoid arthritis:**

— Morning stiffness — in and around the joints, lasting at least one hour before maximal improvement

— Arthritis of three or more joint areas — at least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP (proximal interphalangeal [PIP] joints of the hands), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, and MTP joints.

— Arthritis of hand joints — At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.

— Symmetric arthritis — Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).

— Rheumatoid nodules — Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician.

— Serum rheumatoid factor — Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.

— Radiographic changes — Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

— For classification purposes, a patient is said to have rheumatoid arthritis if he/she has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least six weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is not to be made.

From: Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315—24.

For more information on rheumatoid arthritis, see www.rheumatology.org/research/classification/ra.html. ■

DRUG CRITERIA & OUTCOMES™

Intranasal corticosteroids: A class review

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Introduction:

Intranasal corticosteroids are used to treat and prevent the symptoms of allergic rhinitis. Although typically not a life-threatening disease, the symptoms of allergic rhinitis clearly interrupt daily life activities. Approximately 8% of the population exhibits symptoms of allergic rhinitis.[1]

Intranasal corticosteroids modulate allergic rhinitis symptoms in both the early and late stages of inflammatory response to an allergen; the agents block the synthesis and release of inflammatory mediators (e.g., histamine, kinin, leukotriene, prostaglandin) involved in the early response phase. During the late response phase, intranasal corticosteroids decrease epithelial permeability, decrease inflammatory mediator production, decrease the secretory response to the allergen, and decrease the number of inflammatory cells (e.g., basophils, neutrophils, eosinophils) that migrate into the nasal mucosa.[2,3]

The intranasal corticosteroids approved by the U.S. Food and Drug Administration for the treatment and prevention of allergic rhinitis are flunisolide (Nasalide, Nasarel; Dura), beclomethasone dipropionate (Beconase, Beconase AQ; GlaxoSmithKline; Vancenase, Vancenase Pockethaler, Vancenase AQ 84 µg; Schering-Plough), triamcinolone acetonide (Nasacort, Nasacort AQ; Aventis; Tri-Nasal; Muro), budesonide (Rhinocort, Rhinocort Aqua; AstraZeneca), fluticasone propionate (Flonase; GlaxoSmithKline), and mometasone furoate monohydrate (Nasonex, Schering-Plough).[4,5,6]

Pharmacokinetics:

Absorption: Lipid solubility determines the rapidity of absorption of an agent by the nasal mucosa. As lipophilicity increases, the rate of absorption increases. In addition to changes in absorption, increased lipophilicity for intranasal corticosteroids appears to increase retention in the nasal mucosa, produces greater ability to reach glucocorticoid receptors, and allows increased length of binding to glucocorticoid receptors. From highest to lowest, the ranked order of lipid solubility for intranasal corticosteroids is mometasone furoate, fluticasone propionate, beclomethasone diproprionate, budesonide, triamcinolone acetonide, and flunisolide. Intranasal corticosteroids can be absorbed and enter the systemic circulation via the nasal and gastrointestinal system.[7]

Approximately 80% of the intranasal corticosteroid dose is swallowed after administration. The corticosteroid passes through the gastrointestinal system and is subsequently absorbed. No information is available on nasal absorption of intranasal corticosteroids from the nasal mucosa.[3] The systemic bioavailabilities of each intranasal corticosteroid via the gastrointestinal system is as follows:[8]

- beclomethasone dipropionate, 17%;
- budesonide, 11%;
- flunisolide, 20-50%;
- fluticasone propionate, < 2%;
- mometasone furoate, < 0.1%;
- triamcinolone acetonide, 22%.

One factor that may potentially interfere with the absorption of the intranasal corticosteroid in the nasal mucosa is nasal congestion. Two

suggestions to clear the nasal blockage are to blow the nose or administer a topical nasal decongestant five to ten minutes prior to administering the intranasal corticosteroid, although use of topical nasal decongestants is controversial.[4]

Distribution: Distribution of intranasal corticosteroids within areas of the body has not been described.[9,10]

Metabolism: Intranasal corticosteroids are metabolized in the liver. In addition to liver metabolism, beclomethasone dipropionate is metabolized in the lungs and triamcinolone acetonide is metabolized in the kidneys.[4,5,10]

Elimination: Beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide are renally excreted. In addition to urinary excretion, beclomethasone dipropionate and fluticasone also exhibit fecal elimination. Mometasone furoate is eliminated primarily via the bile and, to some extent, in the urine.[4,10]

Potency: Intranasal corticosteroids with greater lipophilicity are more potent. From highest to lowest, the ranked order of potency is mometasone furoate, fluticasone propionate, budesonide, and triamcinolone acetonide. The potency ranked order corresponds with the ranked order for lipophilicity.[8] However, potency is not directly related to clinical efficacy or effectiveness.

Onset of action: Each intranasal corticosteroid has a different onset of action. The onsets of action range from 12 hours to days. Patients can receive some symptom relief within a matter of hours with certain intranasal corticosteroids, but to attain maximum relief, patients should use the intranasal corticosteroids for several days.[4,8] The onset of action of each intranasal corticosteroid is as follows:[8]

- beclomethasone dipropionate, within three days;
- budesonide, within 24 hours, but generally a few days;
- flunisolide, four to seven days;
- fluticasone propionate, 12 hours to several days;
- mometasone furoate, median 35.9 hours, but can begin within 12 hours;
- triamcinolone acetonide, as early as 24 hours, but seven days for maximum benefit.

Efficacy: Lumry[8] found no clinically significant difference in efficacy between the different intranasal corticosteroids. All of the available agents were shown to be effective in reducing nasal blockage or congestion, nasal itching, sneezing, and rhinorrhea. Even though the intranasal corticosteroids appear to be equal in efficacy, some of the agents require more per-nasal administrations than others because of differences in lipophilicity and potency profiles.

Several clinical studies have compared different intranasal corticosteroids, but no single trial is available comparing all the intranasal corticosteroids as a group. Results of several clinical studies comparing clinical efficacy between a variety of the agents are shown here.[8]

Efficacy in seasonal allergic rhinitis:

Fluticasone propionate (200 mg / day) =

- beclomethasone dipropionate (336-400 µg / day);
- flunisolide (200 µg / day);
- triamcinolone acetonide (220 µg / day);
- budesonide (128 µg / day);
- mometasone furoate (200 µg / day)[3];
- beclomethasone dipropionate (200 µg BID or 400 µg / day).

Efficacy in prophylaxis for seasonal allergic rhinitis (administered for eight weeks):

Mometasone furoate (200 µg / day) =

- beclomethasone dipropionate (168 µg BID).

Efficacy in perennial rhinitis:

Fluticasone propionate (200 µg / day)[3] ≥ beclomethasone dipropionate (200 µg BID);

Mometasone furoate (200 µg / day) =

- beclomethasone dipropionate (200 µg BID);
- fluticasone propionate (200 µg / day).

Dosing:

Dosing is variable for the agents; refer to specific product monographs for dosing guidelines.

Formulation:

Some of the intranasal corticosteroids are available in different formulations: aqueous or aerosolized (dry). The intranasal corticosteroids available in an aqueous formulation are Beconase AQ, Vancenase AQ 84 µg, Nasalide, Nasarel, Nasacort AQ, Tri-Nasal, Nasonex, Rhinocort Aqua, and Flonase. Intranasal corticosteroids available in the aerosolized formulation are Beconase, Vancenase Pockethaler, Nasacort, and Rhinocort.[4,6,11] Nasal irritation is more often associated with aerosolized formulations, possibly due to spray volume or force or propellant.[12] All of the aqueous formulations contain benzalkonium chloride as a propellant, except for Nasonex, Rhinocort Aqua, and Rhinocort.[8,11]

Drug interactions:

Drug interactions have not been reported with intranasal corticosteroids. Caution should still be exerted when administrating intranasal corticosteroids with other medications because intranasal corticosteroids can be systemically absorbed.[4,13]

Pregnancy and lactation:

All the intranasal corticosteroids are pregnancy category C. No data are available to indicate whether intranasal corticosteroids are excreted in breast milk with the exception of budesonide. Budesonide is considered safe for breast-feeding mothers.[5,10,14]

Adverse effects:

Common adverse effects of intranasal corticosteroids are nasal irritation, nasal dryness, nasal burning, sneezing, and epistaxis.[4] A potential concern with chronic use of intranasal corticosteroids is the effect of the agents on mucosal histology. However, studies with budesonide, fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, and mometasone furoate did not indicate histologic changes in the nasal mucosa after long-term use.[7,8,15] One long-term study of mometasone furoate suggested that mometasone furoate could potentially reverse some allergy-related histologic changes in the nasal mucosa because of reduction in the extent of inflammatory cell migration into the nasal mucosa.[8] Even though clinical studies indicate no nasal mucosal changes with long-term administration of intranasal corticosteroids, patients on long-term therapy should still have periodic examinations of the nasal mucosa.[15]

Another possible concern with administration of intranasal corticosteroids is hypothalamic-pituitary adrenal (HPA) axis suppression. Several studies in adults evaluating the potential of intranasal corticosteroids to produce HPA axis suppression indicated no overall clinically significant effect. A 5.5 year-long study evaluating the long-term safety of budesonide found no HPA axis suppression. Doses of 200 µg / day and 400 µg / day were evaluated in the study.[16] A four-week study with fluticasone propionate at 200 µg / day and 400 µg / day twice a day found no HPA axis suppression when compared to placebo, but the 400 µg twice a day dose did result in reduced morning plasma cortisol concentrations.[17] Other clinical studies have evaluated intranasal corticosteroid effect on the HPA axis; results were conflicting. Some evaluations reported reduced cortisol concentrations and others did not. The two main factors that appear to contribute to development of HPA axis suppression are dose and duration of treatment.[18]

Conflicting data are also present regarding possible effects of intranasal corticosteroids on growth velocity and the HPA axis in children. Skoner et al[19] evaluated the effect of beclomethasone dipropionate (BDP) on growth velocity in children ages six to nine years old for one year. The dose evaluated was 168 µg twice a day. Results of the study indicated that children who used BDP had a decrease in growth rate when compared to the placebo group, but no difference in cortisol levels were observed for the subjects in either group. Meltzer et al[20] performed a dosing range study with mometasone furoate in children ranging from five to eleven years old over a four-week period. Doses of 25 µg, 100 µg, and 200 µg were evaluated, as well as 168 µg / day of BDP. No significant changes in HPA axis function were found after four weeks of treatment in 130 patients.[20] No information is available to determine the possible effect of intranasal corticosteroids on final growth height in children.[19]

Less common adverse effects of intranasal corticosteroids are *Candida* infections and septal perforations. Septal perforations can occur when patients direct the spray towards the septum rather than the inferior turbinate.[7]

Cataract development has been associated with both inhaled and oral corticosteroids. The Blue Mountain Eyes Study, reported in the *New England Journal of Medicine* in 1997, did not find a definite cause and effect relationship between inhaled corticosteroids and cataract development, but the investigators indicated that an association does appear to exist.[21] Chylac,[22] in an accompanying editorial, commented that the risk of posterior subcapsular cataract development associated with intranasal corticosteroid use may actually have been underestimated by the design of the Blue Mountain study. Additionally, the potential development of ocular adverse events has not been established for each corticosteroid; therefore, no data exist regarding risks with each individual agent.[23]

Oral antihistamines comparison:

Weiner et al[24] reviewed available clinical trials comparing intranasal corticosteroids to oral

antihistamines in allergic rhinitis. Included in the evaluation were beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. The results of the meta-analysis of 16 randomized, controlled trials indicated that intranasal corticosteroids were more effective than oral antihistamines in relieving nasal blockage, nasal discharge, nasal itch, and postnasal drip.

Stempel and Thomas[25] evaluated 13 randomized, double-blind clinical trials comparing intranasal corticosteroids and oral nonsedating antihistamines. The intranasal corticosteroids evaluated were beclomethasone dipropionate, budesonide, fluticasone propionate, flunisolide, mometasone acetonide, and triamcinolone acetonide. Results indicated that intranasal corticosteroids were statistically superior to oral nonsedating antihistamines for relieving stuffy nose and improving overall nasal symptoms.

Leukotriene receptor antagonist comparison;

Pullerits et al[26] compared beclomethasone dipropionate to zafirlukast (Accolate), the leukotriene receptor antagonist. The purpose of the study was to determine if zafirlukast could attenuate the symptoms of allergic rhinitis by antagonizing leukotriene effects in the nasal mucosa. Zafirlukast was not shown to provide benefit with symptoms of sneezing, rhinorrhea, nasal itch, or nasal blockage, while beclomethasone showed statistically significant symptom improvement of nasal symptoms by day 20 of the 50-day trial (zafirlukast is not indicated in the treatment or prevention of allergic rhinitis).

Intranasal cromolyn sodium comparison:

Bousquet et al[27] compared fluticasone propionate to disodium cromoglycate (i.e., cromolyn sodium) in the prevention of allergic rhinitis symptoms. Cromolyn sodium (Nasalcrom) is indicated in the treatment and prevention of symptoms of allergic rhinitis. Fluticasone propionate showed greater improvement in preventing nasal blockage, nasal discharge, sneezing, and nasal itch when compared to cromolyn sodium. Compliance was evaluated in the study, since cromolyn sodium requires four times a day administration, but the difference in compliance between the two treatments groups was not statistically significant.

Intranasal antihistamine comparison:

Berlin et al[28] compared flunisolide (Nasarel) to azelastine (Astelin) to determine effectiveness in controlling allergic rhinitis symptoms. The results indicated that flunisolide was more effective in controlling symptoms of nasal congestion and sneezing, while azelastine was more effective in controlling symptoms of rhinorrhea.

Cost:

In general, the intranasal corticosteroids range in cost from $30-$50/month, based on the average wholesale price (AWP). AWP for each of the intranasal corticosteroids available on the market is show below:[29]

- Nasarel 25 mL = $43.51;
- Nasalide 25 mL = $45.59;
- Beconase 16.8 g = $46.14;
- Beconase AQ 25 g = $47.32;
- Vancenase 16.8 g = $44.74;
- Vancenase AQ 84 µg, 19 g = $57.52;
- Vancenase Pockethaler 7 g = $47.15;
- Nasacort 10 g = $45.82;
- Nasacort AQ 16.5 g = $44.46;
- Tri-Nasal 15 mL = $31.75;
- Rhinocort Aqua 5 mL = $48.00;
- Rhinocort 7 g = $39.50;
- Flonase 16 g = $56.03;
- Nasonex 17 g = $54.76;

Conclusion:

Allergic rhinitis can cause a decrease in productivity and absenteeism from work or school because of the significant symptomatology associated with the disease.[25] Intranasal corticosteroids have been shown to provide symptomatic control (e.g., nasal blockage, rhinorrhea, itching), as well as modifying the underlying disease process. No difference exists in effectiveness between the different intranasal corticosteroids. As a result, cost, convenience of administration, and age indication can help provide a basis for formulary decisions.

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Review: Budesonide inhalation suspension

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Introduction:

Inhaled corticosteroids are commonly used as anti-inflammatory agents to help prevent recurrent asthma exacerbations. The 1997 National Heart, Lung and Blood Institute (NHLBI) guidelines recommend their use in many patients with mild persistent, moderate persistent, and severe persistent asthma. Corticosteroids are generally considered to be the most potent long-term "controller" asthma medications available.

Inhaled corticosteroids needed

By reducing inflammation, current research indicates that reduction / prevention of airway tissue remodeling may be possible. Airway remodeling has been associated with the chronic symptoms that are commonly linked to this disease.[1] The lack of a nebulizable corticosteroid has complicated the treatment of persistent asthma in young children and infants who are unable to properly manipulate metered-dose-inhalers (MDIs).

Previous corticosteroid treatment for children included inhaled corticosteroids via MDI delivery, with the MDIs fitted with a spacer / holding chamber to improve drug delivery. If control was not achieved through this method, then systemic corticosteroids were considered.[2] Although nebulized cromolyn sodium has been

shown to be an effective alternative for infants and young children with persistent asthma, in many cases, this agent lacks the efficacy provided by corticosteroids.[1]

The Food and Drug Administration (FDA) has recently approved budesonide inhalation suspension (Pulmicort Respules) by AstraZeneca Pharmaceuticals. The budesonide active ingredient is identical to the Pulmicort Turbuhaler, save for the delivery system. Thus, budesonide is now available as the only corticosteroid for nebulization, for use in air-driven jet nebulizers. When administered on a regular basis, Pulmicort Respules have been shown to improve lung function, decrease asthma symptoms, and reduce the use of as-needed inhaled beta-agonists.[2]

Indications:

Budesonide inhalation suspension (Pulmicort Respules), approved by the FDA in August 2000, is the first and only nebulizable corticosteroid. The agent is indicated for the maintenance treatment of asthma and as prophylactic therapy in children ages 12 months to 8 years.

Clinical pharmacology:

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. Corticosteroids have been shown to exhibit a wide range of inhibitory activities against multiple cell types (mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and nonallergic mediated inflammation. The anti-inflammatory effects of corticosteroids are thought to provide efficacy in the treatment of asthma. Studies have shown a favorable ratio between the topical anti-inflammatory activities and systemic corticosteroid effects in asthmatic patients for budesonide at a wide range of doses. This effect is likely due to the high local anti-inflammatory effects, 85-95% first pass metabolism of orally absorbed drug, and low potency of metabolites.[2]

Pharmacokinetics:

Absorption: In asthmatic children 4 to 6 years of age, the total absolute bioavailability (lung and oral) of Pulmicort Respules following nebulization via jet nebulizer was approximately 6% of the labeled dose.

Distribution: In asthmatic children 4 to 6 years of age, the volume of distribution at steady-state was 3 L / kg, approximately the same as that for healthy adults. Budesonide is 85-90% bound to plasma proteins, which is constant over concentration ranges from 1-100nmol / L. Budesonide shows little or no binding to corticosteroid-binding globulin.

Metabolism: In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized by the Cytochrome P450 3A isoenzyme to two major metabolites. The corticosteroid activity of each metabolite is less than 1% of that for the parent drug. Reduced liver function may affect the metabolism of budesonide.

Excretion: Budesonide is excreted in the urine and feces as the inactive metabolites.[2]

Clinical trials:

Three randomized, double-blind, placebo-controlled parallel group U.S. clinical trials of 12 weeks duration each were conducted in 1,018 pediatric patients ages 6 months to 8 years. Patients had persistent asthma with varying severity and disease duration. Doses of 0.25 mg, 0.5 mg, and 1 mg administered either once or twice daily by face mask or mouthpiece were compared to placebo to determine the appropriate dosing over a range of asthma severity. Among the primary endpoints were daytime and nighttime symptoms. Compared to placebo, treatment with Pulmicort Respules significantly decreased both daytime and nighttime symptoms scores ($P < 0.05$) at doses of 0.25 mg once daily (in one study), 0.25 mg twice daily, and at 0.5 mg twice daily. The agent significantly decreased either daytime or nighttime symptoms scores, but not both, at doses of 0.5 mg once daily and 1 mg once daily ($P < 0.05$). Pulmicort Respules significantly reduced the need for bronchodilator therapy in all of the study doses ($P < 0.014$-$P < 0.038$). In one of the studies, significant improvements were seen in FEV1 at doses of 0.5 mg once daily ($P < 0.044$) and 1 mg once daily ($P < 0.033$), and at doses of 0.5 mg twice daily ($P < 0.043$) in another study. Morning PEF was significantly improved in patients receiving Pulmicort Respules 0.25 mg once daily ($P < 0.03$; one study), 0.25 mg twice daily and 0.5 mg twice daily ($P < 0.03$).[3-5]

Dosage:

The recommended starting dose of Pulmicort

Respules, when previous therapy was a bronchodilator alone, is 0.5 mg total daily dose, administered once or twice daily. The highest recommended dose for these patients is 0.5 mg/day. When previous therapy consisted of inhaled corticosteroids, the recommended starting dose of Pulmicort Respules is 0.5 mg total daily dose, given once or twice daily. The highest recommended dose in this case is 1 mg/day. For those whose previous therapy consisted of oral corticosteroids, the recommended starting dose of Pulmicort Respules is 1 mg total daily dose, administered once or twice daily. The highest recommended dose in this case is 1 mg/day.

Administration:

As noted above, the agent is administered (five to 10 minutes per treatment) via a jet nebulizer (not for use in ultrasonic nebulizer). The Pari-LC-Jet Plus nebulizer and Pari Master compressor were effective in clinical trials when used with a facemask or mouthpiece. Initial improvement is typically seen within two to eight days, although the maximum benefit may take as long as four to six weeks. Pulmicort should be titrated to the lowest effective dose to avoid adverse effects. Gradual reduction of systemic corticosteroids may begin after one week of Pulmicort Respules therapy.

Adverse reactions:

The incidence and type of adverse events for Pulmicort Respules reported in clinical trials were comparable to those for placebo. At total daily doses of 0.25 mg, 0.5 mg, 1 mg, and placebo, adverse events were: respiratory infections 34-38%, rhinitis 7-12%, cough 5-9%, otitis media 9-12%, viral infection 3-5%, gastroenteritis 4-5%, ear infection 2-5%, and epistaxis 1-4%. Oral and oropharyngeal fungal infections occurred in 2-4% of the patients.

Contraindications:

Pulmicort Respules are contraindicated as primary treatment for status asthmaticus and for other acute episodes of asthma. The agent is also contraindicated if the patient has a history of hypersensitivity to budesonide or other components of the product.

Warnings:

Caution is advised when switching patients from systemic corticosteroid therapy to inhaled corticosteroids; hypothalamic-pituitary-adrenal (HPA) axis suppression should be monitored. Exposure to corticosteroid therapy may increase patients' susceptibility to infections. Avoid eye exposure when using a facemask, as localized exposure to corticosteroids has been associated with cataract formation. Also, rinsing[2] the face after treatments by facemask helps to prevent irritation which may be caused by the drug, solvents and, or propellants. The patient should rinse the mouth after each budesonide treatment to minimize the risk for fungal infection. Budesonide is a category C prescription. Potential risks and benefits to mother and fetus should be considered before use during pregnancy.

Drug interactions:

Coadministration with ketoconazole may cause increased budesonide plasma levels. As budesonide is a cytochrome P450 3A isoenzyme substrate, the agent has the potential for other drug interactions, especially with drugs which induce and, or inhibit this isoenzyme. However, further data is needed to determine if any drug interactions will be clinically significant, in that the agent is administered by nebulization and systemic absorption is somewhat decreased. The effect of mixing Pulmicort Respules with other medications has not been adequately studied. Currently, Pulmicort Respules should be administered separately from nebulized drugs. Limited data suggest that no increased frequency of adverse events or change in efficacy when budesonide is mixed with either ipratropium (Atrovent) by nebulization or with nebulized albuterol.[6]

Availability:

Pulmicort Respules are available in two strengths: 0.25 mg/2 mL and 0.5 mg/2 mL.

Packaging:

The product comes six aluminum foil envelopes per carton, five single dose Pulmicort Respules per envelope, each containing 2 mL of budesonide suspension (30 total doses).

Storage:

Unused Pulmicort Respules should be kept in the foil envelope to avoid light exposure. Once the aluminum foil has been opened, remaining Pulmicort Respules should be used within two weeks of opening the foil envelope. Store at room temperature.[2]

Cost:

The associated wholesale price (AWP) of both strengths of Pulmicort Respules, per carton of 30 doses, is $126.[6]

Summary:

Based on the available clinical trials required for FDA approval, Pulmicort Respules appear to provide safe and effective treatment for children and infants with non-steroid dependent and steroid-dependent persistent asthma when administered by jet nebulization with either facemask or mouthpiece. Daily dosing is an important option to be considered.[2]

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IN THE PIPELINE

Access Pharmaceuticals Inc. has completed a 400-patient study and the initial results of that trial evaluating OraDisc, the **new formulation of amlexanox** in a polymer disc that adheres to the disease site in the treatment of established canker sores. OraDisc achieved statistical significance over both placebo and no treatment by accelerating healing to Day 5 (the primary clinical endpoint).

Bristol-Myers Squibb reports disappointing results from the first of two Phase III trials for its **neuroprotective agent** BMS-204352 (MaxiPost). The investigational potassium channel agonist showed no significant benefit over placebo for efficacy, safety, or tolerability. A second Phase III trial is scheduled for completion by the middle of 2001, at which time the company says it will have more information about the product.

Millenium Pharmaceuticals has begun a Phase II trial of LDP-02 for **ulcerative colitis**. LDP-02 is a humanized monoclonal antibody under investigation for the treatment of inflammatory bowel diseases, including ulcerative colitis and Crohn's disease.

Clinical studies of Pfizer's **non-nucleoside reverse transcriptase inhibitor** capravirine (formerly AG1549) have been stopped due to toxicity issues (specifically vasculitis in animals). This is expected to delay possible entry of the drug by more than a year. ■

New FDA Approvals

Antifungal caspofungin acetate (Cancidas) for injection by Merck & Co. Caspofungin, an echinocandin or glucan synthesis inhibitor, is an antifungal for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and / or itraconazole).

Snakebite treatment crotalidae polyvalent immune fab-ovine (CroFab) by Savage Laboratories. CroFab has been approved for management of patients with minimal or moderate North American crotalid envenomation. It is a safe option for victims of venomous snakebites from most crotalids (including rattlesnakes, cottonmouths, copperheads, and water moccasins). CroFab should be administered by IV as soon as possible (within six hours) following a poisonous snakebite in patients who develop signs of progressive envenomation. ■