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Pharmaceutical Care Across the Continuum

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Empowered pharmacists make drug monitoring a top priority

Drug monitoring is all the rage in health care today, with the intense focus on patient safety and avoiding medication errors. But are pharmacists fully equipped and empowered to perform drug monitoring for their patients in the way that will bring about the greatest benefit?

John Wodtke, PharmD, MS, a member of the drug information team at Advanced Response Management, sees areas for improvement in the education and work environment of pharmacists before they can initiate those best efforts for patients.

"We have to start with how we define monitoring and the many facets of patient care that fall under that umbrella," Wodtke tells *Drug Utilization Review.* "Drug monitoring, to me, is the process by which we help ensure the intended outcomes of drug therapy are reached while minimizing the known side effects of the drug. This, of course, involves making sure the right drug in the right dose is given to the right patient at the right time.

"When we say the patient must get the right drug, it doesn't mean simply making sure there's not a mix-up so that something other than the intended drug is given," says Wodtke, who was a clinical hospital pharmacist earlier in his career and then assistant director of pharmacy for a large urban hospital. "This also means using our cognitive skills and checking the drug against the intended indication and the specific patient history and physical characteristics."

Saying the patient must get the right dose doesn't simply mean checking the milligram strength on the capsule against that on the medication administration record (MAR), although it does include this step. It also means, Wodtke says, using pharmacokinetic fundamentals and applying them to specific patients to ensure that the strength of the drug ordered and written in the MAR is appropriate for this patient.

"When we say the patient must get the drug at the right time, this doesn't refer simply to morning vs. evening," Wodtke adds. "We must also consider when the drug is given in coordination with food, when that's important, and when it's given in coordination with other drugs and vitamins with which it might bind and have undesirable effects. All of these steps are steps that we hear nearly from day one of pharmacy

school. They are simple words, but absolutely necessary in helping achieve successful patient care. They are a part of the monitoring that must occur in order to help ensure the desired outcomes from drug therapy, but they are by no means all that is involved in monitoring."

Drug monitoring also involves evaluating drug levels in the patient's body, checking for potential drug-drug interactions, watching the patient and the patient's labs for signs of adverse events, and assessing patient compliance as well as patient understanding of the drug, Wodtke says.

"For drugs with a narrow therapeutic index such as phenytoin, digoxin, and aminoglycosides, it's important to monitor the drug concentration in the patient," says Wodtke.

Where it's not possible or convenient to measure the drug level directly, it's important to measure surrogate markers, he says. "Pharmacists need to evaluate INR levels in patients on warfarin, and aPTT levels in patients on heparin."

For patients on antihypertensives, for example, the patient's blood pressure should be monitored. In patients being treated for infections, patient temperature needs to be monitored.

"Checking for potential drug-drug interactions is important for every patient who is on more than one drug. Drugs that should be included in assessing for potential interactions include those that are available by prescription only, those available over-the-counter, and herbal or diet supplements," says Wodtke. Also, drugs that the patient may not receive continuously but that are included in the standing PRN orders should be evaluated for interactions.

Figure supplements into the equation

"There's a large gap for many pharmacists in their knowledge of herbal supplements," Wodtke notes. "The body of available knowledge itself is not well-defined and has gaps of its own, and many side effects and interactions remain unknown because those studies aren't required for supplements. However, the information for herbal medication is growing rapidly. Drugs with a narrow therapeutic index do have some data with herbal supplements, and some key interactions have been found. But there remains a big gap in what pharmacists know about these interactions. These herbal products are not inert. The potential for interactions is very real. Pharmacists can help fill the knowledge gap by reporting any interactions observed between herbs and drugs.

"Adverse events form an important part of monitoring," Wodtke continues. "Any medication can result in an adverse drug event. However, some medications require special monitoring or dose titration to get the desired therapeutic effect while minimizing adverse events. Certain drugs can alert pharmacy staff to the occurrence of adverse events. For instance, a stat diphenhydramine or a one-time methylprednisolone or oral vancomycin dose can signal a potential adverse event. Many pharmacies print out these special orders and require pharmacist follow-up within 24 hours of drug administration."

Often adverse events are brought to the attention of pharmacists by the nursing staff. Pharmacy's relationship with nursing is important for many reasons. Detecting and reporting adverse events is one of them, Wodtke adds.

At one institution described by Wodtke, the floor pharmacists hold monthly meetings with the floor nurses. In these meetings, pharmacists alert nurses to potential side effects of medications that patients on the floor are being given. For example, on an oncology floor where Compazine is given to combat nausea, the nurses are alerted to the potential of extraparamidal effects in their patients, and the adverse events are more likely to be reported.

Wanted: Better reporting and more of it

"Pharmacists have to prioritize their work," notes Wodtke. "All serious adverse events have to be reported. Many events are reported internally and go to the P&T committee, but are never reported externally to the drug manufacturer or to MedWatch. It's critical to Phase IV drug

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surveillance that serious adverse events be reported to drug manufacturers or to MedWatch. It's the accumulation of reports of adverse events that can bring about a change in drug labeling or even initiate a drug recall.

Pharmacists end up having to use their judgment in reporting less serious events. For example, itching from morphine probably often goes unreported since it's an expected side effect and most patients on morphine have standing PRN orders for diphenhydramine.

"Patient understanding of drugs is largely dependent on the counseling they receive from pharmacists," says Wodtke. "In counseling patients, pharmacists need to remember to ask open-ended questions. Minimize the opportunity for 'yes' or 'no' answers. By the end of a counseling session, the patient should be able to tell the pharmacist what each drug he or she is taking is and what it is for. The patient should be able to tell the pharmacist how he'll take the drug, where and how it will be stored, if and when it can be refilled, and which side effects he should self-monitor for."

Pharmacists should be provided time to perform discharge counseling with patients, Wodtke says. One institution he describes has a warfarin counseling program for which the pharmacy department created a standard warfarin information sheet. Pharmacists then counseled patients discharged on warfarin. Warfarin is the primary topic of discussion, but the pharmacists hold the patient's entire drug list in hand and discuss every part of the drug regimen. The pharmacists then are sure to document the discharge counseling activity in the patient chart. The pharmacy department follows up one week after discharge and asks specific questions about the warfarin therapy — such as the dose to be taken, and side effects — to assess patient understanding and retention.

"This hospital chose warfarin, but one or more of the other drugs with a narrow therapeutic index can be targeted in order to benefit patients and help document and prove the important role pharmacists play in effective drug therapy and patient safety," Wodtke says.

Drug recall is symptom of faulty system

The recent recall of alosetron (Lotronex) serves as a good example of the need for effective patient counseling, self-monitoring, and reporting of adverse events.

Is alosetron's fate a call to action?

The recent recall of alosetron (Lotronex) by Glaxo has spurred the American Pharmaceutical Association (APhA) to say it should be a call to action for consumers, pharmacists, and other health care professionals to consider and use medications more carefully. According to APhA, alosetron represents the third prescription medication to be recalled this year, and the sixth drug withdrawn from the market in the past two years due to adverse side effects. APhA states that written patient information alone, while helpful, is not sufficient to fully educate patients. Patient counseling that comes directly from a trained pharmacist is more effective in educating patients about their drugs. ■

"It's impossible to know the exact number of side effect occurrences, ischemic colitis or otherwise, associated with alosetron . . . or any drug for that matter," Wodtke says. "But had more patients been counseled completely to the point of full understanding of their drug with alosetron, it may well be that adverse events would have been reported earlier and the eventual recall of alosetron would have come sooner."

As pharmacists counsel patients about their drugs, they should also encourage patients to report any adverse events to their physicians or pharmacists, according to Wodtke. He also points out that patients can report their own adverse events directly to drug manufacturers or to MedWatch.

"Tracking susceptible organisms within an institution also falls under the umbrella of monitoring," Wodtke says. "For example, a pharmacist may be caring for a patient with *Pseudomonas* infection. The pharmacist gets involved typically because the physician writes an order for an aminoglycoside. The pharmacist may think this will be a simple case of aminoglycoside monitoring and kinetics. The reality is that the pharmacist also needs to monitor continued cultures and sensitivities, then evaluate whether or not the specific aminoglycoside is the one this patient should receive.

Pharmacists, along with their infectious disease committees, must follow organisms within their institutions over time due to the inevitable development of resistance. Protocols and antibiotics of choice have to change on occasion due to

SOURCE

- **John Wodtke**, PharmD, MS, Advanced Response Management, 8717 W. 110th St., Suite 240, Overland Park, KS 66210. E-mail: info@askarm.com.

institution-specific resistance trends."

Making it possible for hospital pharmacists to fit monitoring into their already full schedules is a long-standing problem with no easy solution.

"Pharmacists try to increase time spent in patient care, yet we're also still trying to convince payers to reimburse us for cognitive services, and that effort alone takes huge amounts of our time just in documentation," Wodtke says. "However, there are some efforts that we can make now to allow pharmacists more time to spend on patient care and safety. Minimizing the distributive role of the pharmacist by using technology to its fullest is one step. Pyxis stations and robotics, for example, can reduce the demand on the pharmacist for distribution. Giving technicians more training and responsibility can also help. While we're spending time with documentation and talking to payers about reimbursement, we can also dovetail on those efforts by working on convincing the same payers that we have a significant role in patient care and safety. Pharmacists want to be reimbursed not just for cognitive services, but also because we can contribute significantly to patient safety. Therefore, document, document, document!

"There are several ways that institutions target drugs or patients to be monitored," says Wodtke. "Some make that decision based on which unit a patient is in. What I have seen a lot is that, because of the current shortage of pharmacists, institutions perform drug monitoring based on specific target drug therapies. Drugs that have potential serious side effects, drugs with a narrow therapeutic index, and drugs that are expensive usually top the list of those that are monitored."

Three steps to better monitoring

According to Wodtke, there are several steps pharmacy directors can take to better enable pharmacists to perform monitoring.

1. Time. "More time is paramount, of course, but things that might be a little easier to provide include decentralized, bedside access to patient charts and lab data. Electronic patient charts that include long-term patient history from previous admissions and/or doctor visits may be expensive, but they are very effective in smooth patient care.

2. CE. "Continuing education is a must. Pharmacists must know precisely what they're doing. Experience and repetition are invaluable, but pharmacists must continue to educate themselves and not become complacent. The ability and access to use computers to their fullest extent will help. Even a simple calculator is a great tool in drug monitoring," Wodtke says.

3. Peer support. "We should never overlook our peers. The old adage that 'two heads are better than one' certainly applies in pharmacy. It goes both ways, too. We should feel free to ask a colleague for his/her opinion or to double-check our calculations, but we should also be willing to do the same for others when asked.

"There are unlimited opportunities for pharmacists to provide effective intervention on behalf of patients by monitoring. Time, however, is not unlimited. Pharmacy directors can work together with their pharmacy teams to determine the methods that can be implemented in their institutions to give pharmacists more time to spend in patient care and effective monitoring. The goal is patient safety. Proactive steps toward that goal by everyone at all levels of pharmacy will be required to get closer to achieving the goal."

(Editor's note: Results from a survey by the American Society of Health-System Pharmacists (ASHP), the *2000 ASHP National Survey of Pharmacy Practice in Acute Care*, cover pharmacists' role in patient wellness activities, including monitoring. The survey can be found in the Dec. 1, 2000, issue of the *American Journal of Health-System Pharmacy*. A summary report containing graphs and charts of the survey data may be obtained from Eli Lilly by calling (800) 874-2778.) ■

Research grants promote patient safety research

The National Patient Safety Foundation (NPSF) has announced winners of its 2000 NPSF Research Awards. Four grants, worth up to $100,000, were awarded for projects focused on patient safety. The objective of NPSF is to "promote preventable injuries in health care and the adverse consequences to patients that may result." For more information, visit www.npsf.org. ■

Shortage of pharmacists is a long-term problem

Based on results of a report on the national pharmacy work force shortage recently released to Congress, the American Society of Health-System Pharmacists (ASHP) is calling for new federal funds and incentives to help fill the void.

William A. Zellmer, deputy executive vice president of ASHP, notes that this shortage prohibits patients from receiving the fullest quality of care that they need and that pharmacists are trained to provide.

"This imbalance in the supply and demand of pharmacists is a long-term issue. As such, it requires long-term solutions," Zellmer tells *Drug Utilization Review*.

Government should step up to the plate

One part of the solution, as posed by ASHP, is federal funds to encourage colleges of pharmacy to expand enrollment. "The model exists for this endeavor," says Zellmer. "We saw it done as part of a capitation program in the '70s. Once incentive is in place, existing colleges of pharmacy can expand their infrastructures. That includes increasing the number of clinical faculty and practice sites."

As this growth occurs, enrollment can also increase.

"The shortage of pharmacists is very clearly related to the quality of health care patients receive," Zellmer says.

The broad-reaching effect on patient care and safety is what Zellmer expects will spur federal funding. "Additional funding needs to go toward post-graduate training of pharmacists, too," Zellmer asserts. "Hospitals are increasingly asking for pharmacists with residency training. We need to increase the number of available residency programs in order to try to keep up with the demand for residency graduates."

SOURCE

- **William A. Zellmer**, Deputy Executive Vice President, American Society of Health-System Pharmacists, 7272 Wisconsin Ave., Bethesda, MD 20814. Telephone (301) 657-3000.

"We're still too focused on the mechanical aspects of pharmacy," Zellmer tells *DUR*. "Instead, pharmacists need to focus on their clinical skills. The more we can use automation and technicians to perform distributive tasks, the more pharmacists can be freed to focus on specific patient care aspects. Without standardized training for technicians, pharmacists remain reluctant to turn dispensing responsibilities over to the technicians. Therefore, we also need to rethink the training and roles of technicians."

The shortage of pharmacists is a multifaceted problem requiring solutions from all angles. "It's time to start getting serious about providing and implementing the solutions," says Zellmer. ■

Hotline set up for pharmacists in crisis

Addresses devastating impact of med errors

The American Society of Health-System Pharmacists is partnering with the American Psychological Association (APA) for a program to provide pharmacists with assistance in dealing with the personal emotional difficulties many experience after being involved in a serious medication error.

Pharmacists often experience this kind of trauma when a medication error results in serious patient harm or even death. Through this new program, pharmacists can call (800) 964-2000 to reach a referral service operated by the APA. The APA will put callers in touch with their specific state's psychological association, which will then make recommendations to the caller for a local psychologist. The local psychologist can assist the pharmacist by offering coping mechanisms for potential job loss, professional sanctions, feelings of guilt, and inability to talk with others about the event. The program is designed to provide pharmacists with the tools necessary to put the event into perspective and be able to face their sometimes hostile environments. For more information about this program, visit the ASHP web site at www.ashp. com / public / news / ShowArticle. cfm?id=1929. ■

Drug information sources offered

Here is a newly updated list of drug information sources that can be of help to you in your day-to-day practice:

• The Council on Family Health, with the Food and Drug Administration and the National Consumers League, have updated the consumer guide ***Drug Interactions: What You Should Know.*** This free guide is intended to help those who use medications — whether they be prescription, over-the-counter, or dietary supplements — avoid potential interactions between those medications. The publication details different types of drug interactions and provides consumers with lists of questions to ask their health care providers.

• The science of pharmacoeconomics enters the realm of medicine daily. More and more, pharmacists are having to make decisions for their institutions based on the economic issues of drugs. The peer-reviewed journal ***PharmacoEconomics*** is now among the journals indexed by the National Library of Medicine in its Medline database. The journal covers pharmacoeconomic decision making, outcomes research, and quality-of-life assessment.

• First DataBank has a new forum and new capabilities for **AHFSfirst**. AHFSfirst has been available for several years in desktop format for single users and networks. This drug information resource is now available for multiple users via intranet or the Internet. AHFSfirst packages AHFS Drug Information monographs from the American Society of Health-System Pharmacists and the National Drug Data File (NDDF) from first DataBank. For years, AHFS has provided monographs, and NDDF has provided clinical, descriptive, and pricing information for all drugs approved by the Food and Drug Administration. NDDF data already match drug information in many hospital pharmacy systems. The Web edition of AHFSfirst allows detailed searches in either database alone by typing in a drug name, then selecting NDDF Plus clinical data or full-text AHFS drug monographs. Other new capabilities include the system's product identification feature to identify more than 10,000 drug products based on imprint data, color, shape, and other physical characteristics. Additionally, pharmacists can create a list of drugs to immediately check for any drug-drug interactions and duplicate therapies. Drug-drug interaction alerts are linked to interaction monographs to help the user in making the appropriate decision for the patient. Accessing the system via the Internet saves the time and effort of loading updates to individual users or servers.

• Facts and Comparisons has launched **DrugFacts.com** as a primary drug information resource available to health care providers on the internet. The resource is available both on a free basis and by subscription. Free access is offered to all to Facts and Comparisons titles including *A-Z Drug Facts, Medfacts*, and the *Guide to Popular Natural Products*. Premium resources such as *Drug Facts and Comparisons, Drug Interaction Facts*, and the *Review of Natural Products* are available on a subscription basis and can now be updated without the distribution and maintenance of paper. About 20% of DrugFacts.com is free at its Web site. Another 50% is available to those who register on the site — free of charge. The remaining 30% of information is available only by paid subscriptions.

• To fully use and apply the information available in the medical literature, pharmacists must be able to critique clinical drug studies. To this end, the American Pharmaceutical Association is publishing the textbook *Principles of Scientific Literature Evaluation: Critiquing Clinical Drug Trial,* by Frank J. Ascione, PhD. ■

New relief in sight for dry mouth

Watch and listen for signs and complaints of dry mouth in your patients. Dry mouth, or xerostomia, often goes untreated. More than 20% of Americans over age 50, about 15 million people, suffer xerostomia. Adding those under the age of 50 who suffer from xerostomia secondary to other medical conditions (such as diabetes or rheumatic diseases) or to drugs that induce xerostomia, the number increases to about 25 million.

Amarillo Biosciences Inc. plans to partner with Natrol Inc. to market the dietary supplement Salive to treat dry mouth. Salive is a pharmaceutical grade anhydrous crystallatine maltose and has been shown in clinical trials conducted by Amarillo Biosciences to "relieve complaints of

dry mouth, enhance salivary function, and promote oral comfort." Salive will be marketed under the name Natrol Dry Mouth Relief. ■

Goat serum for AIDS is dangerous

The Food and Drug Administration (FDA) has alerted health care providers and patients to potential danger surrounding an unapproved experimental product for treating HIV / AIDS. According to the FDA, the goat antiserum used in treating HIV / AIDS is not currently approved for this indication or for any human clinical study. This unapproved product, produced in goats as an antiserum against HIV / AIDS, was the subject of a clinical hold by FDA, prohibiting its use until safety questions are resolved. The sponsor of the agent has warned that the antiserum currently in circulation was stolen from a storage facility, is potentially extremely dangerous, and should be considered contaminated material. For further information, see the *FDA Talk Paper* at www.fda.gov / bbs / topics / ANSWERS / ANS01061.html. ■

New FDA Approvals

These drugs have received final approval from the Food and Drug Administration:

Oral contraceptive desogestrel / ethinyl estradiol (Cyclessa) by Organona Inc.

Fomepizole (Antizol) injection by Orphan Medical Inc. Fomepizole is approved for **suspected or confirmed methanol poisoning**, either used alone or in combination with hemodialysis.

Antiviral agent oseltamivir (Tamiflu) oral suspension by Hoffman-La Roche. Oseltamivir is now available for oral use for the treatment of uncomplicated acute illness due to influenza in patients older than 1 year of age who have been symptomatic for no longer than two days. The agent significantly reduced the total composite time to freedom from illness (resolution of fever, alleviation of coyza and cough, and parental opinion of return to normal health and activity) by 1.5 days compared to placebo. Adults who have difficulty swallowing the capsule may use the oral suspension.

Diabetes agent nateglinide (Starlix) by Novartis. Nateglinide is approved for use as monotherapy, as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes. In addition, this approval provides for the use of nateglinide concomitantly with metformin to improve glycemic control. Nateglinide is available in 60 mg and 120 mg tablets.

Anticoagulant bivalirudin (Angiomax) injection by the Medicines Co. Bivalirudin has received approval for use as an **anticoagulant in patients with unstable angina** undergoing percutaneous transluminal coronary angioplasty. ■

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IN THE PIPELINE

AeroGen Inc. has initiated Phase II clinical trials using its AeroDose **insulin inhaler** in diabetics. The studies are designed to characterize the delivery and efficacy of inhaled insulin in Type 2 diabetics.

Alliance Pharmaceutical Corp. says enrollment is complete for its pivotal Phase II/III trial for perflubron (LiquiVent), an intrapulmonary agent for the treatment of **acute lung injury and acute respiratory distress syndrome**. Perflubron is an oxygen-carrying liquid agent under development with fast-track designation from the FDA. The liquid is administered to the lungs of patients supported by a mechanical ventilator and is anticipated to decrease the number of days that mechanical ventilation is required by patients.

Amylin Pharmaceuticals Inc. has submitted a New Drug Application to the FDA for its lead **diabetes agent**, pramlintide acetate (Symlin). Amylin wants to market pramlintide as an adjunctive therapy to insulin for the treatment of patients with Type 1 or Type 2 diabetes who use insulin. Pramlintide is a synthetic form of human amylin, a hormone secreted with insulin by the pancreas. In clinical trials, pramlintide demonstrated the ability to improve blood glucose control significantly without weight gain and without increase in severe hypoglycemic event rates.

AstraZeneca announces Crestor as the trade name for its investigational **HMG CoA reductase inhibitor**, rosuvastatin calcium. Rosuvastatin was formerly referred to as ZD4522. More than 4,000 patients have been enrolled in Phase III clinical trials for the drug. It is expected that data from some of these trials will be presented at the American College of Cardiology meeting in March 2001.

Cellegy Pharmaceuticals Inc. announces initiation of an expanded Phase I/II trial for its product, Tostrelle, a transdermal testosterone gel designed for the treatment of **female sexual dysfunction**. Low levels of testosterone in females can lead to muscle and bone mass, and decreased energy level, in addition to decreased libido.

Cell Genesys Inc. reports positive results of its GVAX **prostate cancer vaccine**. Phase II data have demonstrated anti-tumor activity in patients with advanced metastatic prostate cancer who have failed hormone therapy. Thirty-four of 55 patients in the trial had metastatic prostate cancer in the bone with positive bone scans at start of therapy. These 34 were assigned to either low-dose (n=24) or high-dose (n=10) treatment with GVAX as monotherapy. Post treatment follow-up of these 34 patients showed a trend toward prolonged progression free survival (measured by bone scan). The median time to progression was 140 days for the high-dose group and 85 days for the low-dose group. The remaining 21 patients who did not have positive bone scans at start of study was 179 days.

Epimmune Inc. reports results of tests showing that its vaccine designed to treat breast, colon, and lung cancers stimulates strong immune responses in animal models and in human cells used in lab tests. Vaccines such as this that are able to boost the immune system's ability to recognize and destroy tumor cells may meet a currently unmet need in cancer armamentarium. ■

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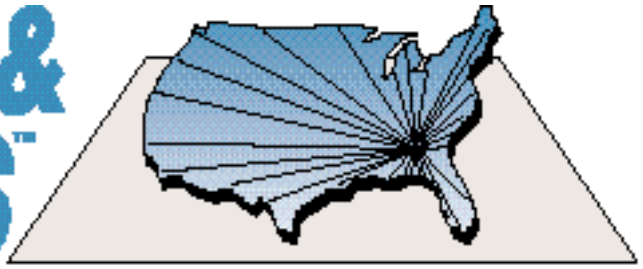

Lepirudin (Refludan) for the treatment of HIT

By **Tina Hussey**, PharmD
Clinical Specialist, Drug Information
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Chapel Hill

Introduction:

Heparin-induced thrombocytopenia (HIT) can be a serious complication of heparin therapy and occurs in two ways.[1-3] The milder form of HIT occurs in about 10% to 20% of patients and usually develops after one to four days of heparin therapy, resulting in a mild thrombocytopenia.[2-3] Platelet counts usually remain above 100,000 per microliter.[2] This form of HIT, type I, occurs due to a direct interaction between heparin and platelets.[2-3] The more serious form of HIT, type II, is attributed to an immune-mediated reaction to heparin. This form of HIT usually occurs after five to 10 days of heparin therapy, with the platelet count dropping to between 30,000 and 55,000 per microliter. The type II reaction is much more severe and can be associated with life-threatening thromboembolic complications. The incidence of this more critical form has been shown in the literature to vary from 0% to 30% depending on study population, heparin regimen, and heparin type. Although HIT more commonly occurs in patients receiving larger doses, it has been shown to occur in patients receiving small doses, as well.[2-3]

Low-molecular-weight heparins (LMWH) are obtained by depolymerization of unfractionated porcine heparin, resulting in fragments weighing less than 10,000 daltons.[2-3] LMWH have almost 100% cross-reactivity with unfractionated heparin and should not be recommended for patients with HIT unless cross-reactivity is absent by in vitro platelet aggregation assays. Danaparoid is a low-molecular-weight heparinoid that differs from unfractionated heparin and LMWH. Danaparoid is a mixture of heparin sulfate, dermatan sulfate, and chondroitin sulfate.[1-3] Although each component is structurally different from unfractionated heparin, the cross-reactivity with heparin-dependent antibody approaches 10% to 20%.[2-3] Ancrod is a defibrinogenating agent extracted from snake venom that is distinct from heparin and has not been shown to have cross-reactivity.[2] Ancrod does not suppress thrombosis in all cases and is not readily available in the United States. Argatroban is a synthetic direct thrombin inhibitor that very recently received FDA approval for the prevention and treatment of HIT.

The anticoagulant agent hirudin is found naturally in medicinal leeches (*Hirudo medicinalis*).[4] Medicinal leeches have been used in hemostasis since ancient times, necessitating at least 50,000 leeches annually to obtain adequate amounts of hirudin for this purpose.[4] Lepirudin, a recombinant hirudin, is approved by the FDA for anticoagulation in patients with HIT and associated thromboembolic disease in order to prevent further thromboembolic complications.[5-6]

Indications:

Lepirudin (Refludan), by Aventis Pharmaceuticals (formerly Hoechst Marion Roussel), is indicated for anticoagulation in patients with HIT and associated thromboembolic disease to prevent further thromboembolic complications.[5]

Pharmacology:

Lepirudin is a recombinant hirudin derived from yeast cells.[5] Lepirudin is composed of 65 amino acids and is identical to natural hirudin except for the substitution of leucine for isoleucine at the N-terminal end and the absence of a sulfate group on the tyrosine at position 63. Lepirudin binds to free and clot-bound thrombin to block its thrombogenic activity. The activity of lepirudin is measured in antithrombin units (ATUs). One ATU is the amount of lepirudin required to neutralize one unit of World Health Organization preparation

of thrombin. The activity of lepirudin is about 16,000 ATU / mg.

Pharmacokinetics:

Lepirudin primarily distributes into extracellular fluids with an initial terminal half-life of 10 minutes.[5] In young healthy volunteers, the terminal half-life is approximately 1.3 hours. The clearance of lepirudin has been shown to differ depending on renal function, age, and gender. The clearance of lepirudin is proportional to glomerular filtration rate; the elimination half-life has been shown to be prolonged up to two days in some patients with renal dysfunction. In 16 patients with renal impairment (creatinine clearance < 80 mL / min), the mean clearance of lepirudin was 61 mL / min. The clearance of lepirudin is reduced by about 25% in women compared to men and 20% in younger individuals compared to the elderly. In 18 healthy young subjects aged 18 to 60 years, the mean clearance was 164 mL / min compared to 139 mL / min seen in 10 healthy elderly subjects aged 65 to 80 years. The metabolism of lepirudin has not been well-established; however, it is thought to be metabolized by the release of amino acids from catabolic hydrolysis of the parent compound. Approximately 48% of the drug is eliminated in the urine as unchanged drug or fragments of the parent drug.

Pharmacodynamics:

The pharmacodynamic effect of lepirudin on the proteolytic activity of thrombin has been assessed using the activated partial thromboplastin time (aPTT).[5] An increase in aPTT was observed with increasing plasma concentrations of lepirudin. No saturable effect was seen at a dose of 0.5 mg / kg body weight given by intravenous bolus, which was the highest dose tested.

Clinical trials:

The effectiveness of lepirudin for HIT was evaluated in two multicenter, prospective, open-label, historically controlled clinical trials; these trials, HAT-1 and HAT-2, are the basis for the FDA-approved indication of lepirudin for HIT.[5-7] The trials had similar study design, primary and secondary objectives, and used similar dosing regimens. Both studies used the same historical control group which was compiled from a recent retrospective registry of patients with HIT. The historical control group consisted of 120 patients with HIT who were treated with therapies that did not include lepirudin (e.g., danaparoid, phenprocoumon, LMWH, aspirin, thrombolytics) or were not treated with anticoagulation. In both trials, patients were divided into four categories with different dosing regimens based on body weight (BW) as follows:[5-7]

- A1 — acute HIT patients with thrombosis (HAT-1, n=51; HAT-2, n=65)

  Dosing: IV bolus: 0.4 mg / kg BW; IV infusion: 0.15 mg / kg BW / h x 2-10 days
- A2 — acute HIT patients with thrombosis receiving thrombolytics (HAT-1, n=5; HAT-2, n=4)

  Dosing: IV bolus: 0.2 mg / kg BW; IV infusion: 0.1 mg / kg BW / h x 2-10 days
- B — HIT patients without thrombosis (HAT-1, n=18; HAT-2, n=43)

  Dosing: Continuous infusion: 0.1 mg / kg BW / h x 2-10 days
- C — HIT patients undergoing cardiopulmonary bypass (HAT-1, n=8; HAT-2, n=4)

  Dosing: Priming of heart lung machine: 0.2 mg / kg BW; IV bolus: 0.25 mg / kg BW; Additional boluses: 5 mg (to maintain Ecarin Clotting Time [ECT] > 250 seconds or Activated Coagulation Time [ACT] > 350 seconds)

Changes in dose were made to maintain aPTT ratio (patient aPTT at a given time over an aPTT reference value, usually the median of the laboratory normal range for aPTT or the patient's baseline aPTT prior to anticoagulation) between 1.5 and three.[5-6] For aPTTs below the desired range, the infusion rate was increased by 20% and the aPTT was repeated four hours later. For aPTTs above the desired range, the infusion was discontinued for two hours then restarted at 50% of the previous rate with no boluses given. In patients receiving oral anticoagulation, the dose of lepirudin was decreased while still maintaining aPTT at least 1.5 times baseline values while the INR was less than two. Lepirudin was discontinued when the INR was more than 2.

Patient demographics were similar between treatment groups and historical controls, except for age.[5-6] Patients in the historical control group tended to be older than patients treated with lepirudin. The primary endpoints for HAT-1 and HAT-2 were platelet recovery and effective anticoagulation. Platelet recovery was defined as an increase in platelet count by at least 30% of nadir to values greater than 100,000. Effective anticoagulation was defined as aPTT ratio greater than 1.5 with a maximum total 40% increase in the initial infusion rate. Platelet counts were not monitored closely in the historical control group and most patients in this group did not receive therapy that affected aPTT; therefore, comparisons could not be

made based on the primary endpoints. Between patient groups, however, comparisons could be made. Of patients in group A1, 90% in the HAT-1 study met the primary endpoint of platelet recovery; 95% of those in HAT-2 met the same endpoint. All patients in group A2 (in both studies) had platelet recovery. Those reaching the primary endpoint of successful anticoagulation included 84% of patients in group A1 and 60% in group A2 (for HAT-1), and 77% of patients in group A1 and 33% in group A2 (for HAT-2). The percentage of patients reaching the primary endpoints when evaluating groups combined is as follows:[5-6]

- HAT-1: Eighty-six percent (all groups combined) met platelet count endpoint, 77% met anticoagulation endpoint, 65% met combined endpoints.
- HAT-2: Ninety-two percent (all groups combined) met platelet count endpoint, 74% met anticoagulation endpoint, 69% met combined endpoints.

Patients receiving lepirudin were compared to historical controls with respect to combined endpoints of thromboembolic complications, limb amputations, and death.[6] In HAT-1, 71 patients receiving lepirudin were compared to 120 historical controls, and in HAT-2, 59 patients receiving lepirudin were compared to 120 historical controls. A significant difference between the groups in the combined endpoint at days 7 and 35 was found in HAT-1. At day 7, the incidence of the combined endpoint was 9.9% in those receiving lepirudin compared to 23% in historical controls. At day 35, the incidence was 25.4% in the lepirudin group and 52.1% in historical controls. In HAT-2, the cumulative incidence at day 7 for the lepirudin group was 17.9% compared to 21.3% in historical controls. At day 28, the cumulative incidence was 33.2% and 40.3%, respectively.

Adverse reactions:

The most common adverse events occurring in the HAT-1 and HAT-2 studies were hemorrhagic, including:[6]

- bleeding from puncture sites and wounds, 14.1%;
- anemia or isolated drop in hemoglobin, 13.1%;
- other hematoma and unclassified bleeding, 11.1%;
- hematuria, 6.6%;
- gastrointestinal and rectal bleeding, 5.1%
- epistaxis, 3.0%;
- hemothorax, 3.0%;
- vaginal bleeding, 1.5%.

Nonhemorrhagic events included fever (6.1%), abnormal liver function (6.1%), pneumonia (4%), sepsis (4%), allergic skin reactions (3%), heart failure (3%), abnormal kidney function (2.5%), unspecified infections (2.5%), multiorgan failure (2%), pericardial effusion (1%), and ventricular fibrillation (1%). Additional information from clinical pharmacology studies and clinical studies other than HIT show that intracranial bleeding occurred in 0.6% (seven out of 1,134 patients) of patients with acute myocardial infarction who received both lepirudin and thrombolytic agents.[5] In addition, airway reactions (e.g., cough, bronchospasm, stridor, dyspnea) occurred in 1% to 10% of patients receiving lepirudin in these studies.

Pregnancy and lactation:

Lepirudin is rated a pregnancy category B drug,[5] meaning either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in their first trimester.[8] Studies have found no evidence of harm to the fetus at intravenous doses up to 30 mg / kg / day in pregnant rats (1.2 times the recommended maximum total daily dose in humans) and rabbits (2.4 times the recommended maximum total daily dose in humans).[5] Studies did show that pregnant rats given lepirudin during organogenesis and perinatal-postnatal periods exhibited an increased incidence of maternal mortality. In pregnant rats, lepirudin does cross the placental barrier at intravenous doses of 1 mg / kg. Because there are no controlled studies of lepirudin in pregnant women, and animal studies do not always predict what happens in humans, it is recommended that lepirudin be used during pregnancy only if the benefits to the mother outweigh the potential risks to the fetus.

It is not known whether lepirudin is excreted in breast milk.[5] Considering that many drugs are excreted in breast milk and that there is the potential for serious adverse events in the infant, a decision should be made to discontinue nursing or to discontinue the drug. The importance of the drug to the mother should be taken into account.

Contraindications:

Lepirudin is contraindicated in patients with known hypersensitivity to hirudin.[5]

Warnings:

Intracranial bleeding following the administration of lepirudin concomitantly with thrombolytic therapy has occurred and can be life-threatening.[5]

For patients at increased risk of bleeding, the potential risks of bleeding should be assessed compared to the anticipated benefits.[5] In particular, this includes the following conditions: recent puncture of large vessels or organ biopsy; anomaly of vessels or organs; recent cerebrovascular accident, stroke, intracerebral surgery, or other neuroaxial procedures; severe uncontrolled hypertension; bacterial endocarditis; advanced renal impairment; hemorrhagic diathesis; recent major surgery; and recent major bleeding (e.g., intracranial, gastrointestinal, intraocular, or pulmonary bleeding).

Reductions in the bolus and maintenance dose of lepirudin in patients with renal failure must be made.[5] Relative overdoses can occur in these patients even at standard doses.

Dosage and administration:

Adult patients with HIT or associated thromboembolic disease should be initially treated with lepirudin 0.4 mg / kg (maximum 44 mg) intravenously (slowly, over 15 to 20 seconds) as a bolus, followed by lepirudin 0.15 mg / kg (maximum 16.5 mg / h) as a continuous intravenous infusion.[5] Patients weighing more than 110 kg should receive the maximum initial bolus of 44 mg and the maximum initial infusion dose of 16.5 mg / h.

The loading dose and infusion rate of lepirudin should be reduced in patients with renal impairment.[5] Dosage adjustments should be based on creatinine clearance (ClCr), when determined by a reliable method and by serum creatinine (SCr) when ClCr is not available. In all patients with renal impairment, the bolus dose should be reduced to 0.2 mg / kg. Recommendations for reductions in infusion rate are as follows:[5]

- 0.075 mg / kg / h (50% of standard rate) for ClCr 45-60 mL / min or SCr of 1.6-2 mg / dL;
- 0.045 mg / kg / h (30% of standard rate) for ClCr 30-44 mL / min or SCr of 2.1-3 mg / dL;
- 0.0225 mg / kg / h (15% of standard rate) for ClCr 15-29 mL / min or SCr of 3.1-6 mg / dL;
- Avoid or stop infusion for ClCr < 15 mL / min or SCr of > 6 mg / dL. Additional intravenous boluses of 0.1 mg / kg can be considered every other day if the apt ratio falls below 1.5.

Monitoring parameters and dose adjustments:

The aPTT ratio should generally be used to adjust the infusion rate of lepirudin.[5] The aPTT ratio is the patient's aPTT at a given time over an aPTT reference value. The reference value is usually the median of the laboratory normal for aPTT. The target range for the aPTT ratio should be between 1.5 and 2.5. Higher aPTT ratios have been shown in clinical studies to increase the risks of bleeding episodes without increasing the clinical efficacy. A baseline aPTT ratio should be obtained prior to initiating therapy with lepirudin. Lepirudin should not be started if the baseline aPTT ratio is 2.5 or greater to avoid initial overdosing. After starting therapy, the initial aPTT ratio should be obtained four hours after the start of the infusion with follow-up aPTT ratios obtained at least once daily. More frequent monitoring is recommended in patients with renal or liver impairment.

An aPTT ratio outside of the target range should not be acted upon until it is confirmed unless there is clinical need to react immediately.[5] If a confirmed aPTT is above the target range, the lepirudin infusion should be held for two hours and restarted at 50% of the original infusion rate with no additional bolus. The aPTT ratio should be obtained four hours after the start of the infusion. If the confirmed aPTT is below the therapeutic range, the infusion rate should be increased in increments of 20%. The aPTT ratio should be obtained four hours later. An infusion rate of more than 0.21 mg / kg / h should not be used unless the patient has been tested for coagulation abnormalities, which might prevent an appropriate response in aPTT.

Drug interactions:

Thrombolytics given concomitantly with lepirudin may increase the risk of bleeding and enhance the effect of lepirudin on aPTT prolongation.[5] Concomitant administration with warfarin may also increase the risk of bleeding.

Dosage forms available:

Lepirudin is supplied in vials that each contain 50 mg of lepirudin as a white powder for injection or infusion.[5]

One vial of lepirudin is required to make the bolus injection.[5] Two vials of lepirudin are required to make a 500 mL bag with a final concentration of 0.2 mg / mL for intravenous infusion. At an associated wholesalers price (AWP) of $126 per vial, the cost of lepirudin in one bag would therefore be approximately $252. The recommended standard infusion rate for a 70 kg patient is 53 mL / h; a 500 mL bag would last about nine hours. This patient would need approximately three bags per day. Therefore, for a 70 kg patient, the cost for a bolus dose and continuous infusion would be approximately $882.

The doses of danaparoid vary depending on the

patient's condition, weight, history of HIT, and other factors.[9] Generally, the recommended dose of danaparoid for patients with HIT and established DVT (thrombosis less than five days old) is 2,500 antifactor Xa units given as an IV bolus, then 400 units / hour (4 hours), then 300 units / hour (4 hours), then 150-200 units / hour for five to seven days. AWP for a 0.6 mL ampule of danaparoid is $112.80. Therefore, a 70 kg patient would require approximately 7,700 antifactor Xa units on the first day of therapy which would cost approximately $1,157. Subsequent days of therapy would cost approximately $541 based on a continuous infusion of 150 units / hour.

Discussion:

Lepirudin is available with approval by the FDA for anticoagulation in patients with heparin-induced thrombocytopenia.[5,6] Danaparoid and ancrod have been used as well, but are not FDA-approved for this indication.[1-3] Ancrod is not currently available in the United States. Danaparoid appears to have a 10% to 20% cross-reactivity in vitro with heparin-dependent antibody. Lepirudin does not cross-react with heparin-induced antibodies, as demonstrated by rapid and sustained platelet recovery.[5,6] In addition, the half-life of lepirudin is approximately 10 minutes, which allows for easy titration up or down in the case of an adverse event.[5] The half-life of danaparoid is approximately 24 hours.[10]

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Cerivastatin (Baycol) for cholesterol

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Indications:

Cerivastatin (Baycol), by Bayer Corp., is classified as an antilipemic agent and is indicated for treatment of elevated cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia after dietary cholesterol and saturated fat restrictions have failed.[1,2]

Pharmacology:

The coenzyme 3-hydroxy-3-methylglutaryl (HMG-CoA) reductase is responsible for conversion of HMG-CoA to mevalonate, a precursor of cholesterol. Cerivastatin is an inhibitor of the HMG-CoA reductase coenzyme. By preventing production of cholesterol in the liver, cerivastatin promotes synthesis of low-density lipoprotein (LDL) receptors. An increased production of LDL receptors results in enhanced uptake of LDL and, ultimately, reduced plasma levels of circulating LDL. LDLs have been identified as a major culprit in cardiovascular disease.[2,3]

Pharmacokinetics:

Absorption: The absolute bioavailability of cerivastatin is 60%. Linear pharmacokinetics are demonstrated with cerivastatin at doses between 0.05 mg to 0.4 mg per day. Mean time to maximum concentration approximates 2.5 hours. Administration with food does not affect the rate or extent of absorption of cerivastatin.[2]

Distribution: Cerivastatin is greater than 99% bound to plasma proteins.[4] The volume of distribution is approximately 0.3L / kg.[2]

Metabolism: The cytochrome p450 enzyme system plays a role in the metabolism of cerivastatin to its metabolites. The isoenzymes responsible for metabolism are 3A4, 2C8, and 2A6. Two active metabolites, M1 and M23, are formed from demethylation and hydroxylation of the parent compound. The parent compound is responsible for the majority of the lipid-lowering effects.[2,4]

Excretion: Undetectable amounts of cerivastatin are found in the urine and feces. Approximately 30% of the drug is excreted in the

urine as metabolites. The elimination half-life of cerivastatin ranges between two and three hours.[2]

Renal Impairment: Patients with moderate to severe renal impairment (ClCr ≤ 60mL / min) have shown up to a 23% increase in drug concentrations and a 47% increase in half-life than in healthy individuals (ClCr ≥ 90 mL / min).[2]

Hemodialysis: Cerivastatin has not been studied in patients with end-stage renal disease. However, due to the high degree of protein binding, cerivastatin is not expected to be removed by hemodialysis.[2]

Selected clinical trials:

Hanefeld and colleagues[5] evaluated the safety and efficacy of cerivastatin 0.3 mg and 0.4 mg vs. placebo in 349 patient with primary hypercholesterolemia. All cerivastatin and placebo doses were administered by mouth. Primary hypercholesterolemia was defined as an LDL cholesterol ≥ 190 mg / dL, in association with at least one risk factor. Risk factors included male gender, current cigarette smoker, history of premature coronary heart disease in the family, hypertension, HDL cholesterol concentrations < 35 mg / dL, history of cerebrovascular or peripheral vascular disease, coronary disease, and obesity. Patients 18 to 75 years of age who were ambulatory with a triglyceride level ≥ 350 mg / dL were included in the study. Patients were excluded from the study if they had a contraindication to statin therapy, severe hypertension, myocardial infarction within the past six months, congestive heart failure (New York Heart Association class III or IV), or cardiac arrhythmias. Other exclusion criteria included a history of cerebrovascular event, malignancy, endocrine disorders (e.g., diabetes mellitus and hypothyroidism), pancreatitis, muscular or neuromuscular disease, or impaired gastric absorption. Females of childbearing potential were excluded from participation, as were night shift workers and patients on concomitant lipid-lowering therapies. Patients taking immunosuppressive agents, erythromycin, niacin, or any form of corticosteroids were excluded from participation in the study. In addition, patients with elevated creatine kinase (CK) levels (greater than three times the upper normal limit) or liver function tests (LFTs) (greater than one and one-half times the upper normal limit) were excluded.[5]

A total of 349 patients were treated with cerivastatin 0.3 mg (n = 140), cerivastatin 0.4 mg (n = 138), or placebo (n = 71) once daily for eight weeks. All patients received American Heart Association Step-1 dietary counseling. Prior to initiating therapy, patients participated in an optional four-week dietary stabilization phase based on investigators' recommendation. A six-week placebo run-in phase prior to randomization allowed patient assessment to dietary adherence and medication compliance. Baseline cholesterol parameters were also evaluated during this phase of the study. Adverse drug reactions were documented at each visit. Patients were withdrawn from the study if CK levels reached 10 times the upper normal limit, if CK levels were greater than five times normal on two occasions, or if CK levels were greater than three times normal accompanied by muscle weakness or pain. In addition, LFTs greater than three times the upper normal limit or an LDL cholesterol level less than 60 mg / dL were reasons for study discontinuation.[5]

The primary endpoint measured was change from baseline in LDL cholesterol concentrations. Baseline values were calculated as the mean LDL from patient visits 3, 4, and 5. Low-density lipoprotein concentrations were calculated using the Friedewald Formula. The data were analyzed using an intent-to-treat analysis. Patients were included in the final analysis if they had one LDL cholesterol concentration from visits 3, 4, or 5 and one level during the treatment period. Secondary endpoints were change in baseline of total cholesterol, HDL cholesterol, triglyceride, and certain lipid fractions.[5]

The group treated with cerivastatin 0.4 mg had a mean decrease in LDL cholesterol concentrations of 35.8%, whereas those treated with cerivastatin 0.3 mg had a mean decrease in LDL cholesterol concentrations of 32.5%. Statistical significance was not found between cerivastatin-treated patients. Patients receiving placebo experienced a mean increase of 0.2% in LDL cholesterol concentrations. Statistical significance was achieved for both cerivastatin groups compared to placebo ($p < 0.001$). In the cerivastatin 0.3 mg and cerivastatin 0.4 mg groups, 27.9% and 40.6% of patients, respectively, experienced a drop in LDL cholesterol concentrations greater than 40%. Total cholesterol concentrations in the cerivastatin 0.4 mg treatment group decreased significantly from baseline compared to cerivastatin 0.3 mg and placebo (26.8% and 24.3% for 0.4 mg and cerivastatin 0.3 mg; $p < 0.02$). Other lipid parameters including triglycerides and apolipoprotein levels decreased significantly in both treatment groups as compared to placebo. No patients withdrew from the study secondary to an

adverse event related to the study medication. Back pain and headache were the only two adverse events that had a higher incidence among patients on cerivastatin than those on placebo. Back pain was reported in 1.4% of placebo patients vs. 2.9% and 4.3% of patients on 0.3 mg and cerivastatin 0.4 mg, respectively. Headache occurred in 1.4% of placebo-treated patients, 2.1% of patients on cerivastatin 0.3 mg, and 4.3% of patients assigned to cerivastatin 0.4 mg daily.[5]

The data support that cerivastatin 0.4 mg daily was associated with a greater reduction in LDL and total cholesterol concentrations than previously studied doses in patients with primary hyperlipidemia. No increase in adverse events was noted at the higher dosage.[5]

A study by Stein and colleagues[6] demonstrated the safety and efficacy of cerivastatin 0.8 mg. Forty-one patients were assigned to receive either cerivastatin 0.8 mg (n = 28) or placebo (n = 13) by mouth daily for 28 days in this randomized, double-blind, parallel group trial. Patients with primary hypercholesterolemia were evaluated. Patients with recent acute cardiovascular events or interventions; uncontrolled hypertension, diabetes mellitus or other endocrine abnormalities; unstable ophthalmic problems; malignancy; active liver disease; gastrointestinal disorders with potential to impair absorption; pregnant or lactating females; and patients currently taking aspirin, corticosteroids, rifampin, immunosuppressants, antidiabetic medications, or other lipid-lowering agents were excluded.[6]

Cerivastatin 0.8 mg lowered LDL cholesterol by 44% over a 28-day period, whereas placebo-treated patients experienced a 1.2% increase in LDL cholesterol concentrations ($p < 0.0001$). Total cholesterol and triglyceride concentrations were also reduced by 30.8% and 11.2%, respectively, in the cerivastatin-treated group (Table 1). High-density lipoprotein (HDL) was raised 3.2% from baseline in the cerivastatin-treated group, while a decrease of 1.2% was noted in placebo-treated patients. Eighteen of 28 patients (64%) in the cerivastatin-treated group experienced one adverse event and seven of 13 patients (54%) in the control arm reported an adverse event. Events were classified as mild or moderate. Reported events occurred at the following rates in cerivastatin- and placebo-treated patients, respectively: headache (n = 10, 36%; n = 2, 15%), pharyngitis (n = 3, 11%; n = 0, 0%), back pain (n = 2, 7%; n = 1, 8%), arthralgia (n = 2, 7%; n = 1, 8%), and rash (n = 2, 7%; n = 0, 0%). No adverse effects resulted in discontinuation of medication.[6]

Adverse reactions:

More than 4,000 patients have been evaluated in clinical trials. Cerivastatin was generally well-tolerated. Adverse reactions occurring in greater than 5% of 1,263 patients treated with cerivastatin include headache (n = 124; 9.8%), pharyngitis (n = 160; 12.7%), sinusitis (n = 80; 6.3%), rhinitis (n = 136; 10.8%), and accidental injury (n = 64; 5.1%). These reactions were similar to those experienced by placebo-treated patients. Other adverse events included arthralgias (n = 55; 4.4%) and myalgias (n = 29; 2.3%), back pain (n = 50; 4%), and dyspepsia (n = 53; 4.2%).[2]

Increases in LFTs have been observed with cerivastatin. Patients should have baseline LFTs measured prior to initiating therapy and again at six and 12 weeks. Thereafter, LFTs should be evaluated periodically. Most liver toxicity occurs by week six of therapy. If LFTs increase greater than three times normal, then cerivastatin should be discontinued.[2]

Myopathy accompanied by an increase in CK has been observed rarely with cerivastatin. Increased risk of myopathy occurs if cerivastatin is given in combination with cyclosporine, erythromycin, antifungal agents with azole structures, fibric acid agents, and niacin.[2]

Pregnancy and lactation:

Cerivastatin is pregnancy category X. The drug caused incomplete bone formation in the vertebrae of rats at oral doses of 0.72 mg/kg. Drug concentrations in plasma were six to seven times higher than the human exposure for rats. In pregnant rats given cerivastatin 2 mg/kg, the drug was found in fetal liver, gastrointestinal tract, and kidneys. No growth abnormalities were observed in rabbits receiving doses as high as 0.75 mg/kg. Safety of cerivastatin in pregnant human patients has not been established; however, rare cases of fetal abnormalities have been reported with other HMG-CoA reductase inhibitors used during pregnancy. If a patient becomes pregnant while on cerivastatin, the medication should be discontinued immediately.[2]

Contraindications:

Patients with active liver disease or an unexplained increase in transaminase levels should avoid treatment with cerivastatin. Cerivastatin is contraindicated in pregnant and lactating females. Females of childbearing potential should also avoid cerivastatin therapy. Cerivastatin is contraindicated in patients with hypersensitivity to any component of the medication.[2]

Warnings:

Patients with a history of liver disease or alcoholism should be closely monitored while on cerivastatin therapy. Cerivastatin treatment should be temporarily discontinued in patients with circumstances predisposing them to renal failure from rhabdomyolysis.[2]

Dosage and administration:

In addition to a standard cholesterol-lowering diet, patients who have failed diet therapy alone should start drug therapy with cerivastatin 0.4 mg in the evening. Patients with creatinine clearance $\leq$ 60 mL / min should start therapy with lower doses (cerivastatin 0.2 mg or 0.3 mg).[2]

Monitoring parameters:

Cholesterol levels should be rechecked approximately four weeks after initiating therapy. Recommendations for obtaining LFTs include baseline values, at weeks six and 12 of therapy, and periodically thereafter.[2]

Drug interactions:

No clinically significant pharmacokinetic changes have been detected when either warfarin, digoxin, cimetidine, antacids, or omeprazole was given in combination with cerivastatin. Cholestyramine coadministration has shown a decrease in AUC and concentration of cerivastatin. Gemfibrozil coadministration may cause an increased risk of rhabdomyolysis and renal failure. Erythromycin and itraconazole have also been shown to impact cerivastatin concentrations; coadministration may result in increased cerivastatin concentrations and increased half-life. The clinical significance of these interactions is unknown. Cerivastatin is metabolized by both renal and hepatic pathways and may, therefore, be associated with fewer drug interactions than other HMG-CoA reductase inhibitors.[2]

Dosage forms available:

Tablets for oral administration are available in 0.2 mg (light yellow), 0.3 mg (yellow brown), and 0.4 mg (ocher) strengths.[2]

Discussion:

Cardiovascular disease is responsible for more than 900,000 deaths in the United States each year.[7] In addition to smoking and hypertension, hyperlipidemia is one of the most dangerous risk factors for developing coronary artery disease (CAD).[7] In the late 1980s, the Multiple Risk Factor Intervention Trial (MRFIT) showed the association between increased cholesterol levels and coronary artery disease.[8] Decreasing LDL levels may prevent further decline in cardiovascular risk and may even clear the arteries of some pre-existing disease.[7] The National Cholesterol Education Program guidelines recommend decreasing LDL cholesterol to less than 100 mg / dL in patients with coronary heart disease.[3]

Several drugs have been developed to inhibit this rate-limiting step in cholesterol synthesis. Cerivastatin is the newest agent in this class to be approved by the FDA. Although cerivastatin specifically has not been evaluated in clinical trials for CAD, data from trials using pravastatin and simvastatin have demonstrated a decrease in morbidity and mortality in patients with primary and secondary CAD. As with other statins recently approved by the FDA, cerivastatin may demonstrate a class effect in the reduction of CAD and death associated with hypercholesterolemia. Due to this class effect, cerivastatin may prove to be a valuable medication for cholesterol treatment. In the future, more aggressive dosing regimens may bring an additional increase in LDL lowering.[6]

To date, drug interactions with cerivastatin are minimal. Compared to other HMG-CoA reductase inhibitors, cerivastatin has no significant drug interactions with warfarin or digoxin, an important consideration in a large population of patients being either prophylaxed or treated for CAD.

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