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Pharmaceutical Care Across the Continuum

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In new era, pharmacists become more than just dispensers of drugs

The fundamentals are still the bottom line

In keeping with the Information Age, pharmacists have become dispensers of information in addition to — and, in some cases, in lieu of — dispensers of medication. Pharmacists are often key sources of drug information in their various health care environments, including those who make rounds with medical teams and provide input for drug therapy decisions, pharmacists in central and satellite pharmacies who prevent drug-drug and drug-disease interactions, and pharmacists who staff poison control centers and drug information [DI] centers. Wherever pharmacists are, though, they must possess drug information skills.

"Drug information skills are the most fundamental of all skill sets taught in pharmacy because they ensure that students and residents will leave with the skills necessary to allow lifelong learning," says **Nannette Turcasso**, PharmD, BCPS, an assistant professor in the department of pharmacy practice at the Medical University of South Carolina (MUSC) College of Pharmacy and coordinator of the MUSC Drug Information Center, both in Charleson.

"I can't imagine practicing drug information in the 21st century without the use of the Internet."

"Drug information is constantly evolving. DI centers that are affiliated with colleges of pharmacy support an educational mission in terms of teaching the next generation of pharmacists to not only access drug information efficiently but, more importantly, to interpret, assimilate, and apply the information to specific patients in order to improve patient outcomes," Turcasso says. "The purpose of a drug information center is to provide timely, unbiased patient-specific responses to pharmacotherapy questions. Questions commonly focus on issues of dosing administration, management of drug-drug interactions, therapeutic use, pharmacokinetics, nutrition consults, requests for herbal information, and drugs used during pregnancy and lactation.

"The majority of drug information centers are staffed by pharmacists with advanced training in drug information practice, who have expertise in literature retrieval, interpretation, and application to specific patients to improve patient care. These pharmacists also have very good clinical skills."

It is the marriage of literature evaluation and clinical skills that makes those who staff DI centers so valuable to the medical community around them.

"Drug information centers that are primarily hospital-based support P&T committees in formulary decisions," she says. Those centers write drug monographs and class reviews that help P&T committees make decisions regarding the best agents for formulary inclusion.

"They also write newsletters to help keep the hospital professional staff informed of all important changes regarding medication usage, such as drug recalls and withdrawals," she adds.

Where to go for information

Part of drug information training for pharmacists is knowing where to turn when they don't know the answer to a question. Many health professionals aren't aware that their local DI center can help. For questions regarding overdoses and poisonings, a poison control center can provide information to help save a life. Medical information departments of pharmaceutical manufacturers have specialists trained to answer drug-specific questions and typically have more information on their drugs than does anyone else.

There are a growing number of sites on the Web that health care professionals and patients can access, although information gained there should be verified by other sources as well. Everyone now has access to Medline via "Internet Grateful Med," an on-line service run by the National Library of Medicine in Bethesda, MD.

"Each year, students are becoming more computer-literate and Internet ready. But it's not just a matter of finding information on the Internet. It's the ability to evaluate that information that's truly important," says Turcasso. "I can't imagine practicing drug information in the 21st century without the use of the Internet."

Governmental agencies, such as the Food and Drug Administration and the Centers for Disease Control and Prevention, can be very helpful in seeking answers to questions. "And don't forget your medical library," she adds. "Both the references there and the librarians possess a wealth of information. No matter what the practice setting, pharmacists teach on a daily basis — to physicians, nurses, other pharmacists, and patients.

"Pharmacists could do their colleagues a great service by helping them become [more] familiar and at ease with new information technologies. An inservice to help the professional staff sharpen their searching skills would probably be greatly appreciated. For example, many health professionals aren't aware of how databases differ and when it would be appropriate to use one database over another," she says. ■

With demise of Rezulin, FDA suggests alternatives

Avandia, Actos safer, offer same benefits

Three-quarters of a million patients who used the insulin-sensitizing drug troglitazone (sold by Warner-Lambert Parke-Davis under the brand name Rezulin) have viable options in two other drugs in the same class that have not displayed the liver toxicity associated with Rezulin, according to the Food and Drug Administration.

At the recommendation of the FDA, The Morris Plains, NJ-based pharmaceutical giant withdrew Rezulin from the market on March 21 amid a firestorm of controversy over increasing evidence of liver toxicity in patients taking the drug.

On March 8, the FDA said it had received 88 reports of liver failure "possibly or probably related to use of the drug [Rezulin]"; 61 patients

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died and 10 required liver transplants. Three of the liver-transplant patients died. On March 21, the FDA said in a written statement: "FDA took this action after its review of recent safety data on Rezulin and two similar drugs, rosiglitazone [Avandia] and pioglitazone [Actos], showed that Rezulin is more toxic to the liver than the other two drugs. Data to date show that Avandia and Actos, both approved in the past year, offer the same benefits as Rezulin without the same risk."

"When considered as a whole, the pre-marketing clinical data and post-marketing safety data from Rezulin as compared to similar, alternative diabetes drugs indicate that continued use of Rezulin now poses an unacceptable risk to patients," said **Janet Woodcock**, MD, director of the FDA's Center for Drug Evaluation and Research, in a written statement released several days after the withdrawal of Rezulin from the market. "We are now confident that patients have safer alternatives in this important class of diabetes drugs."

Rezulin also has been pulled from the market in Japan, the only other country where it was sold. After the drug was withdrawn from the U.S. market, the Japanese pharmaceutical firm, Sankyo Company Ltd., said it would halt sales of troglitazone, sold there under the brand name Noscal.

In the March 8 statement, the FDA also acknowledged it had received two reports of liver failure in patients taking Avandia, including one death, that FDA medical staff consider "possibly or probably related to use of the drug." The official statement said there have been no reports of liver failure linked to Actos.

The FDA announced it will present the Rezulin data and the rationale for its decision publicly at a meeting of the Endocrine and Metabolic Drugs Advisory Committee, tentatively scheduled for May 18 and 19.

In announcing it was voluntarily discontinuing the sale of Rezulin, Warner-Lambert said in a written statement, "The company has always believed that it is essential for patients and physicians to receive accurate and objective information regarding benefits and risks of Rezulin. It was for that reason that Warner-Lambert requested a public meeting with the FDA's expert advisory committee. However, repeated media reports sensationalizing the risks associated with Rezulin therapy have created an environment in which patients and physicians are simply unable to make well-informed decisions regarding the safety and efficacy of Rezulin."

In a "Dear Doctor" letter posted on the Rezulin Web site, Warner-Lambert officials said they were making arrangements for wholesale and pharmacy returns of existing stock of the drug. Patients are instructed to contact the company to receive information about reimbursement for unused supplies of Rezulin. A company spokesman said 1.9 million prescriptions had been written for the drug. Its 1999 sales were reported at $625 million.

Many managed care organizations removed Rezulin from their formularies when reports of liver toxicity escalated. Endocrinologists at the Mayo Clinic in Rochester, MN, decided in October to stop prescribing Rezulin because of concerns about the risks, according to **Bruce Zimmerman**, MD, a Mayo endocrinologist and president of the Alexandria, VA-based American Diabetes Association.

Public Citizen calls for revised labeling

The latest round of controversy surfaced in early March after the Washington, DC-based public interest group Public Citizen, which had called for Rezulin's withdrawal from the market in 1998, submitted a petition to the FDA calling for revised labeling on all three drugs in the thiazolidenedione class. "Studies have shown that adverse effects of all three drugs can include liver damage, heart damage, weight gain, fluid retention, low blood pressure, anemia, and possible changes in hormone levels," Public Citizen said in a written statement.

In addition, the organization alleged the class of drugs commonly known as the "glitazones" is not as effective as metformin and sulfonylureas. The FDA has not responded to allegations of toxicities other than liver damage linked to thiazolidenediones. "We're not happy about these results," said **Sidney Wolfe**, MD, director of Public Citizen's Health Research Group, after Rezulin was withdrawn. "Sixty-one people are dead who would be alive if the FDA had acted when they should have."

The group charged that the problems were well known to FDA medical officers who reviewed the drugs before they were approved. Rezulin entered the market in March 1997, Avandia in June 1999, and Actos in August 1999.

Public Citizen is not calling for the withdrawal of Actos and Avandia but is requesting

labeling revisions to warn of possible liver toxicity and advise liver monitoring for patients on the drugs.

Reports of Rezulin's liver toxicity began to emerge a few months after it entered the U.S. market. The drug was pulled from the British market by medical authorities in December 1998 after reports of 130 cases of liver damage worldwide, including six deaths.

Benefits outweigh risks

In March 1999, an FDA expert panel said Rezulin's benefits outweighed the risks associated with the drug. During hearings before the panel, **Stephen Clement**, MD, an endocrinologist at Georgetown University in Washington, DC, testified as a spokesman for the American Diabetes Association. "The American Diabetes Association believes that Rezulin has been a very useful drug for many patients, and its unique mechanism of action has been invaluable for countless individuals who, for many reasons, cannot achieve good glycemic control with the other drugs available."

Clement noted at the time that, despite its "risk of serious adverse events," Rezulin was the only drug available that offered help to certain patients with severe insulin resistance. He added that new therapies and new drugs would soon become available. "At that time, the FDA may need to reassess the benefits of Rezulin as it should all drugs previously approved to treat diabetes. . . ."

Withdrawal pains

In response to the panel's March recommendation, the FDA ordered labeling changes for Rezulin in June 1999 that warned of liver toxicity and recommended close monitoring of liver function for the first year a patient was using the drug. It also said Rezulin should be used only as a combination therapy with other oral agents.

In the interim, the FDA granted priority review status to Avandia, manufactured by SmithKline Beecham, and Actos, manufactured by Takeda Pharmaceuticals American and Eli Lilly and Co., and approved both drugs within a few months.

The day after Rezulin was withdrawn from the market, Public Citizen presented additional allegations in a letter to Donna Shalala, secretary of the U.S. Department of Health and Human Services. The organization wrote that FDA officials harassed FDA physicians "in the context of the recent controversy over Rezulin," and that the FDA had "lowered safety standards" in 1997 when Rezulin and several other controversial drugs were approved.

"The number of drugs already pulled off the market [Posicor, Duract, Raxar, and Rezulin] from those approved in 1997 is twice as many as in any other previous year of approval," wrote Wolfe in his March 22 letter to Shalala. He also mentioned the withdrawal of the weight loss aid Redux in 1996. "In many of these cases, there was either opposition by FDA employees to the approval of these drugs [Redux and Rezulin], unsuccessful urging of stronger product warnings on approval [Duract], or inadequately heeded opposition from several FDA advisory committee members [Posicor]."

Wolfe said a Public Citizen survey of medical officers at the FDA's Center for Drug Evaluation and Research in late 1998 found 27 instances in which a drug was approved over a medical officer's objection and 14 instances in which FDA officers were told not to present adverse information at FDA advisory committee hearings.

At *Drug Utilization Review*'s press time, the FDA declined to comment on Public Citizen's demands for a criminal investigation of alleged irregularities in Warner-Lambert's reporting of evidence of hepatotoxicity that emerged in clinical trials on troglitazone.

ADA Statement on Rezulin

The American Diabetes Association strongly encourages patients to work closely with their health care team to help decide the best treatment option. The American Diabetes Association emphasizes that patients should *not* make any medication decisions without the help of their health care team.

Further, the American Diabetes Association encourages physicians to discuss with their patients the withdrawal of the drug from the market, and available treatment options.

Source: American Diabetes Association, Alexandria, VA.

Two physicians involved in Rezulin clinical trials say their conclusions were not properly reported by Warner-Lambert.

Janet McGill, MD, an endocrinologist, principal researcher, and associate professor of medicine at Washington University in St. Louis, says she reported atypical elevated liver enzymes in two of 10 patients in her part of the 1994 Rezulin trials, and a third patient experienced an allergic reaction to the drug. That information was downplayed in the data the company submitted to the FDA, she charges.

One patient, McGill says, had liver enzymes five times the normal amount, although none of her patients suffered liver failure. "What does this mean? It means that the FDA is looking only at cases of complete liver failure and not considering 'sick livers.' I saw two cases of liver problems in patients who had no problem before that. Behind the liver failure, there may be 10 times as many cases of people who were made ill by the drug."

The FDA's findings

Another physician, Mohammed Saad, MD, deputy chief of endocrinology and diabetes at the University of California at Los Angeles told CBS television that a patient in his study on Rezulin died of liver failure during the trial, but when he cautioned medical students about Rezulin's risks, Warner-Lambert complained.

Saad, who could not be reached for comment, told CBS, "I have been teaching young doctors for 20 years now. This never happened before. I thought they were using pressure tactics that were inappropriate."

In May 1997, the FDA's principal Rezulin investigator, Robert Misbin, MD, investigated Warner-Lambert's data, according to reports on CBS news, and found patients with liver enzymes up to 30 times normal. An FDA internal document shows Warner-Lambert privately admitted its report to the FDA was "not correct," according to CBS. Another draft document "shows the FDA allowed the company to cross out mention of the most severe cases," said the news report.

Before Rezulin was withdrawn from the market, Misbin took the unusual step of sending a letter to Congress saying he was "frustrated" in his efforts to persuade his superiors to remove Rezulin from the market. Once a supporter of the drug, Misbin told legislators there are now safer drugs available. ■

Clinipad recalls contaminated products

No injuries or complaints reported

The Clinipad Corp. in Rocky Hill, CT, is voluntarily recalling all povidone-iodine, tincture of iodine, benzoin tincture, acetone alcohol, and alcohol antiseptic products (swabsticks, prep pads, towelettes, and pouches), and Cliniguard protective dressings labeled as "sterile" that were manufactured in the last three years, according to a March 9 letter from Nelson M. Ford, president and CEO of Clinipad. The letter can be viewed at www.fda.gov/medwatch/safety/2000/clinip.htm and the complete list of products at www.fda.gov/medwatch/safety/2000/clinip1.htm.

The company made this voluntary recall due to confirmed microbial contamination in some lots of its sterile products, including one lot with *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and coagulase-negative *Staphylococcus*, which was recalled in December 1999. While Clinipad has received no confirmed reports of patient complaints or injuries as a result of contamination of these products, the potential for microbial contamination exists, and the company is unable to assure the sterility of products labeled and sold as sterile. Nonsterile products appearing on the recall list also are being recalled because the company cannot assure the products meet their microbial release specifications.

Advice to professionals

A March 29 letter from David W. Feigal Jr., MD, MPH, director of the Center for Devices and Radiological Health, advised health professionals that prepackaged procedure kits and trays may include some of the above-mentioned recalled products from Clinipad. More than 140 manufacturers prepare a variety of procedure kits and trays that include one or more of the Clinipad products.

The Food and Drug Administration's Center for Biologics Evaluation and Research has posted information regarding methods and products that may be used for skin preparation prior to the collection of blood and blood components. This information is available at www.fda.gov/cber/infosheets.htm. The Clinipad Corp. can be reached at (860) 571-0100. ■

NEWS BRIEFS

Janssen stops Propulsid marketing in U.S.

Janssen Pharmaceutica Inc. in Titusville, NJ, has voluntarily decided to stop marketing Propulsid (cisapride) in the United States effective July 14. The timing should provide a period during which patients and physicians can choose and initiate alternative treatment.

As of Dec. 31, 1999, Propulsid was associated with 341 reports of heart rhythm abnormalities, including 80 reports of deaths. Most of those adverse events occurred in patients who were taking concomitant medications or who were suffering from underlying conditions known to increase the risk of cardiac arrhythmia associated with Propulsid. Physicians treating patients for whom they believe the benefit of Propulsid outweighs the risk associated with taking it are encouraged to contact Janssen at 800-JANSSEN. The company will continue to make the drug available for patients meeting specific criteria for a limited-access protocol. The FDA Talk Paper on this subject can be viewed at www.fda.gov/bbs/topics/ANSWERS/ANS01007.html. ▼

New health book available

Health Data Sourcebook, a comprehensive manual that provides information regarding availability of hundreds of health care data sets from government agencies, associations, and commercial data vendors, has been released by NationsHealth Corp. in Memphis, TN.

The information in the manual is organized by categories, including demographic and psychographic data; vital statistics; health facilities; health professionals; need, demand, and utilization; and insurance and managed care. Within each category, a description of the data is presented, followed by a list of sources.

The book helps readers find, access, and evaluate available health care data. The book can be purchased for $95 by calling NationsHealth at (901) 276-3009. There is a money-back guarantee.

The goal of the corporation is to establish a national Internet-based warehouse of data. Information about the warehouse, expected to be fully operational by the middle of 2000, can be seen at www. nationshealthdata.com. ▼

Vials made nonsterile

In a recent letter to health professionals and dialysis clinicians, Sherri L. Brown, MD, director and senior safety officer with Amgen Inc. in Thousand Oaks, CA, shared information about problems that have arisen with multiple use of labeled, single-use Epogen (epoetin alpha) vials. Twenty-one episodes of bacteremia or pyrogenic reactions were reported in patients receiving Epogen at a U.S. dialysis unit.

An investigation by the Centers for Disease Control and Prevention showed that unused Epogen remaining in single-dose preservative-free vials was collected and pooled into common vials for use in other patients. That led to extrinsic bacterial contamination of Epogen.

Amgen officials said that while multiple-dose vials of Epogen contain preservatives, single-dose vials do not. Therefore, once a needle has been introduced into the vial, the sterility of the product no longer can be guaranteed.

Further, Epogen labeling directs that unused portions of the drug from single-dose vials should be discarded. The text of Amgen's letter can be viewed at www.fda.gov/medwatch/safety/2000/safety00.htm#epogen. For additional information, call Amgen's professional services department at (800) 772-6436. ▼

Alpha blocker cited

The American College of Cardiology recommends that physicians discontinue use of an alpha blocker, Cardura (doxazosin), for treating hypertension. The recommendation follows a study by the National Heart, Lung, and Blood Institute that showed those receiving Cardura had 25% more cardiovascular events and were twice as likely to be hospitalized for heart failure than those receiving the diuretic chlorthalidone. Currently, about 1 million Americans take an alpha blocker to help control their hypertension. ▼

New format available for MSDS database

Pharmacists track chemicals available at their institutions and maintain current Material Safety Data Sheets (MSDS) on those chemicals. Enterprise, FL-based SOLUTIONS Software's MSDS database is now available in a new version for Windows. The database includes more than 250,000 generic and trade name chemicals. It is now available on a single DVD-ROM and has the ability to search by company, chemical abstracts service, trade name / product ID, ingredients, or any other field in any combination.

In addition, the data records contain all fields required by the Occupational Safety and Health Administration and the 16-part MSDS standard. The MSDS records and lists resulting from searches can be viewed on-screen, printed, or exported to disk files for additional processing. To order, call Richard Dunkel at (407) 321-7912 or e-mail solution@env-sol.com. ▼

NSAIDs in elderly increase risk of CHF

Use doubled odds of hospital admission

A study published in the March 27, 2000, issue of *Archives of Internal Medicine* shows that use of nonsteroidal anti-inflammatory drugs (NSAIDs) can exacerbate development of congestive heart failure (CHF).[1] The authors performed a matched case-control study of the relationship between NSAID use and hospitalization with CHF. Cases (those admitted to hospitals with a primary diagnosis of CHF) and controls (those admitted to the same hospitals but without CHF) were interviewed for a thorough history of recent use of aspirin and other NSAIDs.

Results of the study show that recent use of NSAIDs in elderly cases (mean age 76.6 years, n=365) doubled the odds of hospital admission for CHF over that of controls (mean age 75 years, n=658). Both high dose and long plasma half-life of NSAIDs appear to increase the risk of CHF occurrence. In addition, the tendency of NSAIDs to antagonize the actions of diuretics and angiotensin-converting enzyme inhibitors may factor into the increased risk of CHF in elderly NSAID users. Also, there appears to be an increased risk in patients with a history of heart disease, even if that history did not include CHF.

Reference

1. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients. *Arch Intern Med* 2000; 160:777-784. ■

From the Editor

Feed your 'pocket brain'

The pocket brain is the newest feature of *Drug Utilization Review.* Here is this month's item.[1] Readers are encouraged to send suggestions for future items (with source noted) to the editor at ruthnoland@hotmail.com.

Pregnancy Risk Factors

Pregnancy risk factors (A, B, C, D, and X) indicate the level of risk a drug poses to the fetus. They do not refer to the risk to a baby from breast-feeding. The definitions for these factors are those used by the Food and Drug Administration [44 *Fed Reg* 37,434-37,467 (1980)].

Category A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Category B: 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 (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening

situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X: Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Reference

1. Briggs GG, Freeman RK, Yaffe SJ, eds. *Drugs in Pregnancy and Lactation*. 4th ed. Baltimore: Williams & Wilkins; 1994. ■

New FDA Approvals

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

✔ **Antineoplastic drug Viadur (leuprolide acetate implant) by ALZA Corp.** Viadur is indicated for palliative treatment of advanced prostate cancer. Each implant contains 72 mg leuprolide acetate (equivalent to 65 mg leuprolide free base) and is inserted subcutaneously in the inner aspect of the upper arm to deliver a continuous dose of leuprolide. Implant must be removed after 12 months of therapy, at which time another implant may be inserted.

✔ **Antiepileptic agent Zonegran (zonisamide) by Dainippon Pharmaceutical USA Corp.** Zonegran is indicated as adjunctive therapy in treatment of partial seizures in adults with epilepsy. Chemically classified as a sulfonamide and is unrelated to other antiepileptic drugs. Supplied as 100 mg capsule for oral administration to be given once or twice daily.

✔ **Apnea agent Cafcit (caffeine citrate) Injection by Boehringer Ingelheim Pharmaceuticals Inc.** Cafcit has received FDA approval for short-term treatment of apnea of prematurity (AOP) in infants between 28 and 33 weeks gestational age. Cafcit received Orphan Drug Status and is the only product approved for treatment of AOP. Available in ready-to-use 3 mL single-dose vials containing caffeine citrate at a concentration of 20 mg/mL (60 mg/vial), equivalent to 10 mg/mL caffeine base. Cafcit is dosed once daily. ■

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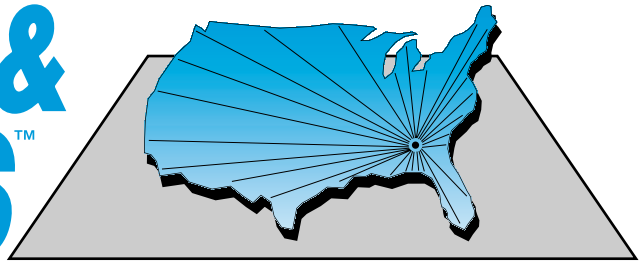

A review of tranexamic acid (Cyklokapron)

By **Karen Birmingham**, PharmD
Pharmacy Practice Resident
Medical University of South Carolina, Charleston

Indications

Tranexamic acid, manufactured by Pharmacia and Upjohn, is indicated for the prevention or reduction of bleeding and reduction of requirement for replacement therapy in hemophiliac patients who are undergoing tooth extraction. It is to be used only for a period of two to eight days.[1]

Pharmacology

Tranexamic acid is an antifibrinolytic agent synthetically derived from the amino acid lysine. During fibrinolysis, plasminogen adheres to lysine receptors on the surface of the fibrin molecule and is subsequently converted to plasmin by tissue plasminogen activator. Plasmin splits fibrin into large constituents, which are further degraded into more soluble components. A balance in the fibrinolytic system is maintained by the formation of a complex between plasminogen and fibrin and the resulting activation of plasminogen. If there is an excess of soluble fibrin, increased hemorrhage occurs.[2]

Tranexamic acid maintains the stability of fibrin clots by adhering to lysine binding sites and competitively inhibiting the activation of plasminogen, which prevents the formation of plasmin. At high concentrations, the drug noncompetitively inhibits existing plasmin.[1,3-4] In vitro studies have demonstrated that the potency of tranexamic acid is up to 10 times greater than that of aminocaproic acid, another lysine derivative.[1,3] Additionally, bond strength to fibrin surface receptors is greater for tranexamic acid than aminocaproic acid. In normal individuals, tranexamic acid prolongs thrombin time, but not coagulation time. Platelet counts and serum blood factor concentrations are unaffected by the drug.[1]

Pharmacokinetics

When taken orally, approximately 30% to 50% of tranexamic acid is absorbed from the gastrointestinal tract. Food intake does not appear to alter bioavailability. Peak plasma concentration is achieved approximately three hours after oral administration.[1] The drug is considered therapeutic at a plasma concentration of 10 mcg / mL, and therapeutic concentrations may remain for seven to 17 hours, depending on the tissue in which the drug is monitored.[3]

The volume of distribution of tranexamic acid ranges from 9 to 12 liters.[1] Less than 3% is bound to plasma protein (i.e., plasminogen). There is no binding to serum albumin.[1,3,5] Tranexamic acid diffuses across the blood-brain barrier.[2] In certain tissues, such as cerebrospinal fluid and aqueous humor, tranexamic acid concentrations are much lower than in serum. Joint fluid concentrations are equal to serum concentrations.[5] The drug is primarily filtered by the glomerulus, and the renal clearance rate mimics the plasma clearance rate of greater than 110 mL / min.[1,5] Urinary excretion of an oral dose and an intravenous dose 24 hours after administration is 40% and 90%, respectively. More than 95% of a dose is eliminated as unchanged drug.[1]

Selected clinical trials

The effect of tranexamic acid on hemorrhage associated with tooth extraction was investigated in patients with hemophilia A (classic hemophilia, n = 20) or hemophilia B (Christmas disease, n = 8).[6] The purpose of the trial was to determine if tranexamic acid reduces blood loss and the requirement for replacement therapy with plasma products in patients undergoing tooth extraction. Participants ranged in age from 13 to 65. Subjects who had hematuria at enrollment or within one month prior to enrollment were excluded from the trial. Two hours before

the tooth extraction procedure, patients were given either a 1 g oral dose of drug or placebo. Factor VIII or IX was administered one hour prior to surgery. All patients were treated with 1,000 mg of tetracycline per day, divided into four doses. Patients received either placebo or tranexamic acid at a dose of 1 g three times a day for five days. Fecal and oral blood loss were measured daily. If excess bleeding occurred, appropriate replacement therapy was administered. Laboratory tests included quantitation of factors VIII and IX, fibrinolysis assay, hematological indices, assessment of renal and liver function, and 12-lead electrocardiograms.[6]

The investigators reported a statistically significant decrease in blood loss in the treatment group ($p < 0.025$). Blood factor replacement was necessary in two patients in the treatment group, while 11 patients required transfusions in the placebo group. The authors failed to comment on the statistical significance of this finding. Both plasma fibrinogen and erythrocyte sedimentation rate were significantly increased in the control group on the last day of treatment ($p < 0.05$). Fibrinolysis was significantly decreased by tranexamic acid ($p < 0.05$). There were no differences in renal or liver function or electrocardiograms in either group, nor were any adverse events reported. Blood urea was significantly increased in both groups due to dental surgery ($p < 0.05$). The investigators concluded that tranexamic acid therapy during and after dental extraction reduces blood loss and requirement for blood factor transfusion in patients with either hemophilia A or B.[6]

The effect of tranexamic acid treatment on postoperative bleeding and need for replacement therapy was evaluated in patients with hemophilia who were undergoing oral surgery.[7] They compared three groups of individuals. The first group (group A) consisted of 17 patients, who received preoperative and postoperative replacement therapy as well as substitution therapy for bleeding with factor VIII/IX:C. In addition, tranexamic acid was administered in doses of 37-123 mg/kg of body weight daily.

Treatment duration varied from three to six days. Four patients in group A were given prophylactic antibiotics. Group B included 14 patients who received factor VIII/IX:C preoperatively and postoperatively, in addition to tranexamic acid at doses of 45-105 mg/kg of body weight. No substitution therapy was administered for hemorrhage. Treatment was continued for six to eight days. These patients also performed oral rinses with 10 mL of a tranexamic acid 5% mouthwash four times a day. This regimen was continued for five to seven days. Six patients in group B received antibiotic prophylaxis. Group C consisted of 11 patients. Replacement therapy was given to patients who demonstrated spontaneous factor VIII/IX:C activity that was less than 10% of the normal activity. Other patients received no substitution therapy but were treated with higher doses of tranexamic acid (72 to 106 mg/kg of body weight). Tranexamic acid 5% mouthwash was administered to all patients four times a day. Treatment duration for systemic therapy and oral rinses were six days and five days, respectively. Antibiotic prophylaxis was administered to 10 patients in group C.[7]

Seven patients in group A experienced 13 postoperative hemorrhages. All had received six days of systemic treatment with tranexamic acid. Nine of these bleeding occurrences required replacement therapy with factor VIII/IX:C. In group B, there were no episodes of postoperative bleeding, which was significantly different from group A ($p < 0.05$). Four patients in group C experienced hemorrhages postoperatively. They had all received preoperative replacement therapy. Five of six bleeding episodes required replacement therapy.

There was a statistically significant reduction in the amount of replacement factor given to the third group in comparison to both of the other groups ($p < 0.01$). The investigators observed no difference in the number of postoperative hemorrhages with regard to antibiotic prophylaxis. They concluded that treatment with both local and systemic tranexamic acid decreases postoperative hemorrhage in patients with hemophilia. In addition, the authors concluded that requirement for factor VIII/IX:C replacement therapy is reduced in patients treated with tranexamic acid. They also stated that fibrinolysis in the mouth may be a contributor to bleeding after oral surgery and that it may be controlled by oral rinsing with tranexamic acid.[7]

Adverse reactions

Retinal lesions have been observed in animal studies following either oral or intravenous tranexamic acid at doses of 125-1,600 mg/kg/day. This range represents doses that are three to 40 times higher than the typical human dose of tranexamic acid. The drug was administered anywhere from one week to one year. The occurrence and severity of retinal damage appears to be related to dose and may be reversible at low doses. Retinal alterations have not been observed

in human clinical trials; however, vision changes such as blurriness and impaired color vision are the most commonly reported adverse effects.[3,5] Hypotension, giddiness, or lightheadedness may occur with rapid intravenous administration.[1,4-5] Nausea, vomiting, and diarrhea may occur but usually cease if the dose is reduced.[1,3-5] Thromboembolic events[1,3] and obstruction of central retinal vessels have been documented.[1] Rare occurrences of menstrual discomfort have been reported.[3] There have been incidents of ureteric blockage[1,8] and renal cortical necrosis associated with use of tranexamic acid.[9]

Pregnancy/lactation

Tranexamic acid is categorized as pregnancy risk factor B, which is defined by one of the following: 1) no fetal risk has been demonstrated in animal studies but no studies have been performed with pregnant women, or 2) a fetal risk has been observed in animal studies but has not been verified in pregnant women.[10] To date, there have been no controlled trials conducted with pregnant human subjects. Transplacental passage of the drug does occur which results in similar serum concentrations of tranexamic acid in cord blood and maternal blood.[5,10]

Tranexamic acid was used to treat vaginal bleeding in 12 women who were in the final trimester of pregnancy. They received 1 g orally every eight hours for seven days. All 12 delivered healthy babies. Thrombogenesis secondary to tranexamic acid during pregnancy has not been demonstrated. Lactating women who received two days of treatment with the drug displayed breast milk concentrations of tranexamic acid equal to 1% of the serum concentration. The effect of this amount on a nursing infant is unknown.[10] Tranexamic acid has been measured in semen, but it does not appear to affect sperm activity.[5]

Contraindications

Use of tranexamic acid is contraindicated in patients who have color vision abnormalities, subarachnoid hemorrhage,[4-5] hematuria, or any history of thrombosis.[3]

Warnings

Patients should be monitored closely for any signs or symptoms of retinal alterations or visual disturbances. A baseline ophthalmic exam should be performed prior to initiation of therapy and at regular intervals throughout the course of treatment. Any visual changes require discontinuation of the drug. In cases of renal impairment, dosage should be reduced to reduce the risk of medication accumulation. Leukemia related to tranexamic acid occurred in mice who were given doses of 5 g/kg of body weight. Rats who received tranexamic acid for approximately two years in amounts exceeding the maximum tolerated dose experienced increased incidence of hyperplasia and certain tumors of the biliary system. This was not demonstrated in studies performed on another strain of rats. Mutagenicity related to tranexamic acid therapy has not been shown. There have been no controlled studies performed in children. Studies suggest that tranexamic acid may be safely used in the elderly population.[3,5]

Dosage and administration

Tranexamic acid should be administered in combination with replacement therapy prior to tooth extraction in patients with hemophilia. For intravenous therapy, the recommended dose for prophylaxis immediately before the procedure is 10 mg/kg of body weight. Rate of injection should be 100 mg/min or less.[3] Subsequent treatment is administered at the same dose three to four times a day for a period of two to eight days. Doses should be adjusted for renal impairment as outlined in the **table below**.

Dosing Adjustment for Tranexamic Acid in Renal Impairment[1]

Serum Creatinine	Intravenous Dosing
1.36-2.83 mg/dL	10 mg/kg BID
2.83-5.66 mg/dL	10 mg/kg QD
> 5.66 mg/dL	10 mg/kg every 48 hours or 5 mg/kg every 24 hours

BID = twice daily, QD = once daily

Drug interactions

Concurrent use of tranexamic acid with anti-inhibitor complex, Factor IX complex[1,3] or estrogen-containing products may increase the potential for thrombosis. Thrombolytic agents and tranexamic acid antagonize the effects of each other, therefore efficacy may be decreased if concomitant administration occurs.[3]

Dosage forms available

The oral formulation of tranexamic acid is no longer available (personal communication, Larry Frigo, Pharmacia and Upjohn, Feb. 18, 2000). The intravenous formulation is supplied in ampules of 10 mL at a concentration of 100 mg/mL. It should

be stored at 15° to 30° C and should not be frozen. An oral solution may be prepared as a 1:1 mixture of intravenous tranexamic acid and sterile water. Tranexamic acid is compatible with most components found in intravenous fluids used for infusion (e.g., dextran, electrolytes, carbohydrates, amino acids). Heparin and tranexamic acid are compatible when mixed together. The drug is incompatible in the same solution with penicillin and should not be added to blood products.[3]

Discussion

Tranexamic acid is approved for prevention or reduction of bleeding and reduction of requirement for replacement therapy in patients with hemophilia who are undergoing tooth extraction. Tranexamic acid controls hemorrhage by inhibiting fibrinolysis and stabilizing fibrin clots.[1] Agents similar to tranexamic acid that are currently available include aminocaproic acid[11] and desmopressin (DDAVP).[12] Aminocaproic acid is indicated for hemorrhage due to fibrinolysis and for bleeding after surgery. It is not currently approved by the FDA for hemorrhage associated with oral and dental surgery in hemophiliac patients.[3]

DDAVP is approved for use in patients with hemophilia A if serum factor VIII activity levels are greater than 5%. The drug is an effective intraoperative and postoperative hemostatic agent in this patient population. It is not indicated for use in patients with hemophilia B or for any patients with factor VIII activity of 5% or less.[13] DDAVP has been used in combination with tranexamic acid for minor hemorrhage induced by fibrinolysis, such as that associated with dental procedures.[14]

Several clinical trials have documented the efficacy of tranexamic acid for perioperative hemorrhage associated with dental surgery in patients with hemophilia A and B. These studies included a small number of patients. In addition, the number of patients evaluated in the different treatment groups was not well-documented. It should be noted that participants in the studies received oral tranexamic acid and that this formulation is no longer available.

Although an optimal dose of tranexamic acid was not established, the doses utilized in the investigations were effective in reducing bleeding episodes and decreasing the requirement for blood factor replacement. The adverse effects associated with tranexamic acid appear to be mild and are primarily related to high-dose therapy (such as gastrointestinal disturbances) or infusion rate (e.g., hypotension).

Tranexamic acid also has been used for control of intraoperative and postoperative bleeding associated with cardiac surgery. Although this is not currently an FDA-approved use, several studies have demonstrated the effectiveness of tranexamic acid when compared to placebo[15] and other agents[16] for perioperative hemorrhage.

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