AMERICAN HEALTH CONSULTANTS

DRUG UTILIZATION REVIEW

Pharmaceutical Care Across the Continuum

IN THIS ISSUE

■ What's in the future for hospital pharmacies? In this issue, *DUR* probes the shapes of things to come for:

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Forecasting the future: Technology, education to expand pharmacy's role

No one has an exact road map of the future of pharmacy. Even an educated guess is just that — a guess. Nevertheless, being aware of some of the more likely possibilities can help pharmacists prepare for whatever eventuality finally crops up, simultaneously build an expanded professional role, and provide better care for patients.

Seeking to explore pharmacy's prospects, *Drug Utilization Review* turned to highly credentialed, talented pharmacists working across the spectrum of practice settings. These professionals shared their varied views regarding pharmacy administration, technology, drug information, the Food and Drug Administration (FDA), patient privacy, managed care, ethics, herbal alternatives, DUR, and drug delivery systems.

Here's what they're thinking:

On pharmacy administration…

"I see the pharmacy director being a clinical business person," says **Ray Wilkins**, RPh, MS, director of pharmacy at Truman Medical Center, Hospital Hill in Kansas City, MO. "PharmDs are now getting MBAs and MPHs. They will be tomorrow's clinical directors. They'll need the clinical acumen and the business savvy to make decisions that are sound both clinically and financially.

"There's already a big transition underfoot to a clinical and business background for pharmacy directors. They have to know all the ins and outs of technology, drug therapy enhancements, and the significantly increased costs of new drugs — and all of this has to be measured through outcomes and the potential reduction of cost to the facility. Pharmacists have to be heavily involved. They're helping dismiss patients from the hospital earlier and, hopefully, helping keep patients out of the hospital.

"The best thing that could happen in the future for pharmacy administration is for the pharmacy director and the pharmacy department to be viewed throughout the facility as very valuable clinical resources," Wilkins tells *DUR*.

Along with this departmentwide recognition, the pharmacy director would be at a level commensurate with the chief of nursing and medical

director. "Once the pharmacy director is at that level, people will see significant enhancements in delivery of pharmacy services and in quality of patient care," he suggests. "The worst thing that could happen to pharmacy administration in the future is for pharmacy directors not to try to fully utilize technology and its capabilities."

On technology…

"We're already seeing the effects of technology on pharmacy practice through Pyxis machines and other medication delivery systems," notes Wilkins. "We're doing away with unit dose systems and moving forward to cartless systems with drugs stored in equipment at the nursing unit."

With these new systems, the pharmacist gets a copy of the drug order, inputs that order into the clinical informatics system, and reviews the order based on the specific patient diagnosis and concomitant drugs, he explains. After the pharmacist has authorized the order, the nurse can then pick up the patient profile on consult and access the drugs for the patient — avoiding the need to send first doses from the pharmacy. The nurse can access a few emergency drugs with overrides, but the typical order must go through pharmacy before nursing accesses a drug.

"I see us going to barcoding on the drug package itself, on the patient's armband, and on the medication administration record. Then, before the nurse administers a drug, all three barcodes must match up. This will have a positive effect on the role of the pharmacist," says Wilkins. "This system will help take the pharmacist from the distributive function to a more cognitive service. The role of the pharmacist is becoming more that of reviewing orders and determining whether or not the order is for the right drug and the right dose for the patient at that point in time. Pharmacists will have more time to use their clinical skills for things like reviewing the patient's disease state, reviewing renal status, and adjusting doses appropriately."

This sentiment is confirmed by **Larry Liberti**, RPh, MSc, president of Pharmaceutical Information Associates (PIA) of Fairless Hills, PA.

"Computerization will improve the ability to get more information about the patient to the pharmacy so that better drug-selection decisions can be made by the physician and verified by the pharmacist," says Liberti. "As we learn more about individual patient variances, we'll be able to tailor drug therapy more specifically. There will always be the need for the physician to prescribe. But with technology, pharmacists can be better gatekeepers and verify that appropriate therapy is being used."

Pharmacists' increasing reliance on technicians means technology can help pharmacists support the hospital staff more efficiently.

"We'll be able to use technology for better quality control," says Liberti. "It will also serve as cost-efficient methodology for dispensing drugs."

That technology can appear as robotics or, because many technicians are working under a pharmacist, through the use of technological links. "I'd like to see an electronic link between nurses, physicians, and pharmacists so they can all have input into a single, handheld device that would let everyone know what's going on with patient lab results and other pertinent information at the same time," says Liberti.

Based on the current shortage of pharmacists and the tremendous time demands made upon physicians and residents, "We need to have physician order entry potential via voice recognition," asserts Wilkins.

"I would hope that the physician, pharmacist, and nurse — the team — would be in one room, and the physician would say what the diagnosis is; the pharmacist would make a recommendation for the drugs to be used; the physician would OK the pharmacist's recommendation; the nurse, respiratory therapist, or whoever else is on the team would chime in with recommendations … and all of this would be recorded through voice recognition," he forecasts.

"Nothing would have to be written by hand. Everything would then be translated to one written document that's easy to read. It'll be a long time before that caliber of voice recognition is available, but we're already seeing physician

COMING IN FUTURE MONTHS

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- The effects of growing PBMs
- Evaluating evidence-based medicine
- Pharmacoeconomics and you
- Medicare & Bush — the way it is

order entry available at computers and through Palm Pilot devices. This process would also reduce both the time required to get orders entered and the potential for medication errors.

"I envision having the clinical pharmacist on the floor, available for consultation with the physician prior to the writing of patient orders," Wilkins continues. "In a teaching hospital such as ours, I'd like to see pharmacists [be] able to impact the order at the time it is written. That means having pharmacists round with the medical teams. This is a change that is met with reluctance by some and enthusiasm by others. Those pharmacists who have been in a distributive function for years are reluctant to make the transition to a more clinically oriented practice.

"Recent pharmacy grads and those with residency experience or who have been through clinically oriented programs recognize that this type of practice is more professionally rewarding. In fact, this group of pharmacists is very reluctant to perform distributive functions. You end up with a split staff. It works out OK for now, but as we make the transition to a cartless system, while the need for distribution will still be there, it won't exist to the extent it does today."

Initially, it will be very difficult economically for hospitals to make large jumps in technology, according to Wilkins.

"Historically though, as technology improves, either prices come down or the technology is enhanced for the same price. With this type of technology, those hospitals that are not on the cutting edge as alpha or beta sites will wait until the price is right for their use, and then they'll jump in. Hospitals will try to justify the costs of equipment and software through enhanced patient safety or cost-effective care," he notes. "Once we show that implementation of new technology helps free up pharmacists so that we have the right people available to impact therapeutic decisions, we can show that hospitals are getting an appropriate return on investment by having the most cost-effective care available."

As an analyst, **Don Fearon**, Immediate Response Center analyst at Cerner Corp. in North Kansas City, MO, figures out the location and details of technical problems when they occur and fixes those problems within two hours' time. So he is well-equipped to share another side of technology — that of technical support.

"Everything's moving toward automation, and hospitals are one of last true frontiers for becoming fully automated and paperless," he says. "Handheld devices are widely used today. Physicians are taking laptops and putting them in docking stations, dialing in from home, and then synchronizing with patient data from work to stay on top of the status of their patients. Any time machines are used, though, there's the possibility that they will break or be broken."

Technical support, then, will continue to play an important role in the future of technology as it becomes a fact of life in pharmaceutical practice.

"Technology has already and will continue to greatly improve the availability of drug information," notes Wilkins. "Where it doesn't already exist, we will one day have a computer system in every patient room. Already, there are terminals near rooms. In addition, there is the proliferation of handheld devices that readily provide drug information. For example, ASHP [the American Society of Health-System Pharmacists; find it at **www.ashp.com**] has a handheld device that provides drug information from their AHFS book."

On drug information…

"In the future, there could be a central repository of drug information," says PIA's Liberti. "Pharmacists could call up side-by-side comparisons of drugs being considered for formulary inclusion. Those evaluations then could be presented to the P&T committee with some local interpretation. This would provide a really good starting point. There would be a national overview. Manufacturers could feed information into all the centers. That could include New Drug Application (NDA) data, the manufacturer's assessment of the data, published resources, and expert opinions."

Liberti would like to see more totally independent drug analyses conducted — "not clinical studies, but evaluation of the data," he says. "This could be performed by independent drug information committees. Some countries have independent committees at the regulatory level assess NDA equivalents and regulatory submissions.

"I see having academic teams of specialists perform unbiased assessments of new drugs using standardized formats — such as the AHFS system of categories. The bulk of assessments can be done by an oversight committee, then disseminated to P&T committees," he adds. "That way, preparatory work for P&T committee meetings can be more centralized, saving the duplicative work routinely performed by numerous P&T committees. We could have centralized centers of excellence —

perhaps the NIH [National Institutes of Health; find it at **www.nih.gov**] would be one. This would be a boon to hospital pharmacists. It would also help remove any potential manufacturer bias and provide better interpretation of manufacturer information across many kinds of drugs."

Drug information practice has already changed in a different manner, according to **Gordon Vanscoy**, PharmD, MBA, assistant dean for managed care at the University of Pittsburgh School of Pharmacy.

"Historically, the method of providing drug information was to go to published literature and let the literature help determine practice," he says. "Over the last three years, this method has changed because of technology. Now, when results of a trial are presented at a national meeting, instead of waiting months for those results to be published in a peer-reviewed journal, we go to the Internet to read the results of unpublished data as they were presented to peers at the meeting."

Also, a plethora of journals is available on-line now, he points out. This technological resource reduces the time needed to access articles by omitting the trip to a library to pull articles or the wait for a library service to provide them by mail.

On the FDA…

Change is afoot at the FDA. "We'll have a new FDA commissioner soon. That change alone will likely bring about other changes," says **Kristi Wyatt**, RPh, MBA, director of regulatory affairs at Pharmion Corp. of Overland Park, KS. "The FDA is working under a recent risk-management initiative. This initiative monitors adverse events of drugs more closely and is the impetus behind recent changes required for product labeling. As a result, the FDA is quicker to act in removing products from the market when problems arise."

Some industry insiders believe the FDA has slowed its review time for new drugs and drug products. "There's a limit to how much review time can be shortened," asserts Wyatt. "I think that some temporary increases are to be expected when you're near that limit. New adverse event reporting guidelines were recently released, and they mention changing the regulations in the future."

On patient privacy…

Personal health information protection regulations are on the horizon. On April 12, President George Bush agreed to proceed with privacy regulations written by the U.S. Dept. of Health and Human Services, with the possibility of changing the regulations as written under the Clinton administration. "The regulations initially applied only to the electronic transfer of patient information," says Wyatt. "The final rule as currently written applies to any individually identifiable records communicated in any form — whether electronically, on paper, or orally. Further, patients are allowed access to their records and have the right to correct any misinformation contained in those records. Failure to comply with the regulations is punishable by both civil penalties and federal criminal penalties."

How will technology affect patient privacy?

"That's an issue that no one has an answer to right now," says Wilkins. "The challenge of the new privacy laws under discussion lies in determining how to best protect the patient's privacy and sensitive information given the proliferation of computer systems used in patient care. I don't have an answer for that. What if someone loses a Palm Pilot filled with information about the patients on their service? We need guidelines for what type of information can be entered and carried on Palm Pilot devices."

Patient privacy is an important issue for technological devices and software. Software can be considered a medical device. When it is, the FDA requires that complaints and incidents be documented and reported. "You have to have good security for systems using the Internet to send and receive patient data," notes Cerner's Fearon.

According to Vanscoy, "Key institutions need to take a proactive stance on protection of patient health information. This type of data is extremely valuable. Some institutions, in order to remain solvent, will exploit the data in their possession and sometimes cross lines of privacy. Technology will help ensure the ability to protect patient data, but patient protection must be the first priority of the institution."

On managed care…

Steve McRae, RPh, staff pharmacist at Truman Medical Center, Hospital Hill, views pharmacists as being outside the managed care loop.

"The best thing that could happen with managed care from the pharmacy standpoint is for pharmacists to get back in the loop and have an impact on cost and quality," he proposes. "That's what managed care used to be. This would have to happen on a regional or specific-location basis,

as with a staff model setting. National attempts with big chains produce savings that are all on paper. That's what we're doing right now. Changing one brand to another to reduce cost is not satisfying to pharmacists who want to make a clinical difference for patients. The $5 to $8 they get for their effort isn't satisfying either."

The worst thing that could happen with managed care in the future is already happening, according to McRae. "We're outside the loop. It will be really tough for pharmacy to try to get back into the loop. Costs are already as low as they can go and care is just mediocre to good," he says. "Pharmacists already sell a product for the cheapest price. Anything we want to do for clinical outcomes has to be done for free. Instead of trying to back our way into managed care, we need to get out of it with automation and technician dispensing to decrease costs."

Vanscoy shares a different angle. "I see managed care continuing to strive toward a balance of quality and cost," he says. "Part of what needs to happen, though, is for drug budgets to go beyond the pharmacy. Drug cost is part of the cost of total patient care and should be shared by the institution. Drugs should be viewed as any other technology or tool used in improving patient care."

On ethics…

Ethical decisions made in the future, in one sense, won't be much different from decisions pharmacists currently make, says Liberti.

"We've always had opinions and made decisions based on our ethical standards. We've used them to determine whether or not drugs as prescribed were done so ethically. We will apply these same standards to newer drugs just as we have to the older drugs," he explains. "Dispensing can become complicated by genetic aspects and life-threatening issues. Pharmacists will always say whether or not they want to participate in dispensing. If need be, the task can typically be passed to another colleague with a different view. Pharmacists have been using their own ethics to support or validate physician decisions and they'll continue to do so in the future.

"I believe there will be a heavy pharmacoeconomic influence on setting ethical standards of care. They'll have to be balanced with legal standards of care expected in particular therapeutic areas. The patient's well-being will remain the primary concern, but cost-effective care will be part of the challenge," he continues. "Ethical decisions in institutions will have to be multidisciplinary decisions. They can't be monopolized by any one group. To do so would mean we're going down the wrong path. I see more interdisciplinary standards of care developed."

If a Medicare component to pharmacy becomes law, there will be federal oversight of operations and payment/reimbursement processes, says **Rhonda Beene**, RPh, another staff pharmacist at Truman Medical Center, Hospital Hill.

"There will be no Medicare fraudulent billing. People will be forced to be more ethical and toe the line," she projects. "Regulations will be enforced. I don't see it happening as a result of something people do of their own accord but rather out of the need to survive financially.

"We've seen a huge shift in decision making from 10 years ago," says Beene. "In the past, providers had control. Then managed care and insurance companies took over. After that there was a shift in emphasis to information systems and integration. The recent change has resulted from fraudulent Medicare billing. With that came compliance officers who now determine how hospitals run. Those officers are typically attorneys, and a great deal of power lies in their office. It's important now to step up proactive compliance.

"From the biology standpoint, if we map specific genes and associate different disease states with those genes, then develop gene-specific treatment, ethics will play an important role in how we practice medicine and pharmacy," she adds. "Moral and religious beliefs will have an impact on how comfortable physicians are in prescribing, how comfortable pharmacists are in dispensing, and how comfortable patients are in taking these new medications. We've already seen such issues with RU486. I foresee people becoming uncomfortable, to varying degrees, with anything that alters life or life function.

"Pharmacists who accept and embrace new practices of medicine and pharmacy will be more likely to provide the best patient care in the future," says Beene. "Genomic medicine will provide better care and change the whole focus of medicine and pharmacy practice. Current medicine has been pretty reactive and very much after the fact. Gene therapy could give us the opportunity to be more proactive and allow us to anticipate problems before they occur. We'll have better management of diseases in the future."

To get to that point, though, pharmacists must be properly educated. "I don't foresee our present pharmacy school curricula keeping up with

information of this type. Gene therapy alone could bombard us with information. There will probably have to be some type of formalized educational program," she notes. "Continuing education will be very important for pharmacists already in practice. There might be certificate programs for pharmacists who specialize in genomic medicine.

"I hope to see pharmacists promoted as people who can help manage disease states. In order to gain that recognition, though, we need to be more proactive and be strong advocates of our own profession," asserts Beene. "We need to prove our worthiness so others can feel confident that we can bring something to the table. We need to be proactive in the management of disease states and have more interaction with physicians. In order to demonstrate valuable input, we'll have to stay atop of changes in technology and medications.

"I believe the worst thing that could happen in the future regarding ethics would be complete control by the government over ethical issues," she says. "Expanding Medicare, in and of itself, will mean more oversight from the federal government. The government will definitely have a hand in making ethical decisions, in particular with issues surrounding human genomics."

On herbal alternatives…

"We'll see stricter control on claims made for herbal remedies," Liberti tells *DUR*. "The situation has gotten out of hand now with claims that don't require scientific support. I see an expansion of the Investigational Drug Application and NDA processes for a special category of neutraceuticals. There has to be greater control at some point in time. If we don't do it proactively, there will be a safety problem in the future that will act as the catalyst to set controls into motion.

"Neutraceuticals should come under the scrutiny of the FDA because they are compounds that are ultimately designed to affect the structure and function of the body, just like any other medicinal," he suggests. "There will probably be interactions with the [Federal Trade Commission] and [the U.S. Dept. of Agriculture], but I see the FDA acting as the primary governing body."

FDA control of dietary supplements would simplify the pharmacist's ability to recommend products, according to Liberti.

"Right now we have a lack of standardized information about dosing and content. Compendial standards would help pharmacists give consumers a better sense of which products would best be used in specific situations, as well as provide information about interactions between herbals and drugs," he says. "The overall safety issues associated with these products are just now being defined. As they're better codified, quantitated, and disseminated, we'll see an improvement in the overall safety profile for patients.

"Because most neutraceuticals haven't been subjected to good, quality scientific studies, there could be problems lurking unseen with lack of efficacy or problems of safety," he notes. "We don't know about those problems until they're out in the broader population. If we were to implement a simpler way of screening products through regulatory requirements, that would improve safety and consumer confidence."

On DURs…

"In the future we'll see fewer retrospective drug utilization reviews and more prospective DURs performed," says Wilkins. "There will be an emphasis on outcomes. DURs will evaluate the cost to the system, pro or con, for use of specific agents. DURs will evaluate such issues as a drug's costing more up-front, but then DURs will evaluate the overall cost and potential cost-saving to the system in the long run. DURs will evaluate how able drugs are to prevent return visits to the emergency department and readmissions to the hospital. Of course, patient compliance plays an important part in these matters. DURs will measure patient compliance and the impact of compliance on the effects of drugs."

Technology will play an important part in DURs of the future, according to Wilkins.

"Different delivery systems will make the patient compliance issue more of a non-issue. New delivery systems — whether a completely new system altogether or a new drug reformulated into an already existing delivery system — will make it such that patients don't have to remember when to take their medications," he suggests. "Implanted systems are an example of one such system. These new technologies in drug delivery will help increase outcomes and make drug utilization outcomes research more powerful."

Vanscoy agrees that technology will play a crucial role. "Technology is catching up to DUR,"

he says. "DUR criteria are held in computer systems to assure proper patient selection and management, and then the computers kick out the analyses."

"I see more concurrent DUR evaluation," he adds. "We'll still have to create criteria and translate the parameters, but pharmacy computers can then use the variances to trigger target lists for pharmacists to follow up on. Additionally, we need to focus less on very expensive studies and more on opportunity costs from traditional programs," he says.

On drug delivery systems…

A lot of time will be spent by staff organizing drugs into storage systems and areas, according to Liberti. Sterile areas will be required for some of the new delivery systems. Special areas and equipment will be required for proper preparation of the drugs prior to delivery to the patient.

"A lot more patient instruction will be required as these drugs are dispensed, resulting in more time spent by the pharmacist," he says. "There will be costs incurred to organize pharmacies and the physical plant to accommodate the storage, preparation, and administration of new drug delivery systems."

"Because we're working on the development of long-acting depot forms, there is great promise for enhanced patient compliance," notes Liberti. "However, resistance remains on the part of the patient because many of these drug delivery systems are invasive. They require an injection or implant. Physicians are concerned because of limited options if an adverse event or drug interaction occurs. There's no intuitive way to stop the effect of the drug. Does this put the patient at increased risk?

"That's the balance we have to figure out — safety, compliance, and efficacy. The balance has been a problem for the past 20 years, but nothing's changed the picture for today in any significant way." ■

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New FDA Approvals

These drugs recently received final approval from the Food and Drug Administration (FDA):

Anesthetic sevoflurane (Ultane) by Abbott Laboratories. The FDA has granted approval of sevoflurane for the induction and maintenance of **general anesthesia** in adult and pediatric patients for inpatient and outpatient surgery.

Antiviral valganciclovir hydrochloride (Valcyte) tablets by Roche. The FDA has granted approval of valganciclovir for the treatment of **cytomegalovirus (CMV) retinitis** in patients with acquired immunodeficiency syndrome (AIDS). The drug is available in 450 mg tablets.

DuoNeb (3 mg albuterol sulfate and 0.5 mg ipratropium bromide per 3 mL) inhalation solution by Dey Laboratories. DuoNeb has been approved for the treatment of **bronchospasm** associated with **chronic obstructive pulmonary disease** (COPD) in patients who require more than one bronchodilator.

Galantamine hydrobromide (Reminyl) by Janssen. The FDA has granted approval of galantamine for the treatment of mild to moderate dementia of the **Alzheimer's** type. Galantamine is dosed twice daily and is available in 4 mg, 8 mg, and 12 mg tablets. ■

IN THE PIPELINE

AstraZeneca's budesonide modified-release capsule (Entocort) has been granted priority review status by the FDA. The drug has been filed for the treatment of mild to moderate, active **Crohn's disease**.

Eli Lilly reports that the FDA's Center for Biologics Evaluation and Research has granted priority review to product drotrecogin alfa (proposed brand name: Zovant). The biologics license application was filed in January for the product to be used in the treatment of **sepsis** with associated acute organ dysfunction.

Inex Pharmaceuticals Corp. began enrolling patients in a Phase II trial for its lead product, Onco TCS, as part of a first-line treatment for **aggressive non-Hodgkin's lymphoma**. The trial is being conducted at the University of Texas MD Anderson Cancer Center in Houston. Onco TCS also is being evaluated in a pivotal Phase II/III trial for second or later relapsed aggressive non-Hodgkin's lymphoma and in two Phase II trials.

MGI Pharma Inc. reports commencing a pivotal Phase III trial of irofulven, its anticancer agent for treatment of patients with **advanced-stage pancreatic cancer**. The study compares irofulven to 5-fluorouracil (5-FU) with survival as the primary endpoint. Tumor response and other clinical benefits are the secondary endpoints.

NeoTherapeutics has started a Phase II study of Neotrofin in **Parkinson's disease**. Neotrofin already has been administered to 1,100 patients for the treatment of Alzheimer's disease. ■

DRUG CRITERIA & OUTCOMES™

Review: Angiotensin-converting enzyme inhibitors (ACEIs)

By **Leigh Ann Kipley**, PharmD
College of Pharmacy
The University of Texas at Austin

Introduction

Since their introduction in the 1980s, angiotensin-converting enzyme inhibitors (ACEIs) have helped change treatment strategies for cardiovascular dysfunction. A variety of studies have proved the efficacy of ACEIs in the treatment of hypertension, congestive heart failure (CHF), and myocardial infarction (MI). The ACEIs are structurally heterogeneous in that the functional, or active, side chain binds to angiotensin-converting enzyme. Most of the ACEIs contain a carboxyl side group except for fosinopril and captopril, which have a phosphinyl and sulfhydryl group, respectively. The differences in the binding groups may be responsible for the variable pharmacologic and pharmacokinetic properties of the ACEIs.[1]

Currently, 10 ACEIs are available in the United States. The older ACEIs, which include captopril and enalapril, are dosed multiple times per day, whereas the newer agents are dosed once daily. Representative formulary ACEIs for the treatment of hypertension and CHF include quinapril (Accupril), fosinopril (Monopril), and lisinopril (Prinivil, Zestril).

In January 2000, the *New England Journal of Medicine* published the results from the Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, which reported the cardiovascular effects of ramipril (Altace) in high-risk patients.[2] As with many clinical trials sponsored by pharmaceutical companies, no head-to-head studies exist, which has resulted in significant interest as to whether these benefits are unique to ramipril or are associated with a class effect.

This review focuses on the differences and similarities between typical formulary agents and ramipril. Two additional ACEIs, captopril (Capoten) and enalapril (Vasotec), also will be included in order to compare and establish clinical effectiveness.

Pharmacology

Mechanism of action

Angiotensin-converting enzyme (ACE) catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II has a variety of physiologic effects, including increasing sodium and water retention, which induces left ventricular remodeling, causing vasoconstriction. Bradykinin also is a substrate of ACE and catalyzes the conversion of bradykinin to inactive peptides. When the ACEI is bound to ACE, binding to angiotensin I and bradykinin is inhibited, and both of the above pathways are inhibited. Reductions in angiotensin II production result in vasodilation, reduced cardiac hypertrophy, and decreased sodium and water retention. When bradykinin is unable to bind to ACE, an alternate degradation pathway inactivates bradykinin to prostaglandin. Since prostaglandin is a vasodilator, further reductions in blood pressure may occur.[1,3,4]

Binding groups

All of the ACEIs are 2-methylpropionyl-L-proline analogues that differ by specific individual functional groups binding to the zinc moiety in the ACE binding site. Captopril has a sulfhydryl group, fosinopril has a phosphinyl group, and all of the others have a carboxyl group. The differences in the binding groups lead to variations among the agents. For example, the sulfhydryl group on captopril is believed to be the cause of hypersensitivity reactions. Also, the phosphinyl group on fosinopril is associated with a reduced incidence of cough.

Quinapril contains magnesium and has been reported to have more drug interactions.[1,3,5]

Prodrug

Many ACEIs are prodrugs, which rely on liver metabolism to convert the parent drug to the active drug (denoted with *-at* at the ending of the chemical name). Ramipril, quinapril, fosinopril, and enalapril are converted by the liver to their active counterpart ramiprilat, quinaprilat, fosinoprilat, and enalaprilat, respectively. Lisinopril is the only agent that does not undergo liver metabolism. Captopril is not a prodrug, but is metabolized by the liver to disulfide metabolites.[1,3,5]

Lipophilicity

Lipophilicity characteristics vary between the ACEIs. Lisinopril has significantly reduced lipophilicity compared to the other agents, and fosinopril is the most lipophilic of the ACEIs. In vitro studies and animal data suggest that greater lipophilic properties are associated with more efficient ACE inhibition in tissues. However, an ACEI reaching the tissue does not mean the drug will necessarily bind to tissue ACE.

Although fosinopril and quinapril are more lipophilic than ramipril, ramipril is the only agent that has been studied in human tissue samples to demonstrate binding to human tissue ACE.[5] Unfortunately, the possible clinical benefit of tissue ACE inhibition has yet to be determined. Some researchers hypothesize that an increased ability to inhibit tissue ACE will result in better outcomes. However, additional research is needed to determine if tissue ACE inhibition produces any advantage in the clinical setting.[1,5-7]

Pharmacokinetics

Absorption

Most of the ACEIs are absorbed rapidly after oral administration, with the exception of lisinopril and fosinopril, which are absorbed slowly. Food can affect the absorption of certain ACEIs. For example, the rate of absorption of ramipril is reduced when taken with food, and the rate and extent of absorption of quinapril are reduced when taken with high-fat food. Food does not alter the rate or extent of absorption of fosinopril or lisinopril.[3,8,9]

Distribution

Fosinoprilat and quinaprilat are highly protein-bound; therefore, both agents have a small volume of distribution. Ramipril is only moderately protein-bound, and lisinopril has little protein binding.[3,8]

Metabolism

As noted above, ramipril, quinapril, fosinopril, and enalapril are converted to the active agents via the liver. Fosinopril has more hepatic metabolic involvement than any of the other ACEIs.[3,8,9]

Elimination

Quinapril, lisinopril, captopril, and enalapril are eliminated mainly by the kidneys. Fosinopril and ramipril are eliminated 50% and 70%, respectively, by the kidneys.[3,5,6,8]

FDA-labeled indications

All of the ACEIs of concern in this report are indicated for the treatment of hypertension and CHF. Ramipril, lisinopril, and captopril also are indicated for use after acute MIs. Captopril and enalapril are indicated for left ventricular dysfunction. Only captopril is indicated for use in diabetic nephropathy.[1,9]

Adverse effects

The most common adverse effects associated with ACEIs include cough, central nervous system effects (headache, dizziness), cardiovascular effects (hypotension, angina, syncope), and elevated serum creatinine and potassium. Less common complications include hypersensitivity reactions (rash, angioedema) and acute renal failure.[10]

Cough

The cough is described as dry, nonproductive, and irritating. It appears to be more common in women and nonsmokers. In the HOPE trial, 1.9% of patients discontinued treatment with ramipril due to cough.[2] Incidence varies, with different sources providing incidence ranging from 0.7% to 48%. Discontinuation rates of ACEI agents due to cough range from 1% to 10%. Researchers believe the cough is due to an accumulation of bradykinin. In a few studies, fosinopril has been shown to have a reduced incidence of cough, perhaps due to the phosphinyl binding group. Switching ACEI agents may or may not reduce the occurrence of cough.[2,10-12]

Rash

Rash is the most common type of hypersensitivity reaction associated with the ACEIs. Most

often, the skin reaction manifests as a pruritic maculopapular eruption. Captopril is the ACEI most commonly associated with rash. Rash also has been reported with ramipril. The incidence of rash has been estimated for quinapril, fosinopril, and lisinopril to be 1.4%, 2.2-9.7%, and 1.3-1.7%, respectively.[8,10]

Angioneurotic edema (angioedema)

Angioedema rarely occurs (0.1-0.2% of all patients), but it is potentially life-threatening. The rate of occurrence is highest during the first month of treatment and is not dose-related. The incidences of angioedema among the ACEIs are: ramipril, < 1%; quinapril, 0.5-1%; lisinopril, 0.1%; and fosinopril, < 1%. Black Americans are at increased risk of developing angioedema and may experience more severe symptoms.[3,8,10]

Hyperkalemia

Elevated serum potassium levels have been reported with the use of ACEIs due to the inhibition of aldosterone. The risk of developing hyperkalemia is increased in patients with impaired kidney function and in patients taking potassium supplements or potassium-sparing diuretics. The incidences of hyperkalemia among the ACEIs are: ramipril, ~1%; quinapril, ~2%; lisinopril, ~2%; and fosinopril, ~2.6%.[8,10]

Acute renal failure

Acute renal failure may result from the lack of efferent arteriole vasoconstriction when ACE is inhibited. It is more common in patients with renal artery stenosis or with only a single kidney. ACEIs may reduce glomerular filtration in patients with severe CHF or patients overtreated with diuretics.[3,10]

Contraindications

Ramipril, quinapril, fosinopril, and lisinopril are contraindicated in individuals with hypersensitivity to the respective agent or any member of the ACEIs class. Because ACEIs are classified Pregnancy Category D in the second and third trimester, use during pregnancy is contraindicated.[8,10,13]

Warnings

Neutropenia and agranulocytosis

Neutropenia and agranulocytosis have resulted from the use of captopril, enalapril, lisinopril, and quinapril. No data are available indicating that the other ACEIs do not cause neutropenia and agranulocytosis. Monitor patients with renal failure and collagen vascular diseases.[8]

Angioedema

ACEIs should be avoided in patients who are allergic to any ACEI due to the increased risk of anaphylactic reactions. As noted previously, angioedema of the face, extremities, lips, mucous membranes, tongue, glottis, or larynx has been reported with use of ACEIs.[8]

Proteinuria

Proteinuria has been reported and most often is associated with captopril.[8]

Hypotension

ACEI use in severely salt- or volume-depleted individuals may result in excessive hypotension and should be used with caution. Monitor patients for first-dose hypotension during therapy initiation.[8]

Renal function impairment

Impaired renal function reduces the elimination of lisinopril, ramipril, quinapril, and fosinopril. Treatment with ACEIs has resulted in an increase in blood urea nitrogen and serum creatinine. *Drug Facts and Comparisons* recommends monitoring renal function in all patients upon initiating ACEI therapy. Dosage adjustments may be needed to avoid accumulation.[8]

Hepatic function impairment/failure

Hepatic dysfunction can alter clearance of the ACEIs that are metabolized hepatically. Thus, lower doses of fosinopril and ramipril are recommended in patients with hepatic impairment. ACEIs should be discontinued in patients who develop jaundice or marked elevations in hepatic enzymes.[8]

Elderly

Because elderly patients may have reduced renal function, doses of renally eliminated ACEIs may need to be adjusted. Therefore, dosage reductions are recommended for ramipril, quinapril, and lisinopril. Reduced renal function does not affect the dosing of fosinopril because the agent has dual elimination (renal and hepatic).[8]

Pregnancy

All of the ACEIs are Pregnancy Category C during the first trimester of pregnancy and Pregnancy Category D during the second and third trimester

of pregnancy. ACEI therapy should not be used during any portion of the pregnancy.[13]

Lactation

Captopril does pass into breast milk and should be avoided by nursing mothers. However, only negligible amounts of enalapril were found in breast milk in several studies. All other ACEIs should be avoided during lactation due to lack of safety studies.[13]

Children

The safety and efficacy of the ACEIs in pediatric patients have not been established. Captopril has been used in a limited number of instances. Hypotension, oliguria, and seizures rarely have been reported with captopril use in children.[8]

Precautions

Hyperkalemia

Elevated serum potassium has been reported with use of ACEIs.[8]

Surgery/anesthesia

Anesthesia use during surgery combined with ACEI therapy may result in increased hypotension.[8]

Drug interactions

All ACEIs interact with diuretics/sympathomimetics, resulting in additive hypotension. Additionally, all ACEIs interact with potassium-sparing diuretics, resulting in hyperkalemia. The drugs in this class interact with nonsteroidal anti-inflammatory drugs (NSAIDs), with loss of hypotensive action and deterioration of renal function as effects. All ACEIs also interact with lithium, resulting in lithium toxicity. Quinapril interacts with tetracycline and quinolone antibiotics, resulting in decreased tetracycline absorption and decreased quinolone absorption.[5,8,14]

Dosing and administration

Dosing and administration of ramipril and other representative ACEIs for hypertension and CHF (respectively) are displayed in the accompanying table.[9,15] **(See figure, p. 5.)**

Dosing adjustments need to be made in patients with renal impairment and in the elderly. Patients on ramipril with a creatinine clearance (ClCr) of 10-50 mL/min should receive 50-75% of the normal dose. If ClCr is less than 10 mL/min, they should receive only 25-50% of the normal dose. Patients on quinapril should be given 75-100% of the normal dose if ClCr is 10-50 mL/min, and 75% of the normal dose of ClCr is less than 10 mL/min. No adjustment is necessary for fosinopril if ClCr is greater than 10 mL/min; patients on dialysis should receive 20-50% of the normal dose of fosinopril. Patients receiving lisinopril should receive 50-75% of the normal dose if ClCr is 10-50 mL/min; 25-50% of the normal dose if ClCr is less than 10 mL/min; and 50% of the normal dose if on hemodialysis.[9,15]

Typical formulary agents (quinapril, fosinopril, lisinopril) compared to ramipril

Pharmacology

All of these agents have a common mechanism of action. Ramipril, quinapril, and lisinopril have carboxyl binding groups, whereas fosinopril has a phosphinyl binding group. Lisinopril is the only agent that is not a prodrug; therefore, lisinopril does not rely on the liver for metabolic conversion and activation.

Fosinopril is the most lipophilic, whereas lisinopril is the least lipophilic. Greater lipophilicity has been reported to be associated with more efficient ACE inhibition in tissue. Unfortunately, no data are available to substantiate this claim. Although the lipophilic agents reach the tissue, no data exist suggesting increased ACE tissue inhibition. Ramipril is the only ACEI studied that has been shown to bind to tissue ACE in humans.

Pharmacokinetics

Administering ramipril and quinapril with food reduces the absorption; however, fosinopril and lisinopril absorption is not affected by food. Quinapril and fosinopril are highly protein-bound and subsequently have a small volume of distribution. Ramipril is only moderately protein-bound, whereas lisinopril has little protein binding. Quinapril is mainly eliminated by the kidney, and is activated only by the liver. Fosinopril has equal hepatic and renal clearance. Ramipril has more kidney than liver clearance. Lisinopril is solely eliminated by the kidney and has no hepatic metabolism.

Dosing adjustments

All of the ACEIs included in this discussion are eliminated renally to some extent, and adjusting doses depends on the agent and the patient's renal function. Fosinopril does have an equal amount of hepatic involvement and does not need to be adjusted until the patient undergoes hemodialysis. Because many elderly patients are

Figure

	Initial Dose	Maintenance Dose	Maximum Dose
Ramipril			
Hypertension	2.5 mg q d	2.5-20 mg q d	20 q d
CHF	1.25-2.5 mg bid	5 mg bid	5 mg bid
Quinipril			
Hypertension	10 mg q d	20-80 mg q d	80 mg q d
CHF	5 mg bid	10-40 mg q d	40 mg q d
Fosinopril			
Hypertension	10 mg q d	20-80 mg q d	80 mg q d
CHF	10 mg q d	20-40 mg q d	40 mg q d
Lisinopril			
Hypertension	10 mg q d	20-40 mg q d	40 mg q d
CHF	5 mg q d	5-40 mg q d	40 mg q d

renally and / or hepatically impaired and more sensitive to reductions in blood pressure, dosage adjustments are recommended.

Indications

Ramipril has the same indications as lisinopril, which include hypertension, CHF, and acute MI. Quinapril and fosinopril are indicated only for hypertension and CHF.

Adverse effects

Fosinopril is least likely to cause cough, perhaps because of the phosphinyl group.

Drug interactions

Because quinapril contains magnesium, drug interactions exist with concurrent tetracycline and quinolone therapy. Ramipril, fosinopril, and lisinopril are associated with the classic ACEI drug interactions, which include diuretics, potassium-sparing diuretics, NSAIDs, and lithium.

Dosing

Most of the ACEIs included in this review are dosed once daily in hypertension and CHF. Ramipril is dosed once daily for hypertension and twice daily for CHF.

Efficacy

No head-to-head trials have been performed comparing the agents discussed in this review and ramipril. Therefore, clinical effectiveness can only be estimated using captopril and enalapril as surrogate markers. Clinical trials have demonstrated that ramipril is as effective as enalapril and captopril in treating hypertension and CHF. In addition, quinapril, fosinopril, and lisinopril have been shown to be as effective as enalapril and captopril.

Frishman and colleagues performed a placebo-controlled study of 403 patients evaluating the efficacy of quinapril vs. captopril vs. placebo.[16] Results showed that quinapril had equal efficacy to captopril. Gavazzi and colleagues studied the efficacy of quinapril vs. captopril in CHF in a double-blind, randomized, parallel study with 156 patients.[17] Results showed quinapril to be as efficacious as captopril in CHF.

Goldstein and associates evaluated the efficacy of fosinopril vs. enalapril in a double-blind, randomized study of hypertension in 214 patients.[18] Results showed fosinopril was equal in efficacy to enalapril. Zannad and co-workers conducted a double-blind study of the efficacy of fosinopril vs. enalapril in 254 patients with CHF.[19] Results showed fosinopril more efficacious than enalapril. Nami and colleagues performed a randomized, double-blind study of response rates of monotherapy for hypertension in 80 patients.[20] Study drugs included ramipril, lisinopril, quinapril, and enalapril. Results showed ramipril was equal to lisinopril, which was greater than quinapril, which was greater than enalapril in response rate.

Manthey and colleagues studied the efficacy of ramipril vs. enalapril in CHF in a randomized, double-blind study of 15 patients.[21] Results indicate that ramipril is equal to enalapril in efficacy. deGraeff and associates evaluated the efficacy of ramipril vs. captopril in a randomized, double-blind study of 12 patients with CHF.[22] Results showed that ramipril has a slower onset and longer duration of action than captopril. Acanfora and co-workers conducted a study of the efficacy of quinapril vs. captopril in their

double-blind, randomized study of CHF in 131 patients.[23] Results showed quinapril to be equally efficacious to captopril.

The HOPE trial[2]

Study design

A randomized, placebo-controlled, double-blind, two-by-two factorial multicenter clinical trial evaluated ramipril and vitamin E in high-risk patients with evidence of vascular disease or diabetes plus one other cardiovascular risk factor and with no known evidence of low ejection fraction or heart failure.

Patients

Inclusion criteria included age of at least 55 years, history of coronary artery disease, stroke, peripheral vascular disease, or diabetes, and at least one other cardiovascular risk factor (hypertension, elevated total cholesterol, low HDL, cigarette smoking, or documented microalbuminuria). Exclusion criteria include noncompliance during run-in phase, history of heart failure, low ejection fraction (0.40), prior use of ACEI or vitamin E, uncontrolled hypertension, overt nephropathy, or an MI or stroke within four weeks of study commencement. A total of 10,576 patients were eligible for the study.

Timeline

The study ran from September 1994 to March 1999. Originally, the study was to last five years, but after 4.5 years, evidence clearly demonstrated the beneficial effects of ramipril and the study was terminated.

Sites

Patients were recruited from 129 centers in Canada, 27 centers in the United States, 76 centers in 14 western European countries, 30 centers in Argentina and Brazil, and five centers in Mexico.

Sponsorship

The study was funded by the Medical Research Council of Canada, Hoechst Marion Roussel, AstraZeneca, King Pharmaceuticals, Natural Source Vitamin E Association, Negma, and the Heart and Stroke Foundation of Ontario.

Interdisciplinary review board

The review board at each institution approved the protocol.

Treatment groups

Ramipril 10 mg q d or Ramipril placebo q d
+ Vitamin E 400 IU q d or Vitamin E placebo q d

Primary endpoints

MI, stroke, or death from cardiovascular causes.

Secondary endpoints

Death from any cause, revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes.

Methods

All eligible patients participated in a run-in phase before the study began. Patients received 2.5 mg ramipril once daily for seven to 10 days, followed by matching placebo for 10-14 days. More than 1,000 patients were excluded due to noncompliance, adverse effects, abnormal serum creatinine or potassium levels, or withdrawal of consent. Of the remaining 9,541 patients, 48% were randomly assigned to receive 10 mg ramipril every day, while another 48% were assigned to receive placebo every day. The remaining 2% received low-dose 2.5 mg ramipril daily.

As noted above, treatment duration was set at five years. Upon study initiation, patients were assigned to receive ramipril or placebo at 2.5 mg dose every day for one week, 5 mg every day for the next three weeks, and 10 mg every day thereafter. All patients were also randomized to receive 400 IU vitamin E or placebo daily. The SECURE trial reports the results of the vitamin E companion study and the low-dose ramipril substudy.[24] Follow-up visits were scheduled at one month, six months, and every six months thereafter. At each visit, data were collected on the outcome events, compliance, and adverse effects. Each patient was continued on all other non-ACEI medications prior to study initiation. The MICRO-HOPE, a substudy of the HOPE trial, reported the effects of ramipril on the cardiovascular and microvascular outcomes in diabetic patients, and the results will be discussed later in this review.[25]

Statistics

A total of 9,000 patients were required to achieve a 4% event rate per year for five years, with 90% power to detect a 13.5% reduction in relative risk. Data were analyzed on an intention-to-treat basis. Survival curves were estimated according to Kaplan-Meier procedure,

and treatments were compared with use of the log-rank test. All analyses were stratified for randomization to vitamin E or placebo.

Results

At baseline, patients in the ramipril group had blood pressure of 139/79 mmHg vs. 139/79 mmHg for patients in the placebo group. At one month, ramipril and placebo group blood pressures were 133/76 mmHg and 137/78 mmHg, respectively. At two years, blood pressures measured 135/76 and 138/78 mmHg, respectively. By the end of the study, ramipril patients measured 136/76 mmHg, and placebo group patients measured 139/77 mmHg.

Upon study completion, a 22% relative risk reduction of the combined primary outcome of cardiovascular death, MI, and stroke was observed.

Microalbuminuria, Cardiovascular and Renal Outcomes (MICRO-HOPE) substudy[25]

The HOPE study included a substudy focusing on effects of ramipril on cardiovascular and microvascular outcomes in diabetic patients. A total of 3,577 people were eligible for the substudy, based on the same inclusion and exclusion criteria as the HOPE trial.[2] The primary endpoints also were the same as the HOPE trial, including cardiovascular death, MI, or stroke. Similarly, the secondary endpoints were identical to the HOPE trial. Upon substudy completion, a 25% relative risk reduction of the combined primary outcome of cardiovascular death, MI, and stroke was observed.

At baseline, patients in the ramipril group had blood pressure of 142/80 mmHg vs. 142/79 mmHg for patients in the placebo group. At one month, ramipril and placebo group blood pressures were 136/77 mmHg and 141/79 mmHg, respectively. At two years, blood pressures measured 139/77 and 142/78 mmHg, respectively. By the end of the study, ramipril patients measured 140/77 mmHg, and placebo group patients measured 142/77 mmHg.

Discussion of results from HOPE and MICRO-HOPE

The changes in the primary outcomes in the HOPE trial between the placebo treated group and the ramipril treated group were:

- CV death: 8.1% vs. 6.1% (26% risk reduction);
- MI: 12.3% vs. 9.9% (20% risk reduction);
- stroke: 4.9% vs. 3.4% (32% risk reduction).

The MICRO-HOPE trial specifically looked at the same endpoints in a subset patient population of diabetics and showed the following outcomes:

- CV death: 9.7 vs. 6.2 (37% risk reduction);
- MI: 12.9% vs. 10.2% (22% risk reduction);
- stroke: 6.1% vs. 4.2% (33% risk reduction).

The ramipril-treated group had a slight advantage with better blood pressure control. This independent factor (lower blood pressure in the ramipril group) is estimated by the drug manufacturer to have accounted for 5-7% of the risk reductions shown above.[26]

Although no other ACEIs were evaluated in the HOPE trial, the drug manufacturer does not believe that these benefits can be expected to be an ACEI class effect. To refute the class-effect concept, the pharmaceutical company proposes that ramipril has increased lipophilicity. Lipophilicity is said to improve tissue binding, which might confer better end-organ protection. Unfortunately, there have been few direct head-to-head trials comparing ACEIs that are highly tissue-bound to those with more limited tissue binding. In situations where such comparisons have occurred, the results do not convincingly support the claim of overall superiority for lipophilic ACEIs.

Conclusions

While simple reductions in blood pressure in the ACEI-treated group can explain about 20% of the overall benefits in the primary outcome measures of the HOPE and MICRO-HOPE trials, there remains an additional level of benefit. Without any direct comparison within the HOPE or MICRO-HOPE studies, the likelihood that this benefit represents a "class effect" cannot be excluded. Despite the lack of a provable theory as to why ramipril would uniquely result in these outcomes, the fact remains that no other ACEI has shown these results at this point in time.

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