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New cholestorol treatment guidelines — reaching even lower LDL levels

Physicians debate drug combination or aggressive statin therapy

Now that the National Cholesterol Education Program has updated its clinical practice guidelines on cholesterol management, one of the questions is how health care providers can reach the lower treatment goals for low-density lipoprotein (LDL) cholesterol for patients at high and moderately high risk of a heart attack. The guidelines, for example, offer a new therapeutic option to treat very high-risk patients to levels below 70 mg/dL. **(For more information on the updated guidelines, see *Drug Formulary Review,* September 2004, p. 65.)**

Peter H. Jones, MD, associate professor of medicine and co-director of the Lipid Metabolism and Atherosclerosis Clinic at Baylor College of Medicine in Houston, recently gave a presentation about how to achieve the LDL goals in high-risk patients. He made this presentation at the National Lipid Association meeting in Orlando, FL, in August.

High-dose therapy: Is more really better?

Clinical trial evidence shows that in those very high-risk individuals, a more intense LDL-lowering treatment program is in their best interest, certainly better than a less intensive LDL-lowering program, Jones says. "Most of those trials have tended to focus on monotherapy and they tend to be higher-dose statins, at least the more efficacious statins like high-dose atorvastatin [Lipitor], for instance."

The average LDL of the patient at risk for coronary disease is around 130 to 140 mg/dL, he explains. Getting this patient to 70 mg/dL, therefore, is a 50% reduction.

That might be possible with a high-dose atorvastatin or a high-dose rosuvastatin (Crestor), but a lot of physicians aren't comfortable using those kinds of doses, Jones says. Instead, he advocates using statins in combination with other drugs. "I think combinations of treatments are accessible and tolerable and reasonable for physicians to use with good safety so that more moderate doses of statins along with a bile acid resin like Welchol [colesevelam], or a moderate-dose statin plus the

cholesterol-absorption inhibitor Zetia [ezetimibe] can get you 50% LDL lowering easily."

Lifestyle changes can add extra LDL lowering on top of what is possible with the drugs, he notes. "This 50% of more LDL-lowering range is now feasible in routine clinical practice without doctors having to feel that they are using maximum doses or possibly doses that may have higher adverse events," Jones says.

Combination therapy

In some situations, patients have other lipid problems, such as low HDL or high triglycerides. Combinations that include niacin and possibly the fibrates may help these patients, he says. "Pharmacists and the FDA have always been a little skittish about using fibrates in combination with statins, but the data support that fenofibrate, which is both branded and generic, is a safer combination to use than gemfibrozil. In selective patients, the benefits of those kinds of combinations would outweigh the risks."

Other cardiologists aren't as supportive of the idea of using combination therapies to lower LDL levels. **Steven E. Nissen**, MD, medical director of the Cardiovascular Coordinating Center in the department of cardiovascular medicine at the Cleveland Clinic, is an advocate of more aggressive statin therapy instead.

"There are no data whatsoever on combination therapy having any incremental benefits on events. I am particularly opposed to the use of ezetimibe in combination with statins unless absolutely necessary. The reason is that I am concerned that LDL lowering with agents like ezetimibe will have little or no effect on morbidity and mortality," he says.

In fact, Nissen spoke of this concern in his editorial in the Sept. 15 issue of the *Journal of the American Medical Association* (full text available at: http://jama.ama-assn.org/cgi/content/full/292.11.1365v1). The editorial addressed the A to Z statin trial **(see review, p. 75, for more information;** full text available at http://jama.ama-assn.org/cgi/content/full/292.11.1307v1).

In this editorial, Nissen says that each statin requires careful testing in clinical trials to establish the extent of benefit and risk. This is even more important with regard to nonstatin LDL-cholesterol-lowering therapies, he continues. "Because these agents, such as ezetimibe, have not demonstrated anti-inflammatory effects in the absence of concomitant statin administration, their value in reducing events cannot be assumed and must be tested in well-designed clinical outcome trials."

Nissen also is not a big advocate of bile acid resins because he says they are not well tolerated and their efficacy is limited. He does use fibric acid derivatives and niacin, however. "Niacin is very effective in raising HDL and further lowering of LDL, but there is not a lot of outcome data for niacin either."

Jones and Nissen do agree on this: Statins are going to be the core central treatment.

"The statin is going to be a standard of care in high-risk individuals," Jones says. "Although there are known adverse problems, they are manageable, they are reversible, they are low-incidence, and the benefits do outweigh those risks." ■

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JOURNAL REVIEW

Early, intensive simvastatin does not reach endpoint

High dose linked to muscle-related adverse effects

Some physicians advocate early, aggressive therapy to help reduce low-density lipoprotein (LDL) cholesterol levels. One new study, however, indicates that patients treated with high-dose simvastatin (Zocor) did not show a significant reduction in the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, readmission for acute coronary syndrome (ACS), and stroke. In addition, the higher dose was associated with an increased risk of muscle-related adverse events.

"Both the lack of efficacy and the unfavorable adverse event profile would seem improbable to those familiar with the statin clinical trial literature," says **Steven E. Nissen**, MD, medical director of the Cardiovascular Coordinating Center in the department of cardiovascular medicine at the Cleveland Clinic. He made his comments in an editorial that accompanied the published results of the study in the Sept. 15 issue of the *Journal of the American Medical Association*.

Two other trials have shown safety and efficacy of high-dose statins in ACS patients. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial compared 80 mg/d of atorvastatin (Lipitor) with placebo for four months in 3,086 patients and showed a 16% reduction in events. The Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE IT) compared outcomes of 4,162 patients receiving 80 mg/d atorvastatin or 40 mg/d pravastatin (Pravachol) and also showed a significant 16% event reduction.

"It is hazardous to assume that similar agents always yield identical results," Nissen says. "While a class effect for statins is likely, each agent requires careful testing in clinical trials to establish the extent of benefit and risk."

The international, randomized, double-blind trial studied patients with ACS. One group of 2,265 patients received 40 mg/d of simvastatin for one month followed by 80 mg/d thereafter, compared with a group of 2,232 ACS patients receiving placebo for four months followed by 20 mg/d simvastatin. These patients were enrolled in phase Z of the A to Z trial between Dec. 29, 1999, and Jan. 6, 2003, and were followed up for at least six months and up to 24 months.

Among the patients in the placebo plus simvastatin group, the median LDL level was 122 mg/dL at one month while on placebo and 77 mg/dL at eight months while taking 20 mg/d of simvastatin. Among the patients in the simvastatin only group, the median LDL level achieved at one month while taking 40 mg/d simvastatin was 68 mg/dL and 63 mg/dL at eight months while taking 80 mg/d simvastatin. A total of 343 patients (16.7%) in the placebo plus simvastatin group experienced the primary endpoint compared with 309 (14.4%) in the simvastatin-only group.

No difference was evident during the first four months between the groups for the primary endpoint, but from four months through the end of the study, the primary endpoint was significantly reduced in the simvastatin only group. Myopathy occurred in nine patients (0.4%) receiving simvastatin 80 mg/d, in no patients receiving lower doses of simvastatin, and in one patient receiving placebo.

Analyzing the risk-benefit ratio

Taken together, the MIRACL, PROVE IT, and A to Z trials "demonstrate that the beneficial effects of statin therapy in ACS cannot be predicted entirely from the degree of LDL cholesterol reduction," Nissen says. He notes that the difference in C-reactive protein between treatment subgroups in the MIRACL and PROVE IT trials was 34% and 37%, respectively at the end of the trials. In the A to Z trial, the between-group reduction was 16.7%.

"This finding suggests an intriguing hypothesis, specifically, that the early benefits of statin therapy are derived largely from the anti-inflammatory effects of the drugs; whereas, the delayed benefits are lipid-modulated," he explains.

Practicing physicians and patients need to be reassured that the unfavorable risk-benefit relationship observed in the A to Z trial does not in any way diminish the value of intensive statin treatment in secondary prevention, including ACS patients, Nissen says.

"There was a trend toward reduced events in the A to Z trial, a finding that supports the lower is better concept. The increased myopathy rate

applies only to a specific dose of a single agent and should not tarnish this remarkable class of drugs. It must also be emphasized that simvastatin in doses of up to 40 mg/d has shown excellent safety and efficacy in a series of clinical trials. For now, though, the 80 mg/d dose of simvastatin should be used with caution, particularly because other effective agents are available." ■

Rosuvastatin calcium reaches one-year mark

Physician: Changed perception of statins' potential

Rosuvastatin calcium (Crestor) just passed its one-year anniversary since being approved by the U.S. Food and Drug Administration (FDA). Although by reports it has generated almost $4 billion in annual sales for AstraZeneca, the approval initially brought mixed feelings for many physicians, says **Peter H. Jones**, MD, associate professor of medicine and co-director of the Lipid Metabolism and Atherosclerosis Clinic at Baylor College of Medicine in Houston.

"The efficacy was tantalizing that you could get 50% LDL lowering at a reasonable dose," he says. "But there were obviously some issues or reports of whether there was a greater incidence of adverse events compared to the other statins, specifically relating to muscle. Physicians have had to finally get comfortable with whether it was safe."

Consumer safety concerns

Although AstraZeneca says rosuvastatin is safe and effective, one consumer group says it's not. Public Citizen in Washington, DC, is fighting to have the cholesterol drug banned and to have a criminal investigation of AstraZeneca opened for allegedly delaying the submission to the FDA of reports of serious adverse reactions involving rosuvastatin.

Public Citizen says rosuvastatin has a significant potential to cause kidney damage and failure, as well as muscle destruction (rhabdomyolysis). In the correspondence section of the June 26 *Lancet*, **Sidney M. Wolfe**, MD, director of Public Citizen's Health Research Group, charged that the FDA had evidence before approving rosuvastatin that it caused an increased incidence of rhabdomyolysis, yet the agency approved it anyway. In the letter, Wolfe says that there have been 18 cases of rhabdomyolysis — including 11 in the United States, eight reported cases of acute renal failure, and four of renal insufficiency in patients since marketing of the drug began.

In March, Public Citizen filed a petition with the FDA to have the drug taken off the market. The petition is still pending. In August, Wolfe sent a letter to Lester Crawford, DVM, FDA's acting commissioner, requesting a criminal investigation of AstraZeneca for illegally delaying the submission to the FDA of 23 reports of serious adverse reactions to rosuvastatin in the United States for as long as 97 days beyond the allowable 15-day legal limit for reporting such reactions.

In July, AstraZeneca gave the FDA a 30-page response. The company says the allegation was "one more false, misleading, and inaccurate report from Dr. Wolfe and his organization." None of the 23 events cited required 15-day reporting, the company says. AstraZeneca says the consumer group chose to misrepresent the FDA-approved label for rosuvastatin as well as the agency's guidance to pharmaceutical companies on the requirements for 15-day expedited reporting of serious unlabeled, adverse events. "This latest allegation is once again causing undue concern among patients about the safety profile of Crestor, which remains similar to that of other marketed statins."

Jones appears to agree with the manufacturer. "Being out a year and being out in many countries around the world and the accumulated data, I think that [the greater incidence of adverse effects] is not the case. I don't think there are any greater issues of safety compared to other statins."

Overall, rosuvastatin has changed physicians' perceptions that greater efficacy is important, Jones says. "I need whatever I have in my armamentarium to lower LDL; rouvastatin gives that option. It has helped in changing the perception of what is possible to achieve in patients." ■

'Inappropriate meds' still prescribed to the elderly

Limited study should be a reminder to pharmacists

Many elderly Americans still are being prescribed potentially inappropriate medications, according to a study published in the Aug. 9/23 issue of the *Archives of Internal Medicine.*

The study should be a red flag to pharmacists, to remind them to take a second look at an elderly person's medications, says **Nicole Brandt**, PharmD, CGP, BCPP, assistant professor of geriatric pharmacotherapy and director of Clinical and Educational Programs at the Peter Lamy Center on Drug Therapy and Aging. The center is located in the Department of Pharmacy Practice and Science at the University of Maryland School of Pharmacy in Baltimore.

"Many of these drugs may not be entirely effective for older individuals compared to other drugs, and they may also have more side effects and potentially lead to other negative consequences," she says.

Researchers look at a PBM

To examine the number of potentially inappropriate medications that are being prescribed to the elderly, researchers conducted a retrospective cohort study using the outpatient prescription claims database of a large, national pharmaceutical benefit manager (PBM) [AdvancePCS of Irving, TX, and Scottsdale, AZ]. The researchers compared the database with the Beers revised list of medications that should usually be avoided in elderly patients.

"In the whole scheme of things, [the drugs on the list] have been deemed inappropriate medications because there are other, safer alternatives for older individuals," Brandt says. "Other drugs are available that have fewer side effects, have fewer drug interactions, and have a better efficacy profile."

In the study, the researchers found that 162,370 subjects (21%) filled a prescription for one or more drugs of concern. Amitriptyline and doxepin accounted for 23% of all claims for Beers list drugs, and 51% of those claims were for drugs with the potential for severe adverse effects. More than 15% of subjects filled prescriptions for two drugs of concern, and 4% filled prescriptions for three or more of the drugs within the same year. The most commonly prescribed classes were psychotropic drugs and neuromuscular agents.

Amitriptyline in older individuals is very anticholinergic, Brandt says. "You could monitor for anticholinergic activities, but the key thing is that a lot of our older individuals have memory problems. This potentially could worsen it and cause them to be delirious."

Other agents in the realm of tricyclic antidepressants aren't as anticholinergic and can be just as beneficial without having as many side effects, which include dry mouth, confusion potential, constipation, and worsening of their glaucoma, she adds. "They seem to be tolerated a little bit better in terms of their side effect profile."

Amitriptyline common for diabetic neuropathy

Ruth Emptage, PharmD, assistant professor of clinical pharmacy, Pharmacy Practice and Administration, at the Ohio State School of Pharmacy in Columbus, agrees that there are other choices in most of the cases of the medicines that are on the Beers list of inappropriate drugs. Amitriptyline might not be a bad choice for some of these patients, however, limitations in the study do not make it possible to know for sure, she says.

The researchers admit to several limitations:

- The results reported may overestimate potentially inappropriate prescribing for the uninsured.
- Certain drugs may be used at very low doses as last-resort treatments for the management of pain (amitriptyline) or urinary incontinence (doxepin).
- These data provide no direct insight into the outcomes associated with the use of prescription drugs.
- The researchers cannot be certain that the drugs prescribed and dispensed were actually consumed.
- Finally, and most importantly, there are no data on the reasons why certain prescription choices were made by a specific clinician for a specific patient.

Amitriptyline is listed as an antidepressant, but it may not necessarily be used for that property, says Emptage. "It appears to be the agent most effective for treating diabetic neuropathy.

"I'm sure that in some of the cases [with the elderly patients], amitriptyline is not the best," she continues. "But some of the alternatives for diabetic neuropathy aren't all that effective or the formularies may not cover them."

The PBM's preferred formularies may definitely affect which medications the elderly patients are being prescribed, she says.

The researchers conclude that the "common use of potentially inappropriate drugs should serve as a reminder to monitor their use closely.

The key is to remember that you are dealing with a cohort of older individuals, Brandt suggests. "Is this person really tolerating the drug? [Older individuals] are more sensitive to these side effects. They are more likely to experience these adverse effects or use additional concomitant medications that can be problematic." ■

NEWS BRIEFS

Patients warned of clinical differences in thyroid meds

Two organizations representing clinical endocrinologists have warned patients taking thyroid medication, prescribing physicians, and pharmacists dispensing these drugs that clinically important differences exist between one recently approved generic levothyroxine preparation and the most widely prescribed brand of levothyroxine. The members of these organizations, the American Thyroid Association and the American Association of Clinical Endocrinologists, specialize in treatment of hormonal disorders. In June, the FDA ruled that several generic levothyroxine preparations had the same clinical effect and safety profile as certain branded products. As a result, pharmacists may substitute a patient's current levothyroxine preparation for another.

According to bioequivalence data used to acquire FDA approval, one recently approved generic levothyroxine preparation (Sandoz Levothyroxine Sodium) is significantly more potent than the most widely used brand of levothyroxine (Synthroid). Information from bioequivalence studies submitted to the FDA show that the new generic may be as much as one-eighth more potent (+12.5%) than the widely prescribed branded product.

Furthermore, levothyroxine is a drug known to have a narrow toxic-to-therapeutic ratio with significant clinical consequences of even minor excessive or inadequate dosing. Potential adverse events include osteoporosis, atrial fibrillation, worsening of heart disease, preterm delivery in pregnancy, impaired fetal brain development, and high cholesterol.

The FDA and the societies recommend that patients switching between levothyroxine products have repeat thyroid blood testing to be certain that the treatment dose remains effective and safe. ▼

Higher costs affect MS patients' adherence to medications

Multiple sclerosis patients were less likely to take the generally recommended medications for their condition when their out-of-pocket cost for the prescription drugs rose, according to research from Medstat, a business of The Thomson Corp.

The study, published in the August 2004 *Clinical Therapeutics*, found patients would be 32% more likely to use these medications if their

insurance copayments were reduced by half.

Researchers used health claims data from Medstat's MarketScan database to analyze the treatment patterns of 1,807 multiple sclerosis patients. They tracked use of three new disease-modifying drugs — interferon beta-1a (Avonex), interferon beta-1b (Betaseron), and glatiramer acetate (Copaxone) — which slow the progression of the disease and cost about $10,000 per patient annually.

If drug copayment requirements were to decrease by 50%, the research team found, the proportion of patients who would be treated with these drugs would rise from 41.2% to 54.7%. ▼

FDA issues warnings, label changes

The FDA and Genentech have issued a drug warning to health care providers that there is evidence of an increased risk of serious arterial thromboembolic events, including cerebrovascular accident, myocardial infarctions, transient ischemic attacks, and angina related to bevacizumab (Avastin). The risk of fatal arterial thrombotic events also is increased. In randomized, active-controlled studies conducted in patients with metastatic colorectal cancer, the risks of a serious arterial thrombotic event was approximately twofold higher in patients receiving infusional 5-FU-based chemotherapy plus bevacizumab, with an estimated overall rate of up to 5%. A revised bevacizumab package insert containing more detailed information on arterial thromboembolic events is in development. For more information, see www.fda.gov/medwatch/SAFETY/2004/safety 04.htm#avastin.

Also, Aventis Pharmaceuticals have revised the Clinical Pharmacology, Precautions, and Dosage Administration sections of labeling for enoxaparin sodium injection (Lovenox), describing the need for a dosage adjustment for patients with severe renal impairment (creatinine clearance < 30 mL/min) who have increased exposure to enoxaparin. No specific dosage adjustment is required in patients with mild or moderate renal impairment and in low-weight patients. However, low-weight patients should be observed carefully for signs and symptoms of bleeding. For more information, see www. fda.gov/medwatch/SAFETY/2004/safety 04.htm# lovenox.

Finally, Centocor is informing health care professionals about safety information concerning hematologic and neurologic events with infliximab (Remicade), a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn's disease.

In post-marketing experience worldwide, hematologic events including leukopenia neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab. Accordingly, Centocor has added a Warning on Hematologic Events to the labeling for the product. For more information, see www.fda.gov/medwatch/SAFETY/2004/safety04.htm#remicade. ▼

Survey highlights importance of pharmacist/patient relationship

A national consumer survey commissioned by the American Pharmacists Association (APhA) in Washington, DC, shows that a consumer simply knowing the pharmacist's name correlated strongly with his or her access to information that could avert serious medication risk as well as improve medication outcomes.

The survey showed that consumers are taking risks with their medications:

- Only 40% of consumers read their medication labels.
- Only a few more than half tell their pharmacist what medications they're taking.

Although pharmacists can help consumers make the best use of their medication — and decrease the risks of using medications — most consumers are not yet making the most of their pharmacist. Among the survey findings:

- Only one-third of consumers (34%) reported

COMING IN FUTURE MONTHS

- DFR salary survey
- New guidelines are published on managing HIV
- New strep vaccine shows promise
- The impact of OTC drugs on prescribing patterns
- Confusion about the USP <797> Sterile Compounding Recommendations

knowing their pharmacist's name.

• More than 70% of the respondents said they never ask their pharmacists questions.

Consumers who reported using a number of prescription medicines were more likely to know their pharmacist's name, as were seniors or those in poor or very poor health. The survey showed that consumers who know their pharmacist's name are twice as likely to ask their pharmacist the questions they have. Further, those who know their pharmacist's name:

• Are twice as likely as other respondents to have made an appointment with the pharmacist to discuss their medications.

• Read product labels more commonly.

• Know more commonly the active ingredients in their prescription and nonprescription medications, as well as dietary supplements and herbal products. ■

New FDA Approvals

The FDA has recently approved the following drugs:

• ***Pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA) by Hameln Pharmaceuticals, GmbH, of Hameln, Germany.*** The FDA has approved two drugs, pentetate calcium trisodium injection (Ca-DTPA) and pentetate zinc trisodium injection (Zn-DTPA) for treating certain kinds of radiation contamination. The FDA has determined that pentetate calcium trisodium injection and pentetate zinc trisodium injection are safe and effective for treating internal contamination with plutonium, americium, or curium. The drugs increase the rate of elimination of these radioactive materials from the body.

Pentetate calcium trisodium injection and pentetate zinc trisodium injection should not be administered simultaneously. If both products are available, pentetate calcium trisodium injection should be given as the first dose. If additional treatment is needed, treatment should be switched to pentetate zinc trisodium injection. This treatment sequence is recommended because pentetate calcium trisodium injection is more effective than pentetate zinc trisodium injection during the first 24 hours after internal contamination.

After the initial 24 hours, pentetate zinc trisodium injection and pentetate calcium trisodium injection are similarly effective. Pentetate calcium trisodium injection and pentetate zinc trisodium injection usually are administered into the blood stream. However, in people whose contamination is only by inhalation, pentetate calcium trisodium injection or pentetate zinc trisodium injection can be administered by nebulized inhalation.

The main side effect of pentetate calcium trisodium injection is the loss of certain essential nutritional metals such as zinc, which can be replaced by taking oral zinc supplements. In addition, breathing difficulties have been noted in some individuals treated by inhalation therapy with these products. ■

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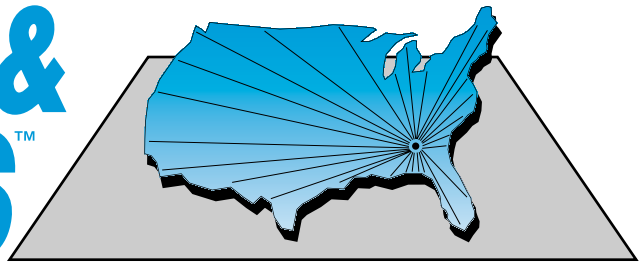

Apomorphine Hydrochloride (Apokyn) Formulary Evaluation

By **Jennifer Lightfoot**, PharmD candidate
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Apomorphine was recognized in 1960 to affect dopamine receptors in the treatment of Parkinson's disease (PD). The U.S. Food and Drug Administration (FDA) designated apomorphine as an orphan drug in 1991 for the treatment of hypomobility in idiopathic stage intravenous (IV) PD patients. At the conclusion of three clinical trials, the FDA approved apomorphine in April for the acute, intermittent treatment of unpredictable "on/off," hypomobility, or "end-of-dose wearing off" in advanced PD patients. Apomorphine hydrochloride is manufactured by Bertek Pharmaceuticals.

Mechanism of action

Apomorphine is a nonergoline dopamine agonist. Apomorphine has an affinity for binding on the dopamine receptors, especially the D_4 receptor. The drug possesses a more moderate affinity for the receptors at the D_2, D_3, and D_5, and adrenergic α_{1D}, α_{2B}, and α_{2C} receptors. Apomorphine has a low affinity for the dopamine D_1, serotonin $5HT_{1A}$, $5HT_{2A}$, $5HT_{2B}$, and $5HT_{2C}$ receptors. An affinity for β_1 and β_2 or histamine H_1 receptors also is noted.

Apomorphine is classified as a dopamine agonist for PD; however, its exact mechanism of action in the treatment of PD is unknown. It is thought to stimulate post-synaptic D_2 receptors in the caudate-putamen section of the brain.

Pharmacokinetics

Absorption: Apomorphine is lipophilic and is rapidly absorbed. This plays an important role in its effectiveness to treat hypomobility. The time to peak concentration ranges from 10-60 minutes following a subcutaneous injection into the abdominal wall **(Refer to Table 1 for comparison to other PD treatments.)**

Distribution: The mean of apparent volume of distribution is 218 L. Maximum concentrations in the cerebrospinal fluid (CSF) are less than 10% of the maximum plasma concentrations and occur 10-20 minutes later.

Metabolism and elimination: The mean apparent clearance is 233 L/hr. The elimination half-life is about 40 minutes (range 30-60 minutes). The route of metabolism in humans is unknown.

Special populations: The clearance of apomorphine does not appear to be influenced by age, gender, weight, duration of PD, levadopa dose, or duration of therapy.

Hepatic impairment: The area under the curve $(AUC)_{0-\infty}$ and maximum concentration (C_{max}) values were increased by 10% and 25%, respectively, in hepatic patients when compared to healthy patients following a subcutaneous injection of apomorphine.

Renal impairment: The $AUC_{0-\infty}$ and C_{max} values were increased by 16% and 50%, respectively, in

Table 1: Time to peak concentrations of common anti-Parkinson's drugs

Drug	Time to peak
Apomorphine (Apokyn)	10-60 minutes
Selegiline (Eldepryl)	Within 1 hour
Entacapone (Comtan)	1 hour
Bromocriptine (Parlodel)	1-2 hours
Ropinirole (Requip)	1-2 hours
Levadopa and carbidopa (Sinemet)	1-2 hours
Pramipexole (Mirapex)	About 2 hours

renal patients when compared to healthy patients following a subcutaneous injection of apomorphine.

Both hepatic and renal impairment would require a dose adjustment. Specific dosing guidelines for the use of apomorphine in patients with hepatic and renal failure currently do not exist.

Dosing and administration

The manufacturer recommends the use of trimethobenzamide (Tigan) 300 mg three times a day (tid) orally to be started three days prior to initial dose to decrease the incidence of nausea and vomiting. The $5HT_3$ antagonists should not be used because of potential interactions. The combination may lower blood pressure and cause patients to lose consciousness and blackout.

The dose of apomorphine should be based on effectiveness and toleration. Start the dose at 0.2 mL (2 mg) and titrate up to a maximum dose of 0.6 mL (6 mg) or a total daily dose of 20 mg. The average daily dose in most patients is 0.3 mL (3 mg) to 0.6 mL (6 mg) three times daily.

Start patients with a test dose of 0.2 mL (2 mg). Then begin an increasing titration of 0.1 mL (1 mg) increments every few days on an outpatient basis. If patients do not respond to the test dose, then increase at the next observed off time to 0.4 mL (4 mg). If the patient tolerates the 0.4 mL (4 mg) test dose, then therapy should be started at 0.3 mL (3 mg) on an as-needed basis. An increase in 0.1 mL increments can be made if needed.

When dosing patients with mild-to-moderate renal or hepatic failure, the initial test dose should be decreased to 0.1 mL (1 mg).

***Administration*:** Apomorphine is administered as a subcutaneous injection. Patients should be instructed to change the injection site each time the drug is administered. Suggested sites are the abdomen, upper arm, and upper leg.

Pregnancy rating: Category C

Strengths and dosage forms: Apomorphine is supplied as solution (10 mg/1 mL) in 2 mL glass ampules (carton of five) and 3 mL cartridges (carton of five). The 3 mL cartridges are used with a manual reusable, multiple- dose injector pen. The pen can deliver doses up to 1.0 mL in 0.02 mL increments. Six needles and a carrying case are provided with the pen.

Adverse reactions, interactions, and contraindications

Apomorphine has a similar adverse drug reaction profile to that of other agents used in the treatment of PD, in that each has been associated with causing nausea, syncope, dyskinesia, somnolence, and hallucinations. The major side effect incidences for apomorphine hydrochloride vs. placebo are listed in **Table 2**.

Drug-drug interactions: The drug should not be used in combination with $5HT_3$ antagonists due to the potential for hypotension and loss of consciousness. Apomorphine may cause hypotension if given in combination with antihypertensive medications and vasodilators, dopamine antagonists, and drugs that prolong the QT/QT_c interval. Drugs that may aggravate PD symptoms should not be given concurrently with apomorphine (i.e., metoclopramide).

Contraindications: Apomorphine administered concomitantly with ondansetron may cause profound hypotension and loss of consciousness. The use of apomorphine with the $5HT_3$ antagonist class (including, for example, ondansetron, granisetron, dolasetron, palonosetron, and alosetron) is contraindicated.

Apomorphine is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients (notably sodium metabisulfite).

Warnings and precautions

AVOID INTRAVENOUS ADMINISTRATION: Serious adverse events (such as intravenous crystallization of apomorphine, leading to thrombus formation and pulmonary embolism) have followed the intravenous administration of apomorphine.

Dyskinesias: Apomorphine may cause dyskinesia or exacerbate pre-existing dyskinesia. During clinical development, dyskinesia, or worsening of dyskinesia was reported in 24% of patients.

Priapism: Apomorphine may cause prolonged painful erections in some patients.

Table 2: Adverse effects of apomorphine compared to placebo

Yawning	85%
Dyskinesia	35%
Somnolence or drowsiness	35%
Nausea and/or vomiting	30%*
Postural hypotension or dizziness	20%
Rhinorrhea	20%
Chest pain/pressure/angina	15%
Hallucination or confusion	10%
Edema/swelling of extremities	10%

* Pre-treat with trimethobenzamide.

Cost

As of June, only the average wholesale price of apomorphine was available per the manufacturer ($23/day + $3/day for trimethobenzamide).

Clinical trial summary

There are three clinical trials that support the use of apomorphine in Parkinson's patients. All three trials used the Unified Parkinson's Disease Rating Score (UPDRS) to measure clinical effectiveness. The UPDRS is a standard test that evaluates the patient's motor skills, emotional and mental status, and overall physical status relating to the side effects of PD. The UPDRS primarily uses subjective data to evaluate a patient. The lower the overall score a patient receives the better the outcome. The scoring range is 0-176 points.

A prospective, randomized, parallel, double-blind, placebo-controlled study was conducted with 29 patients who had advanced idiopathic PD (Dewey et al, 2001). First, in an office setting, medications were withheld from patients overnight to direct a hypomobility state. Twenty patients were assigned to the treatment and nine to placebo. Patients given apomorphine were initiated at a 0.2 mL (2 mg) dose and then titrated by 0.2 mL (2 mg) until the goal response (a 90% reduction in the UPDRS) was achieved; 18 patients in the treatment group experienced a therapeutic response. The average dose of apomorphine hydrochloride was 5.4 mg. None of the patients receiving placebo experienced any benefit. The mean changes in the UPDRS Part III scores were a reduction of 23.9 points for apomorphine and 0.1 point reduction for the placebo group ($P < 0.0001$). The outpatient phase consisted of the patients continuing their regular anti-PD medications along with the highest titrated apomorphine dose received in the inpatient phase. The patients were evaluated for 30 days. After two weeks, the option of titration of the apomorphine dose was allowed. The results of the outpatient phase were a two-hour reduction in "off" hours per day by the apomorphine group and no hours reduced in the placebo group. Apomorphine aborted 95% of the "off" events, while placebo only aborted 23%.

Sherry et al conducted a prospective, randomized, placebo-controlled, crossover design to measure the safety and effectiveness of subcutaneous apomorphine in the treatment of "off" episodes in PD patients. The study sample consisted of 62 participants who had been using apomorphine for at least three months and were optimized on their PD regimen. Patients were placed into four groups. The first group received apomorphine at the regular dose plus 0.2 mL additional apomorphine. The second group received apomorphine at the regular dose plus 0.2 mL placebo. The third group received placebo. Finally, the fourth group received apomorphine at the regular dose.

Efficacy was determined by the change in the UPDRS. The doses were given at the first sign of an "off" episode. The results at 10 and 20 minutes for the post-dose changes were a reduction in the UPDRS of 19.9 and 24.4 points, respectively, for the pooled apomorphine groups. The placebo groups pooled results, after 10 and 20 minutes, posted a reduction of 5.6 and 7.4 points, respectively.

In a prospective, randomized, placebo-controlled, crossover study, Bertek Pharmaceuticals (unpublished data in product insert) examined the safety and effectiveness of subcutaneous apomorphine in the treatment of "off" episodes in PD patients. The study sample consisted of 17 participants who had been using apomorphine for at least three months in addition to oral PD medications. Patients received a single dose of apomorphine at their regular dose or placebo at the same volume amount. The dose was initiated at the first "off" event occurring after administration of the morning PD medications. The efficacy was measured as a change in the UPDRS. The results were a baseline change of 20 points for apomorphine and 3 points for placebo on the UPDRS.

The trials discussed here show the advantages of using apomorphine to treat the hypomobility of PD. More research needs to be conducted to compare apomorphine to other PD medications. The trials were similar in having a small sample size, which does not adequately represent the population. Likewise, the trials use the UPDRS to evaluate the efficacy of using apomorphine, which may introduce bias into the trial because the data collected are subjective data. Statistical analysis information was only available for the Dewey trial. The trial used intention-to-treat analysis with an expected 10%-20% dropout rate (three of the 29 participants dropped out) and a power of 87%, allowing a 13% chance of a Type 2 error.

Place in therapy/advantages

Apomorphine is considered a rescue drug for PD patients who repeatedly experience hypomobility periods due to the wearing-off of anti-PD medications (usually levadopa). The hypomobility stages can be disabling to the patient. Some patients rebut to an "off" state with panic attacks, screaming, or excessive sweating. A main benefit of

use is reduced incidence and time of hypomobility ("off" periods). Compared to other anti-PD agents, apomorphine on average reduces the "off" period by two hours. The only other Parkinson's therapies that are comparable are ropinirole and tolcapone, which reduced the off period on average by 1.9 and three hours, respectively, in noncomparative trials.

The major advantage of apomorphine is that it demonstrates the fastest onset of action of all the PD drugs, acting in as fast as 10 minutes; no other anti-Parkinson's agent can compare with this rapid onset of action. The onset of action also is convenient for patients who suspect that an "off" state is approaching and can quickly combat the state. Apomorphine's positive clinical effects can last up to an hour.

Formulary considerations

It is recommended that apomorphine be classified as formulary status. It should be limited formulary status for advanced PD patients where other drugs have not adequately controlled acute "on-off" and "end-of-dose" hypomobility episodes. A small drug supply will be maintained. Compared to the other anti-PD medications, the main advantage of apomorphine is more rapid onset.

Steps should be taken to manage the possibilities of medication errors and other safety issues: "look-alike, sound-alike" confusion with morphine, subcutaneous administration only, need for concurrent anti-nausea therapy, contraindication with 5-HT_3 antagonists or metoclopramide, QT_C interval prolongation, dosage adjustment in renal/hepatic dysfunction, and possible worsening of dyskinesias.

Resources

• Belden H. New rescue drug cleared for Parkinson's "off-periods." *Drug Topics*. May 17, 2004;148:17.

• Bertek. Apokyn [package insert]. Research Triangle Park, NC; 2004.

• Bowron A. Practical considerations in the use of apomorphine injectable. *Neurology* 2004;62(Suppl 4):S32-S36.

• Dewey RB. Management of motor complications in Parkinson's disease. *Neurology* 2004;62(Suppl 4):S3-S7.

• Dewey RB, Hutton T, LeWitt PA, et al. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for Parkinsonian off-state events. *Arch Neurol* 2001;58:1,385-1,392.

• Dipiro JT, Talbert RL, Yee GC, et al. *Pharmacotherapy: A Pathophysiologic Approach.* 5th ed. New York City: McGraw-Hill; 2002:1,089-1,099.

• U.S. Food and Drug Administration. FDA approves Apokyn for the acute treatment of episodes of immobility in Parkinson's patients. Available at: www.fda.gov/bbs/topics/ANSWERS/2004/ANS01284.html. Accessed June 3, 2004.

• Lees A. Drugs for Parkinson's Disease. *J Neurol Neurosurg Psychiatry* 2002;73:607-610.

• Lexi-Comp (*Lexi-Drugs. comp+ specialties*) [computer program]. Lexi-Comp; June 5, 2004.

• Ostergaard L, Werdelin L, Odin P, et al. Pen-injected apomorphine against off phenomena in late Parkinson's disease: A double-blinded, placebo-controlled study. *J Neurol Neurosurg Psychiatry* 1995;58:681-687.

• Sherry JH, Guyton PJ, Van Lunen B, et al. Continued efficacy and safety of subcutaneous injections of Apokyn in treatment of "off" episodes in patients with Parkinson's disease. *Neurology* 2003;60:A81.

• Stocchi F, Vacca L, DePandis MF, et al. Subcutaneous continuous apomorphine infusion in fluctuating patients with Parkinson's disease: Long-term results. *Neurol Sci* 2001;22:93-94.

• Van Laar T, Jansen E, Essink A, et al. A double-blind study of the efficacy of apomorphine and its assessment in "off-periods" in Parkinson's disease. *Clin Neurol Neurosurg* 1993;95:231-235. ■

CE *Questions*

Pharmacists participate in this continuing education program by reading the article, using the provided references for further research, and studying the CE questions. Participants should select what they believe to be the correct answers. Participants must complete a post-test and evaluation form provided at the end of each semester (June and December) and return them in the reply envelopes provided. A certificate of completion requires a passing score of 70% or higher. When a passing test and evaluation form are received, a certificate and answer guide will be mailed to the participant.

This CE program will improve participants' ability to:

- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
- **Assess** clinical trial data and explain how the results influence formulary decision making.
- **Perform** cost-effectiveness analyses.

13. Apomorphine is lipophilic and is rapidly absorbed, which plays an important role in its effectiveness to treat hypomobility.
    A. True
    B. False

14. Both hepatic and renal impairment would require a dose adjustment.
    A. True
    B. False

15. Apomorphine should only be administered:
    A. intravenously.
    B. orally.
    C. subcutaneously.
    D. All of the above

16. Apomorphine may cause hypotension if given in combination with:
    A. antihypertensive medications.
    B. vasodilators.
    C. dopamine antagonists.
    D. All of the above