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IN THIS ISSUE

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Joint Commission issues alert on vincristine administration

'Tragic errors' continue to occur, the organization says

Saying "tragic errors" related to vincristine administration continue to occur, the Joint Commission on Accreditation of Healthcare Organizations in Oakbrook Terrace, IL, issued a *Sentinel Event Alert* in July.

The errors take place when vincristine is administered intrathecally rather than intravenously. There have been 49 documented cases of this error, reports **Michael R. Cohen**, RPh, MS, ScD, president of Institute for Safe Medication Practices in Huntingdon Valley, PA. Cohen says he provided assistance to Andrew Seger, PharmD, senior research pharmacist at Partners HealthCare Systems and the Division of General Medicine and Primary Care at Brigham and Women's Hospital in Boston, in documenting the cases. Most of the patients involved in those errors have died.

Plenty more cases of the erroneous vincristine administration don't get reported, Cohen says. The Joint Commission suggests that health care organizations may choose not to report the error because of concerns over legal discoverability of the information. "It doesn't happen all that often, but when it does, it is one of the most devastating medication errors," he says. **(For information on a new law passed to encourage the reporting of adverse events, see p. 67.)**

Once the drug is injected intrathecally, little can be done to reverse the painful process. The patient slowly deteriorates and progressively loses function as the drug affects the nervous system. "It is so horrible to see someone become slowly paralyzed and lose organ function," Cohen says.

The United States Pharmacopeia (USP) has a dispensing standard and requirements for vincristine labeling. Some health care workers may not be aware of these requirements, the Joint Commission says. USP requires that a label stating, "FATAL IF GIVEN INTRATHECALLY. FOR IV USE ONLY. DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION," be applied to each syringe by the person doing the dispensing. Each syringe also should be placed in an overwrap that carries the same label warning.

A health care worker can remove the overwrap, however, making it easier for a physician to overlook the labeling on the syringe.

In addition, catheters used for lumbar punctures may have fittings that are identical to those that are used for intravenous injections, Cohen says. This can increase the possibility that the vincristine will be mistaken for a drug to be injected intrathecally.

Recommendations for handling vincristine

In its alert, the Joint Commission offered recommendations for preparing, dispensing, and administering intravenous vincristine (and other vinca alkaloids):

Dilute intravenous vincristine in a volume — ideally for IV infusion in a minibag — that precludes administration via the intrathecal route. The Joint Commission says that a report has shown that the use of vincristine sulfate doses diluted in 0.9% sodium chloride for injection and packaged in minibags or in 30 mL syringes showed no evidence of physical or chemical instability.

If vincristine is to be administered via syringe, clearly label each vincristine syringe: "FATAL IF GIVEN INTRATHECALLY. FOR IV USE ONLY. DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION." Each syringe also must be placed in an overwrap carrying the same label warning.

Do not dispense intravenous vincristine (or any intravenous medication) in a manner that would permit it to be administered at a time and location where intrathecal medications are administered. If a dedicated location for intrathecal administration is not possible, the pharmacy should not dispense intravenous vincristine to a location where intrathecal medications are administered until it receives confirmation that intrathecal drug administration is not imminent or has been completed.

Conduct a "timeout" with at least two qualified health care professionals to independently verify and document the drug, dose, and route at the time of pharmacy preparation of intravenous vincristine *and* before each administration of intravenous vincristine.

The Joint Commission also made recommendations for drugs that are intended for intrathecal administration:

- Prepare intrathecal medications in the pharmacy as close as possible to the time of administration, label them with an appropriate short expiration time (such as eight hours), and then deliver them to and administer them in a designated (ideally separate) location, at a regular, specified time of the day or week.
- Establish a list of drugs that can be administered intrathecally, designate specific locations where intrathecal administration may be done, and ban all other injectable drugs from those physical locations during times when intrathecal injections are administered.
- Conduct a "timeout" with at least two qualified health care professionals to independently verify and document the drug, dose, and route at the time of pharmacy preparation of drugs for intrathecal administration *and* before each intrathecal administration of such drugs.

Wrap intrathecal drugs within a sterile bag, which is then wrapped again in a sterile towel or another bag labeled: "FOR INTRATHECAL USE ONLY." Wraps or packages must be removed *immediately* prior to injection only by the person administering the medication. ■

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Thomson American Health Consultants has designated up to 6 contact hours annually for this program. Participants will receive ACPE statements of credit within 6 weeks after receipt of the post-test and evaluation form, provided a passing grade of at least 70% is achieved. Health system pharmacists and pharmacy benefits managers are the target audience of this activity; however, anyone involved in prescribing, dispensing, patient counseling, formulary selection, or reimbursement processes might benefit from participation.

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New law legally protects adverse event information

Pharmacists should be encouraged to report medication adverse events (AEs) and their underlying causes under a new law signed by President Bush on July 29.

The Patient Safety and Quality Improvement Act of 2005 amends the Public Health Service Act to designate patient safety data as privileged and confidential. The data are therefore legally protected.

The law also prevents accrediting bodies from taking action based upon a health professional reporting this information. One accrediting body, the Joint Commission on Accreditation of Healthcare Organizations, has hailed this law as a "a breakthrough in the blame and punishment culture that has literally held a death grip on health care."

The American Medical Association has studied this law and presents the following summary:

• The law establishes a confidential reporting structure in which physicians, hospitals, and other health care professionals and entities can voluntarily report confidential and legally privileged "Patient Safety Work Product" (PSWP) on errors to certified Patient Safety Organizations (PSOs), as part of a "Patient Safety Evaluation System."

• PSOs would analyze PSWP, provide feedback to providers, and may report nonidentifiable PSWP to a database (which may be linked to a network of databases facilitated by the Department of Health and Human Services [HHS]).

• PSOs may be public or private and must meet certain defined criteria to be certified by HHS.

• PSWP cannot be used in civil, criminal, or administrative proceedings (including disciplinary actions) against a provider.

• Information on a crime is not PSWP and not privileged or confidential.

• The law defines the circumstances under which PSWP may be disclosed without violating or waiving confidentiality and legal privilege.

• Information or evidence available from original records (e.g., medical records), and information that is not PSWP and can be collected under other laws (e.g., state reporting requirements), would not be limited or affected.

• The law does not preempt stronger state protections.

• An adverse event cannot be taken for good-faith reporting of PSWP to a PSO.

• An accrediting body cannot take an accrediting action against a provider based on the provider's good faith participation in reporting PSWP.

• The confidentiality protections of the Health Insurance Portability and Accountability Act of 1996 are maintained.

• HHS, through the Agency for Healthcare Research and Quality, will report on methods to reduce errors and increase patient safety.

• HHS is required to facilitate a network of databases to provide interactive evidence-based management resources for providers, PSOs, and others. ■

Study: Number of adverse events involves med errors

Facility used CPOE system and on-site pharmacists

A teaching hospital further improved its existing safety mechanisms after a study of critically ill patients found a significant number of adverse events involving medications.

Researchers at the health care institution wanted to study the incidence and nature of serious medical errors in critical care settings. They conducted a one-year observational study, between July 2002 and June 2003, of medical intensive care unit (MICU) and coronary care unit (CCU) patients during nine, three-week periods.

The researchers looked at a total of 391 patients with 420 unit admissions during 1,490 patient days. They found 120 adverse events in 79 patients (20.2%), including 66 (55%) nonpreventable and 54 (45%) preventable adverse events. The researchers also found 223 serious errors.

Among the adverse events, 13% were life-threatening or fatal. Among the serious errors, 11% were potentially life-threatening.

Medications were involved in a large proportion of the adverse events, the researchers say. Among the incidents, 56 (47%) were due to adverse drug events (ADEs), including 19 preventable ADEs and 37 nonpreventable ADEs. Medications also were responsible for 78% of the most serious errors. Wrong dosage was the most common medication error.

The medication categories most frequently associated with errors were cardiovascular drugs (24%), anticoagulants (20%), and anti-infective agents (13%). Anti-infectives and cardiovascular

drugs are probably the most common medications on the unit, says **Jeffrey M. Rothschild**, MD, MPH, assistant professor of medicine at Brigham and Women's Hospital/Harvard Medical School in Boston, and lead author of the study. "Anticoagulants are not, but they are more difficult to use. We find, for instance, that insulin and heparin are high-risk and are particularly associated with problems."

Going into the study, the researchers didn't know what their adverse event rates would be, Rothschild says. "They turned out to be somewhat comparable to other studies. We thought we would do better on the medication side because we have good, existing safety mechanisms."

These mechanisms included computerized physician order entry (CPOE) and on-site pharmacists. "It shows that the incidence is probably much higher in most other institutions [that don't have these mechanisms]," he says. "Any of the medication errors that we found were despite the presence of the pharmacists."

Investigators have studied the value of having pharmacists participate in patient rounds in the intensive care unit (ICU), Rothschild says. "[The literature has] shown that it is equivalent to computerized order entry in efficacy. In places that don't have CPOE, it is a great interim step. We happen to do both in some of our units."

At his institution, the clinical pharmacists are teaching house staff about proper prescribing. Rothschild adds that "the pharmacists pick up a lot of things before the orders are even entered. They are great assets if they can join physicians on rounds in the ICU setting."

The pharmacists can't be everywhere all the time, however. Their participation in patient rounds or even availability on the unit usually is Monday through Friday, 7 a.m. to 4 p.m., Rothschild reports. "Things will obviously only be caught a third of the week because of the 24/7 nature of critical care."

Since the study, the institution added more safety interventions, including a new web-based incident reporting system, introduction of smart intravenous infusion pumps, and bar-coded medication administration.

"Our system is getting better," Rothschild says. These interventions are now set up to catch errors that might have slipped through at administration under the previous system.

For more information about the study, see the August 2005 issue of *Critical Care Medicine*. The study was sponsored by the Agency for Healthcare Research and Quality in Rockville, MD. ■

■ Research News ■

Study: Customizing simple regimen raises adherence

Those with acute conditions stick to plan more often

Hospital admissions related to poor medication adherence cost the United States billions of dollars a year. Two physicians recently reviewed the literature and discussed adherence to medication in the Aug. 5 issue of *The New England Journal of Medicine*.

The rates of patients with acute conditions adhering to their medication regimen are typically higher than those with chronic conditions, say **Lars Osterberg**, MD, and **Terrence Blaschke**, MD. Osterberg is chief of general medicine at VA Palo Alto (CA) Health Care System and clinical assistant professor of medicine at Stanford (CA) University School of Medicine.

Blaschke is professor of medicine and molecular pharmacology at Stanford.

Studies show that adherence to medications for patients with chronic conditions drops the most after the first six months of therapy.

Physicians don't have a strong ability to recognize medication nonadherence, the authors say. To help physicians, Osterberg and Blaschke compiled a list of the major predictors of poor adherence to medication, according to studies of predictors.

In the article, the authors also included the references for each study.

Here are some of the items on the list:

- Presence of psychological problems, particularly depression.
- Side effects of medication.
- Patient's lack of belief in benefit of treatment.
- Presence of barriers to care or medications.
- Complexity of treatment.
- Cost of medication, copayment, or both.

However, even patients who lack these indicators may miss taking medications as prescribed, the authors say. "Thus, poor adherence should always be considered when a patient's condition is not responding to therapy."

The authors then discuss interventions that can be used to improve adherence. These can be grouped into four general categories: patient education, improved dosing schedules, increased hours when the clinic is open (including evening hours), and improved communication between physicians and patients.

Since many factors can contribute to a patient not adhering to a medication regimen, a single approach will not be effective for all patients, they say. The authors have adapted some strategies for improving adherence to a medication regimen. Here are a few:

• Identify poor adherence.

— Look for markers of nonadherence: missed appointments ("no-shows"), lack of response to medication, missed refills.

— Ask about barriers to adherence without being confrontational.

• Provide simple, clear instructions and simplify the regimen as much as possible.

• Encourage the use of a medication-taking system.

• Listen to the patient, and customize the regimen in accordance with the patient's wishes.

• Consider more "forgiving" medications when adherence appears unlikely.

— Medications with long half-lives.

— Depot medications.

— Transdermal medications.

Practitioners should always look for poor adherence and can enhance adherence by emphasizing the value of a patient's regimen, making the regimen simple, and customizing the regimen to the patient's lifestyle, the authors conclude. "Patients who have difficulty maintaining adequate adherence need more intensive strategies than do patients who have less difficulty with adherence, a more forgiving medication regimen, or both." ■

FDA wants Purdue Pharma to pull Palladone

The FDA has asked Purdue Pharma LP to withdraw its pain management drug hydromorphone hydrochloride (Palladone) from the market. The agency made this request after acquiring new information about serious and potentially fatal adverse reactions that can occur when hydromorphone extended-release capsules are taken together with alcohol.

When mixed with alcohol, hydromorphone's extended release mechanism is harmed. This can lead to dose-dumping. The consequences of dose dumping at the lowest marketed dose (12 mg) of hydromorphone could lead to serious, or even fatal, adverse events in some patients and the risk is even greater for the higher strengths of the product, the FDA says. The agency says Purdue Pharma has agreed to suspend all sales and marketing of hydromorphone pending further discussions. Hydromorphone was approved in September 2004 and already includes the standard opioid warning against the use of alcohol and the drug. The FDA, however, says it does not believe that the risk of serious, and potentially fatal, adverse events can be effectively managed by label warnings alone and a risk management plan.

For more information, see www.fda.gov/cder/drug/infopage/palladone/default.htm. ▼

One-fifth of women don't fill meds because of cost

A national survey of women finds that a substantial percentage of women cannot afford to go to the doctor or get prescriptions filled. The Kaiser Family Foundation report, *Women and Health Care: A National Profile,* is based on a national survey of 2,766 women ages 18 and older.

As health care costs grow, more than one-quarter of nonelderly women (27%) and two-thirds of uninsured women (67%) report they delayed or went without care they believed they needed in the past year because they could not afford it, compared to 24% and 59%, respectively, in 2001. In addition, 20% of women ages 18 and older say they did not fill a prescription in the past year because of the cost.

Additional key findings related to prescription drugs include:

• Women (56%) are more likely than men (42%) to use a prescription medicine on a regular basis, and are also more likely to report difficulties affording their medications.

• Forty-one percent of uninsured women say they did not fill a prescription due to costs, as did one in six women (17%) with private coverage and nearly one in five women with Medicaid (19%).

• One in seven (14%) women also report that they skipped or took smaller doses of their medicines in the past year to make them last longer. ▼

FDA issues transdermal fentanyl patch advisory

The FDA has issued a Public Health Advisory regarding the safe use of transdermal fentanyl patches in response to reports of deaths in patients using the narcotic medication for pain management. In addition, a patient information sheet and an alert to health care professionals were issued identifying several important safety precautions for the use of fentanyl transdermal patches.

These safety precautions include but are not limited to patient education regarding signs of overdose, proper patch application, use of other medications while using the patch, safeguards for children, and proper storage and disposal.

The FDA is conducting an investigation into the deaths associated with these patches. The agency has been examining the circumstances of product use to determine if the reported adverse events may be related to inappropriate use of the patch or factors related to the quality of the product. It is possible that some patients and their health care providers may not be completely aware of the dangers of these narcotic drug products and the recommendations regarding their safe use.

For more information, go to: www.fda.gov/cder/drug/infopage/fentanyl/default.htm. ▼

FDA announces Class I recall of infusion pumps

Baxter Healthcare Corp. has initiated a worldwide recall of all models of its Colleague Volumetric Infusion Pumps because they can shut down while delivering critical medication and fluids to patients, the FDA has announced. Baxter has received six reports of serious injury and three reports of death associated with this shutdown problem. The affected models are: 2M8151, 2M8151R, 2M8161, 2M8161R, 2M8153, 2M8153R, 2M8163, and 2M8163R.

Based on its information, the FDA has determined that this action is a Class I recall, the most serious type of recall. Baxter has notified customers that it has voluntarily stopped shipping Colleague Volumetric Infusion Pumps until the problems are resolved. The company also advised customers in March to stop using any pumps that exhibit a failure code beginning with 402, 403, 533, 535, or 599, related to these electronic problems. Additionally, Baxter advised customers to take out of service any pumps that exhibit failure codes 810:04 and 810:11 related to air-in-line sensor problems, until they are inspected by authorized service personnel.

In addition to the shutdown problem, the device may exhibit two additional failure modes:

• Users may inadvertently press the on/off key instead of the start key when attempting to start an infusion.

• Disconnecting or connecting the pump from the hospital monitoring system while the pump is powered "on" can result in a failure code, requiring the infusion to be restarted.

Also, these failures may occur during the infusion of therapy. Health care institutions should have a contingency plan to mitigate any disruptions of infusions of life-sustaining drugs or fluids. ▼

Disetronic Medical Systems recalls insulin pumps

Disetronic Medical Systems in Fishers, IN, has announced a voluntary nationwide recall of its D-TRON adapters, used with the D-TRONplus insulin pump, because they can potentially overdeliver a maximum amount of up to 1.8 IU of insulin. Use of these recalled adapters may pose a potential life-threatening situation to certain children using the pump. Other users who are insulin-sensitive also may be at increased risk. The affected D-TRON adapters are part number REF 3000803, Lots 4013674 through 4022628. Other adapter lots are not affected.

A valve inside the D-TRON adapter seems to sporadically fail to close completely. This may occur up to 15 minutes after replacing the adapter and priming the set. If this happens, the pump will give an A-4 alarm and will continue to deliver insulin.

Overinfusion also may occur with no alarm if the pressure does not drop below the alarm threshold, although the company does not have any reports of such cases.

There have been no reports of injury or death associated with the use of the affected D-TRON adapters. Disetronic has notified the caregivers and physicians of the pump users 13 years of age and younger to immediately discontinue the use of the affected adapters. The caregivers also have been provided with new D-TRONplus adapters, which can be identified by the part number. The new part number is located on each adapter and is REF 04574826001. Only adapters that are not affected by the recall now are being shipped by Disetronic, to ensure that customers of all ages will have the new adapters as soon as possible. ■

New FDA Approvals

• ***New indication for celecoxib (Celebrex) by Pfizer.*** The FDA has approved the selective COX-2 inhibitor celecoxib (Celebrex) for a new indication, the relief of the signs and symptoms associated with ankylosing spondylitis.

The FDA also finalized the prescribing instructions for celecoxib for all approved uses, including additional warnings about potential cardiovascular and gastrointestinal risks. The label recommends that celecoxib be prescribed at the lowest effective dose for the shortest duration consistent with individual patient treatment goals. The recommended dose for celecoxib is 200 mg daily for osteoarthritis and 200 mg to 400 mg daily for adult rheumatoid arthritis. For the management of the signs and symptoms of ankylosing spondylitis, the recommended dose of celecoxib is 200 mg daily in single or divided twice per day doses. If no effect is seen after six weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after six weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options. The approved dose for the prevention of intestinal polyps associated with familial adenomatous polyposis is 800 mg daily.

• ***Pediatric indication for levetiracetam (Keppra) by UCB Pharma.*** The FDA has approved the anti-epilepsy drug levetiracetam (Keppra) as add-on therapy in the treatment of partial-onset seizures in children 4 years of age and older with epilepsy. The FDA approved this new pediatric indication for levetiracetam under a six-month priority review.

The approval of levetiracetam for children was based on findings from one multicenter, randomized, double-blind, placebo-controlled pivotal study conducted at 60 sites in North America, in 198 children 4-16 years of age with partial-onset seizures with or without secondary generalization uncontrolled by standard antiepileptic drugs (AEDs). Study participants were taking one or two other AEDs at entry. The study consisted of an eight-week baseline period and a four-week titration period, followed by a 10-week evaluation period.

When measuring efficacy, those taking levetiracetam had a significantly larger reduction (26.8%) in weekly seizure frequency over placebo, on average. Additionally, responder rates (the portion of patients achieving a 50% or greater reduction in seizures) for patients taking levetiracetam were 44.6% vs. 19.6% for placebo (both with a $P = 0.0002$ compared to placebo).

In pediatric patients, 4-16 years of age, the most common adverse events associated with levetiracetam in combination with other AEDs were somnolence, accidental injury, hostility, nervousness, and asthenia. Levetiracetam is associated with somnolence, fatigue, and behavioral abnormalities as well as hematological abnormalities.

Levetiracetam is available in 250 mg, 500 mg, and 750 mg tablets and a grape-flavored (100 mg/mL) oral solution for patients who prefer a solution or have difficulty swallowing tablets. Levetiracetam dosing must be individualized

COMING IN FUTURE MONTHS

- Guidelines focus on postoperative atrial fibrillation
- *Staphylococcus aureus* infections huge burden on hospitals
- Guidelines to treat acute pain released
- Ibandronate sodium (Boniva) drug evaluation
- ASHP urges consistent use of pharmacists in small and rural hospitals

according to renal function status.

• ***New indication for pregabalin (Lyrica) by Pfizer.*** The FDA has approved pregabalin (Lyrica) for adjunctive treatment of partial-onset seizures in adults with epilepsy. The FDA approved pregabalin in December 2004 for the management of diabetic peripheral neuropathy and postherpetic neuralgia. Pregabalin is an alpha-2-delta ligand with a newly defined mechanism of action that is believed to work by calming hyperexcited neurons.

The efficacy of pregabalin was established in three double-blind, controlled trials involving 1,052 patients. At the start of treatment with pregabalin, patients experienced approximately 10 seizures a month despite taking one to three other antiepileptic medications. Patients receiving adjunctive treatment with pregabalin experienced a reduction in the frequency of partial seizures by up to 51%. Pregabalin can be given to patients two times or three times a day.

Pregabalin will be designated a controlled substance, recommended for classification in the category with lowest potential for abuse or misuse relative to controlled substances in other categories.

• ***New indication for moxifloxacin HCl (Avelox) by Schering-Plough.*** The FDA has approved the once-daily antibiotic moxifloxacin HCl (Avelox) for the treatment of complicated skin and skin structure infections (cSSSI) in adults caused by methicillin-susceptible *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, or *Enterobacter cloacae*.

The FDA approval to treat cSSSI is the fifth indication for moxifloxacin, which is currently approved in the United States to treat acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, and uncomplicated skin and skin structure infections.

Moxifloxacin generally is well tolerated, with adverse events similar to standard therapy. The most common side effects caused by moxifloxacin, which usually are mild, include dizziness, nausea, and diarrhea.

• ***New indication for valsartan (Diovan) by Novartis Pharmaceuticals Corp***. The FDA has approved valsartan (Diovan) for a new indication to reduce cardiovascular death in patients at high risk following a heart attack. The FDA also expanded the drug's heart failure labeling. Valsartan now can be prescribed in a broader range of heart failure patients and no longer is limited to those intolerant of ACE inhibitors.

The FDA approval is based on the results of the VALIANT study, which compared valsartan vs. captopril, an ACE inhibitor, vs. the combination of both in 14,703 patients at high risk for death following a heart attack. In the trial, valsartan was reported to improve survival and reduce cardiovascular events including recurrent heart attack and hospitalizations for heart failure in these patients. There were no differences observed in overall mortality among the treatment groups.

The recommended starting dose for post-myocardial infarction (MI) therapy is 20 mg twice daily (½ 40 mg scored tablet) followed by titration to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg twice daily, as tolerated by the patient. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction.

The most common side effects in heart failure patients taking valsartan were dizziness, hypotension, and diarrhea. The most common side effects in post-MI patients that caused them to stop taking the drug were hypotension, cough, rash, and an increase in serum creatinine levels. Because of the risk of hypotension, caution should be observed when initiating therapy in heart failure or post-MI patients. Evaluation of heart failure or post-MI patients should always include assessment of renal function. ■

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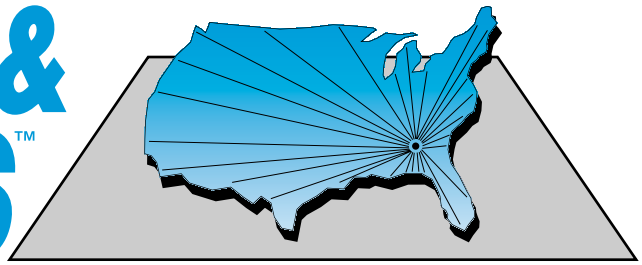

Drug evaluation: Dexmethylphenidate hydrochloride tablets (Focalin)

Part 1: Mechanism of Action, Pharmacokinetics, Indication, Dosage, Contraindications, Drug Interactions, Adverse Reactions, Warnings and Precautions

By **Emily K Pauli**, BS, BMS, PharmD Candidate
Harrison School of Pharmacy
Auburn (AL) University

Dexmethylphenidate, d-MPH (Focalin) is a new methylphenidate (d,l-MPH; MPH) formulation of the active enantiomer only. A variety of methylphenidate products are available but only dexmethylphenidate is the purified active enantiomer.

Mechanism of action

Proposed: Dexmethylphenidate (d-MPH) is a central nervous system stimulant that blocks the reuptake of norepinephrine and dopamine and increases the release of monoamines. The actual mechanism of action is not known.

Pharmacokinetics

■ The pharmacokinetic differences (if any) between d-MPH and d,l-MPH are clinically insignificant.

■ Absorption
— Well absorbed (both d-MPH and d,l-MPH).
— Time to peak in the fasted state is 1-1.5 hours post-dose for d-MPH; 2 hours for the racemic products (d,l–MPH).
— Food delays the time to peak by approximately 1.5 hours but does not affect the C_{max} or AUC for d-MPH or d,l-MPH.

■ Distribution
— Plasma levels decline exponentially following oral administration.
— No data are provided regarding distribution of d-MPH.
— Protein binding of racemic methylphenidate is minimal (15.2%).
— Volume of distribution for d,l-MPH is 1.1-6 L/kg.

■ Metabolism
De-esterification to an inactive metabolite (d-ritalinic acid) for both d-MPH and d,l-MPH.

■ Excretion
— Elimination half-life is 2.2 hours for d-MPH and d,l-MPH.
— d-MPH and d,l-MPH do not inhibit cytochrome P450 isozymes.
— Primarily excreted in the urine (80%) as the inactive metabolite.
— Specific renal excretion data for d-MPH are unavailable. However, approximately 90% of an oral dose of d,l-MPH appears in the urine, mainly as ritalinic acid (about 80%); less than 1% appears as unchanged methylphenidate.

Indication

■ d-MPH
— Treatment of attention deficit hyperactivity disorder (ADHD).
— Efficacy established in clinical trials in patients 6-17 years of age.
— Long-term use (greater than six weeks) has not been evaluated with d-MPH.

■ d,l-MPH
— Treatment of ADHD in **both** children and adults.
— Narcolepsy.
— Disease-related fatigue **(not** FDA-approved).

Dosage

■ d-MPH
— Administered twice daily and at least four hours apart, irrespective of food.
— Thirty to 45 minutes prior to a meal; morning and noontime is recommended.
— Dosing is individualized to the patient and based on response.
— Dosing is for children 6-17 years old; not established in adults and children younger than 6 years of age.
— Treatment naïve: Initiate at 5 mg/day (2.5 mg twice daily); weekly adjustment of 2.5-5 mg daily to a maximum dose of 20 mg/day (10 mg twice daily).
— Treatment non-naïve: Initiate d-MPH at half the dose of other methylphenidate products; weekly adjustments of 2.5-5 mg daily to a maximum of 20 mg/day (10 mg twice daily).
— When changing from d-MPH tablets to d-MPH XR capsules, patients may be switched to the same daily dose using d-MPH XR (maximum dose: 20 mg/day).

■ Racemic methylphenidate (d,l-MPH)
— Administered twice daily and at least four hours apart, irrespective of food.
— Thirty to 45 minutes prior to a meal; morning and noontime is recommended.
— Dosing is individualized to the patient and based on response.

Adult

Immediate-release

◦ 10-60 mg daily; average dose is 20-30 mg daily; administer 2-3 times daily, preferably 30-45 minutes before meals.

Extended-release

◦ Starting dose of Concerta extended-release tablet for new patients is 18 mg once a day in the morning; adjust weekly in 18-mg increments to a maximum of 54 mg per day. Patients converting from immediate-release (IR) or sustained-release (SR) methylphenidate may follow the dosage conversion recommendation shown in **Table 1, above right.**

◦ For methylphenidate extended-release capsules (Metadate CD) the starting dose is 20 mg once daily in the morning before breakfast; increase by 20 mg at weekly intervals to a maximum dose of 60 mg/day taken once daily in the morning.

Table 1: Conversion Guidelines

Previous methylphenidate daily dose	Recommended Concerta dose
5 mg IR twice a day or 5 mg IR 3 times a day or 20 mg SR	18 mg in the morning
10 mg IR twice a day or 10 mg IR 3 times a day or 40 mg SR	36 mg in the morning
15 mg IR twice a day or 15 mg IR 3 times a day or 60 mg SR	54 mg in the morning

Pediatric

Immediate-release

◦ Usual dose is 5 mg twice daily; increased at weekly intervals by 5-10 mg; maximum recommended dose is 60 mg.

Extended-release

◦ For methylphenidate extended-release capsules, the starting dose is 20 mg once daily in the morning before breakfast; increased by 20 mg at weekly intervals to a maximum dose of 60 mg/day taken once daily in the morning.

Dosage forms of comparable methylphenidate products

■ Immediate-release
— Dexmethylphenidate (Focalin)
— Ritalin HCl
— Methylphenidate HCl
— Methylin

■ Extended-release
— Ritalin LA/Ritalin SR
— Metadate CD/Metadate ER
— Concerta
— Methylin ER
— Methylphenidate ER
— Dexmethylphenidate (Focalin XR)

Contraindications

■ Same contraindications for d-MPH and d,l-MPH
— Agitation (patients with marked anxiety, tension, and agitation): d-MPH and d,l-MPH may aggravate the symptoms.
— Hypersensitivity to any methylphenidate

product or component of d-MPH.
— Glaucoma.
— Tics: Motor tics, family history, or diagnosis of Tourette's syndrome; in rare cases MPH has caused Tourette's syndrome.
— Current or recent (within 14 days) treatment with monoamine oxidase inhibitors: Hypertensive crisis may result.

Drug interactions (based on d,l-MPH)

■ Same interactions and frequency of interactions for d-MPH and d,l-MPH
— May decrease the effects of antihypertensive treatments.
— May inhibit metabolism of coumarins, anticonvulsants (phenobarbital, phenytoin, primidone), tricyclic antidepressants, selective serotonin reuptake inhibitors; lower doses of these drugs.

Adverse reactions

■ Same for d-MPH and d,l-MPH
— Paradoxical aggravation: Reduce the dose or discontinue d-MPH.
— The most common reasons (1% for each) for discontinuation were: motor or vocal tics, anorexia, insomnia, and tachycardia.
— Adverse events with an incidence of 5% or more include: abdominal pain (15%), fever (5%), anorexia (6%), and nausea (9%)
— Adverse events reported with use of other MPH products include: angina, arrhythmias, dizziness, headache, drowsiness, dyskinesia, psychosis, changes in blood pressure, cerebral arteriti, or occlusion.
— Although no established casual relationship has been established, the following events have been reported: leukopenia, anemia, elevated liver associated enzymes, hepatic coma, transient depression, alopecia, and neuroleptic malignant syndrome.

Warnings and precautions

■ Unless otherwise noted, these are the same for both d-MPH and d,l-MPH.
■ Depression.
■ Fatigue.
■ Long-term use and growth suppression: Safety of long-term use (more than six weeks) has not been established with d-MPH
— Still controversial that d,l-MPH MAY cause growth suppression after long-term treatment.

■ May exacerbate psychosis.
■ May lower the seizure threshold: Discontinue if seizures occur.
■ Use cautiously in hypertensive patients or in patients with conditions that increase heart rate or blood pressure (heart failure, myocardial infarction, hyperthyroidism).
■ Give cautiously in patients with a history of substance abuse or dependence.
■ Pregnancy Category C.
■ Unknown if excreted in breast milk.
■ Safety and efficacy is not established in children younger than 6 years of age.
Look-/sound-alike drugs for dexmethylphenidate (Focalin):
— Methylin, Ritalin
— Metadate, methylphenidate ■

IN THE PIPELINE

• Genelabs Technologies has received orphan drug designation for prasterone (Prestara), its investigational drug for **lupus**.

• Novartis has announced that its New Drug Application for deferasirox (Exjade) has been granted priority review by the FDA as a once-daily oral iron chelator for the treatment of **chronic iron overload** due to blood transfusions.

• Dendreon Corp. has completed enrollment in its Phase III PROTECT (P-11) clinical trial of APC8015 (Provenge) in **men with nonmetastatic androgen-dependent (hormone-sensitive) prostate cancer**.

• Dynavax Technologies Corp. has initiated a pivotal **Phase III clinical trial of its hepatitis B vaccine**.

• LAB International has initiated enrollment in a Phase I trial for its novel **asthma** product LAB CGRP (Calcitonin Gene-Related Peptide).

• Arginox Pharmaceuticals has begun patient enrollment in TRIUMPH, a pivotal Phase III trial of the drug, Tilarginine Acetate Injection (TAI), for the treatment of **cardiogenic shock**.

• Cell Genesys has initiated a second multicenter Phase III clinical trial of Gvax vaccine for prostate cancer in patients with metastatic hormone-refractory **prostate cancer**.

• Speedel announces the start of its Phase III

study for SPP301, its once-a-day oral endothelin A receptor antagonist in the indication of **diabetic nephropathy**.

• ID Biomedical Corp. has been advised by the FDA's Center for Biologics Evaluation and Research (CBER) that the company's influenza virus vaccine (Fluviral) has been granted a fast-track designation.

• Keryx Biopharmaceuticalshas initiated its pivotal Phase III and Phase IV clinical program with oral sulodexide gelcap (KRX-101) for the treatment of **diabetic nephropathy**.

• CV Therapeutics has initiated a clinical program for CVT-6883, a selective, potent, and orally available A2B-adenosine receptor antagonist, intended to treat **asthma** with once-a-day dosing.

• Sangart has initiated a Phase II clinical trial involving MP4 (Hemospan), a hemoglobin-based oxygen carrier designed to serve as an alternative for **blood transfusions**.

• Cylene Pharmaceuticals has initiated a Phase I clinical trial for CX-3543, its lead candidate for the treatment of **multiple cancers**. ■

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 statement of credit requires a passing score of 70% or higher. When a passing test and evaluation form are received, a statement of credit 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.

9. Dexmethylphenidate, d-MPH (Focalin) is a new methylphenidate (d,l-MPH; MPH) formulation of the active enantiomer only.
   A. True
   B. False

10. Dexmethylphenidate (d-MPH) is a central nervous system stimulant that increases the release of:
   A. norepinephrine.
   B. dopamine.
   C. monoamines.
   D. All of the above

11. d-MPH is indicated for:
   A. treatment of attention deficit hyperactivity disorder.
   B. narcolepsy.
   C. disease-related fatigue.
   D. All of the above

12. The most common reasons (1% for each) for discontinuation of d-MPH include:
   A. motor or vocal tics.
   B. anorexia.
   C. insomnia.
   D. tachycardia.
   E. All of the above