**NEW INDICATION**

**Old Drug Gets New Use Against Nerve Gas**

The FDA has approved pyridostigmine bromide (Mestonon®, ICN Pharmaceuticals; Regonol® Injection, Organon) as a pretreatment to protect military personnel against the effects of Soman nerve gas poisoning. The nerve agent Soman causes loss of muscle control and death from respiratory failure. Pyridostigmine bromide, given before exposure to Soman, along with atropine and pralidoxime (Protopam®, Wyeth-Ayerst) given as antidotes after exposure, increases survival, the FDA says.

Pyridostigmine bromide has been used since 1955 to treat myasthenia gravis, and it was also approved for use during the Gulf War under Investigational New Drug provisions because of its potential to save lives. It is the first drug to be approved under the “animal efficacy rule,” which became effective last year. The rule allows the use of animal data for evidence of a drug’s effectiveness for certain conditions when the drug cannot ethically or feasibly be tested in humans.

(Source: FDA News, February 5, 2003.)

**DRUG NEWS**

**Hemodialysis Catheters Kept Clear with Reteplase**

When a conventional fistula or graft cannot be maintained in patients on hemodialysis, a long-term tunneled catheter may be the only option, even though such catheters have been associated with high rates of infection and thrombotic complications. How can catheters be kept clear?

Urokinase (Abbokinase®, Abbott) was withdrawn from the market, and only limited exploration has been done with alteplase (Activase®, Genentech) for hemodialysis catheters. Researchers from Creighton University School Medical Center in Omaha, Nebraska, decided to evaluate reteplase (Retavase®, Centocor), a recombinant plasminogen activator, in 34 patients with end-stage renal disease who were undergoing long-term dialysis.

Instillation of reteplase restored catheter operation in 74 instances of catheter dysfunction (87% of episodes). Low doses (1 unit) were as effective as higher doses (4 to 6 units). No patients experienced complications, including bleeding, as a result of reteplase administration. The researchers also noted no allergic reactions or other effects among the 30 patients who received repeated doses.

(Source: Pharmacotherapy 2003;23: 137–141.)

**After the Anthrax Scare: Is Ciprofloxacin Still Effective?**

Is the antibiotic that was administered as a protective measure in the U.S. during the anthrax scare in 2001 becoming less effective against other bacteria because of overuse?

In 1994, ciprofloxacin (Cipro®, Bayer) was found to be efficacious against 86% of bacterial samples analyzed; by the year 2000, the rate had declined to 76%.

In a multicenter study, researchers examined data on infections in hospitalized patients in 43 states, including Washington, DC, from 1994 to 2000. Ailments included respiratory and urinary infections caused by various bacteria.

Many organisms had grown resistant to fluoroquinolones, a class of antibiotics that includes ciprofloxacin. The anthrax bacterium was not studied, and the researchers noted that their findings did not mean that the drug was becoming less effective against anthrax, which often affects animals but rarely humans.

Bacteria that became increasingly resistant during the study were all common causes of infections and included *Escherichia coli*.

When a drug is used repeatedly against the same organism, it has the potential to mutate into drug-resistant forms. The greater resistance came at a time when physicians were increasingly prescribing ciprofloxacin and similar drugs for common ailments such as respiratory infections caused by viruses, which are unaffected by antibiotics, the researchers noted. They urged more judicious use of the fluoroquinolones to limit the downward trend.


**Stopping and Restarting Chemotherapy**

In theory, clinicians who treat patients with advanced colorectal cancer can extend treatment indefinitely because of the low cumulative toxicity associated with therapy. However, researchers from the Medical Research Council Colorectal Cancer Group advise that it is safe to stop chemotherapy and then restart the treatment. In fact, doing so can enhance quality of life without compromising survival.

In a study of 354 patients with chemosensitive, advanced colorectal cancer, chemotherapy was safely stopped after 12 weeks and restarted if the disease progressed. The researchers found no clear evidence of a benefit with continuous chemotherapy.

Intermittent therapy, however, caused a reduction in toxicity; patients in the intermittent group received an average of 10 weeks less of trial chemotherapy than those receiving continuous therapy. There was no great difference in the use of second-line chemotherapy, which, the researchers say, can extend the patient’s treatment options. The introduction of second-line treatment can be delayed until the reused regimen fails.
Several guidelines for intermittent treatment have been suggested:

- The induction chemotherapy should last long enough and should be effective enough to ensure that the majority of patients’ responses take place during the induction period; however, a long induction treatment can lead to drug resistance, making rechallenging less effective.
- Patients must respond well to reusing the same chemotherapy drugs.
- Some patients may respond better if there is a long gap between stopping and starting treatment.
- Diligent follow-up is essential to ensure that the treatment can be reintroduced at the first sign of progression and to provide reassurance and symptom control during the interval.


**Adverse Drug Events in Trauma Patients**

Trauma patients are twice as likely to experience adverse drug events (ADEs) as non-trauma patients—even when patients in emergency departments are excluded, according to a study of more than 100,000 patients at LDS (Latter-day Saints) Hospital in Salt Lake City, Utah.

Of 4,320 trauma patients, 98 (2.3%) had ADEs, compared with 1,111 (1.2%) of 96,218 non-trauma patients. The most common ADEs were nausea, vomiting, and itching. More severe effects (and one death) occurred in the patients who were given anticoagulants, but those events were rare.

Only one ADE was directly attributable to a medical error, the researchers say. In fact, many of the ADEs were probably attributable to the type of drug—overwhelmingly, analgesics—and to the sex of the patients; women were 1.5 times more likely than men to have an ADE. Nearly 25% of all trauma patients initially had a low creatinine clearance rate, and 73% of those in the ADE group were women. Because dosages of analgesics are not generally determined by weight, the researchers point out, female patients often receive a proportionally higher dose, which may contribute to the higher risk of ADEs. The researchers suggest that a safer medication-ordering system would include the patient’s weight and the estimated creatinine clearance rate.

Hospital personnel should be vigilant about medication, especially early in the patient’s hospitalization and within a day of surgery; this is the period during which a large number of drugs are often given and when patients might experience the most pain. Personnel should also be on the lookout for drug interactions. Although the clinical pharmacist’s bedside evaluation did not find alcohol, illicit drugs, or anesthesia to be responsible for any ADEs in this study, some patients had taken illicit drugs, particularly opiates, which might have played a role in the occurrence of ADEs.

(Source: *J Trauma* 2003;54:337–343.)

**Immune to Infliximab?**

Some patients with Crohn’s disease may develop antibodies against infliximab (Remicade®, Centocor), thus increasing the risk of reactions to infusion and hampering their response.

Researchers from the University Hospital Gasthuisberg in Leuven, Belgium, monitored 125 patients for 12 weeks after each infusion of infliximab. Evaluations showed that 76 patients (61%) had developed antibodies to the drug. Concentrations of 8.0 mcg/ml or more before an infusion predicted a shorter duration of response (35 days vs. 71 days), and more than twice the risk of infusion reactions.

After an infusion reaction, infliximab disappears quickly from serum, the researchers say, and it is undetectable four weeks after an infusion. Drug concentrations were significantly lower at four weeks among patients who had experienced an infusion reaction than among patients who had never had an infusion reaction (1.2 mcg/ml vs. 14.1 mcg/ml).

Immunosuppressive therapy, however, can turn the tide, lowering antibodies and raising serum concentrations of infliximab. Of 56 patients who were taking immunosuppressive agents, 24 (43%) had a lower incidence of antibodies, compared with 52 (75%) of the 69 patients who were not taking immunosuppressive agents. Because antibodies develop soon after the initial infusion in most patients, the researchers recommend starting immunosuppressive therapy before infliximab therapy.


**Sedatives at the End of Life**

The doctrine of double effect—that a harmful effect of treatment is permissible if it occurs unintentionally as a side effect of a beneficial action—is “almost completely irrelevant” in the case of sedatives given in palliative end-of-life care, according to a case study from St. Christopher’s Hospice in London.

After reviewing information about 237 patients who died in the 62-bed hospice, the researchers concluded that most episodes of sedative use were brief, with no evidence that they had precipitated death. Instead, the episodes were a response to features of a dying process that had already begun. The sedatives were intended not to produce unconsciousness but to relieve symptoms such as agitation and restlessness that were associated with the final stages of terminal illness.

Many of the patients (52%) received no significant sedation at any stage during the last week of their lives. Indeed,
more than half of the patients (56%) who took the drugs had received them only in the last 48 hours of their lives, and most of those patients had taken them only in the last 24 hours.

The patients who received no sedation and those who received sedation for less than 48 hours had the shortest survival from admission (14 days). The patients who received sedatives for the last week of their lives survived for an average of 37 days. However, the reason might be because they may have been admitted for delirium, rather than terminal restlessness, and were thus more fit physically.

Only two cases might have justified the doctrine of double effect, the researchers say. One patient was a man with an astrocytoma whose condition was deteriorating before an acute onset of violent agitation and paranoia. His physician considered that sedation might have shortened his life because of an already poor prognosis. The second patient, a 70-year-old woman with lung cancer and a history of schizophrenia, was admitted for a generally deteriorating condition. She was given a series of sedating drugs for delusions and continuing agitation.

The researchers suggest that sedation might have allowed pneumonia to develop in the presence of lung disease. A characteristic of the clinical picture in both of these types of cases is death, usually within 24 to 72 hours.

(Source: Arch Intern Med 2003;163: 341–344.)

Clonidine Patches: Not for Eating!

Three adult patients in a detoxification unit deliberately ingested clonidine patches (Catapres-TTS®, Boehringer Ingelheim), reportedly to relieve symptoms of opiate withdrawal, and the result was three overdoses. The reporting physicians said that two of the patients chewed and swallowed their patches, and the third licked the patch and threw it away.

The symptoms of clonidine overdose include lethargy, hypotension, and bradycardia. The patients later told a staff member that another patient had suggested that they ingest their patches; the patients may have done so to achieve a psychoactive effect, such as a “high” or a calming effect. As a result of this experience, the doctors have since stopped using clonidine patches in the detoxification unit and warn that the risks of overdose might outweigh the potential benefits.

(Source: Arch Intern Med 2003;163: 367–368.)

HAART and the Heart

Findings from an analysis of more than 23,000 patients indicate that highly active antiretroviral therapy (HAART) is associated with a higher risk of myocardial infarction. What’s more, the risk increases 27% with every year of treatment. However, the overall risk of having a heart attack is still very low, according to the researcher who reported the study at the 10th Annual Conference on Retroviruses and Opportunistic Infections. Only 126 myocardial infarctions were reported from July 1999 through April 2001.

The researchers analyzed 36,479 person-years of data from patients following a HAART regimen that included a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. The investigators advise monitoring patients closely for cardiovascular disease and counseling them about the need to modify known risk factors and about the beneficial effects of HAART in treating human immunodeficiency virus infection.

(Source: www.medscape.com/view article/449473_print.)

Managing Dementia Symptoms

Pharmacists can play an important role in managing behavioral and psychological symptoms of dementia (BPSD) in nursing-home residents, say researchers who conducted a small pilot study in a long-term care facility. The symptoms, which include aggression, delusions, hallucinations, apathy, anxiety, and depression, can be difficult to treat and are usually managed with various psychotropic drugs.

In this study, a physician assistant ruled out and treated any reversible causes of BPSD, such as pain and infection. The nurses then tried nonpharmacological approaches. If the patient did not respond and the staff judged it appropriate to try drug therapy, they consulted the clinical pharmacists. The pharmacists worked with the staff to design a pharmacotherapy plan, wrote the orders, monitored progress and any side effects, and adjusted doses.

The drugs were selected on the basis of the patients’ most troublesome symptoms. The most commonly targeted symptoms were physical and verbal aggression, delusions, sleep disturbances, anxiety, and depression. Only two of the 11 patients had received psychotropic drugs before the study. During the study, the most commonly administered drug was trazadone (Desyrel®, Bristol-Myers Squibb), to which all but two patients responded. Quetiapine fumarate (Seroquel®, AstraZeneca) and sertraline (Zoloft®, Pfizer) were prescribed for these two patients, and they responded favorably.

Overall, the pharmacist-managed consultation service was well received, and treatment was efficient and successful. However, the researchers noted a few kinks in the process. One problem was the use of different terminology to describe the same symptoms. “Agitated,” they point out, can mean anything from restlessness to physical aggression, and...
treatment can vary correspondingly.
(Source: Pharmacotherapy 2003;23: 217–221.)

Which Aspirin to Use?
When physicians prescribe aspirin for their patients to lessen the inflammation associated with atherosclerosis or to prevent a stroke or a heart attack by thinning the blood, they might think about checking whether aspirin therapy is working. A study at Northwestern Memorial Hospital in Chicago found that coated or low-dose aspirin (baby aspirin) did not always reduce blood clotting.

The researchers tested 126 patients who took aspirin after a stroke. After comparing dosages, they found that 56% of patients taking an 81-mg tablet of children’s aspirin showed no change in blood clotting, whereas 72% of patients taking a 325-mg dose of aspirin experienced measurable effects. Similarly, 65% of patients taking coated aspirin at any strength showed no reduction in clotting, but 75% of patients who were taking uncoated aspirin did experience a reduction.

(Source: www.medscape.com/view article/449493_print.)

Extended-Release SNRI for Depression and Anxiety Symptoms
The serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressant venlafaxine (Effexor® XR, Wyeth) has been found to relieve patients’ physical and emotional symptoms related to depression and Generalized Anxiety Disorder (GAD), according to findings presented at the 41st Annual Meeting of The American College of Neuropsychopharmacology (ACNP). This extended-release (XR) drug is believed to increase levels of both serotonin and norepinephrine, two of the brain chemicals thought to be implicated in depression and anxiety. The drug is said to be able to “virtually eliminate” symptoms of depression and GAD.

Effexor® XR was effective in treating the physical and emotional symptoms of patients with GAD and was equally effective regardless of the initial severity of physical symptoms, according to three pooled analyses of 1,841 patients in five double-blinded studies. Patients who received this drug and who were monitored for six months demonstrated continued improvement across the spectrum of symptoms beyond their first eight weeks of therapy.

In depressed patients, the drug demonstrated greater therapeutic effect than other selective serotonin reuptake inhibitors (SSRIs) regardless of the severity of patients’ physical and emotional symptoms.

The most common adverse drug events (ADEs) reported in short-term placebo-controlled depression trials were nausea, dizziness, somnolence, delayed ejaculation, sweating, dry mouth, and nervousness; commonly reported ADEs in short-term GAD trials were nausea, dry mouth, abnormal ejaculation, constipation, and sweating.

Effexor® XR is contraindicated in patients taking monoamine oxidase inhibitors. Therapy with venlafaxine can be associated with sustained increases in blood pressure in some patients, and regular blood pressure monitoring is recommended. Patients should not abruptly discontinue their antidepressant medications.

(Source: ACNP poster presentation; Wyeth Pharmaceuticals news release.)

Women’s Health Prescription Drugs to Double by 2008
The worldwide market for prescription drugs for women’s health is projected to almost double through the year 2007, according to new data released by Kalorama Information in New York City. Manufacturers’ revenues for the year 2002 approached $36 billion and are expected to be almost $64 billion by the year 2008.

The report reveals that the market has been growing at nearly 17% over the past five years, and it is predicted that growth will continue to be in the double digits for the foreseeable future. Growth will be supported by the aging of women around the world, particularly in the U.S., and an increase in product demand, spurred by a still growing women’s health-awareness movement, should expand the total market significantly.

The study covers the products and markets for prescription drugs in all sectors of women’s health, such as autoimmune diseases, cancer, gynecological infections and sexually transmitted diseases, hormone-related indications (including menopause, contraception, and sexual dysfunction), osteoporosis, and urinary bladder disorders. The comprehensive report provides market size and growth projections, competitive market share, and epidemiological and clinical trends for a wide range of conditions, from breast cancer to yeast infections.


New Pain Scale for Patients
Nearly 25 million Americans experience acute pain each year as a result of injury, surgery, or disease. A new tool, the Ultra-
cetTM Rapid Pain Response Scale (Ortho-McNeil), allows patients to characterize their pain through a series of questions designed to make it easier to describe and rate their experience of pain. Patients can use the scale to self-assess the effectiveness or side effects of any medication they are taking for pain control. The accompanying “Daily Diary” enables patients to record and communicate an accurate pain history to their physicians.

(Source: www.ultracet.com; Ortho-
McNeil Pharmaceutical, Inc.)