Drug Monitor

Caution with Concurrent Nucleotide Analogs

With its durable virologic response and convenient once-daily dosing, the nucleotide analog tenofovir is recommended as part of a first-line combination anti-HIV regimen. But prescribing tenofovir with other nucleotide analogs—such as didanosine—should be evaluated carefully, advise researchers from the Cleveland Clinic Foundation, Cleveland, OH and Virginia Commonwealth University Medical Center, Richmond.

They describe a patient with HIV who developed pancreatitis while receiving antiretroviral therapy that included both tenofovir and didanosine. Pancreatitis is a known, dose-dependent adverse effect of didanosine, and several previous case reports have suggested that concurrent use of tenofovir may raise its risk of occurrence. As a result, some clinicians have tried reducing the didanosine dosage to 250 mg/day when tenofovir is included in the regimen, but this latest case report marks the third in which pancreatitis occurred despite this precaution.

The patient in this report had tried several antiretroviral regimens in the past, with little success. Some of these regimens included didanosine, but not tenofovir, with no significant adverse effects. After a two-month washout period, he had begun a new regimen consisting of efavirenz 600 mg and tenofovir 300 mg at bedtime, stavudine 30 mg twice daily, lamivudine 150 mg twice daily, and didanosine enteric-coated 250 mg at 5 AM daily.

Ten weeks later, he had presented to the emergency department (ED) following five days of intractable nausea and vomiting, epigastric abdominal pain without radiation, weight loss, pleuritic chest pain, and chills. He had stopped taking his antiretroviral medications two days before coming to the ED. An abdominal computed tomography scan revealed fat stranding surrounding the pancreas and a small amount of ascites consistent with pancreatitis but no definitive pancreatic necrosis. He was admitted and treated for pancreatitis and dehydration.

Upon discharge three days later, he had only mild epigastric pain and his laboratory values were returning to normal. His antiretroviral regimen was discontinued for a month and then restarted without didanosine. Ten months later, his amylase values remained within normal limits and he was asymptomatic.

The authors suggest that two other factors may have contributed to the pancreatitis in this patient. One was stavudine, which may have increased the risk of interaction. The other was the patient's weight: 60 kg. The authors recommend considering an even lower didanosine dosage of 125 mg/day for such low weight patients, though no published pharmacokinetic data are available.

Source: *Ann Pharmacother*. 2004;38:1660–1663.

Diclofenac on the Spot

With the safety of selective cyclooxygenase-2 inhibitors called into question, patients with osteoarthritis are back to square one, weighing the relief provided by traditional nonsteroidal anti-inflammatory drugs (NSAIDs) against the risk of severe gastrointestinal effects. Results from a randomized, double-blind, controlled trial, however, suggest that a new topical preparation of the NSAID diclofenac may offer benefits with fewer systemic effects.

Researchers from Arizona Research and Education, Phoenix and Dimethaid Health Care Ltd, Marham, Ontario, Canada compared the new solution (1.5% diclofenac sodium in a patented carrier containing the absorption enhancer dimethyl sulfoxide) and a vehicle control (the carrier without the diclofenac) in 326 patients with osteoarthritis of the knee. The patients received 40 drops of the diclofenac or the control solution four times daily for 12 weeks.

Topical diclofenac was significantly better than the control solution in improving patients' pain, stiffness, physical function, and global assessment scores. The greatest difference

over baseline for topical diclofenac was in pain, which declined by 46%. The diclofenac solution also outperformed the vehicle control in a separate analysis of pain on walking (45% versus 33% improvement).

Safety analyses revealed no serious adverse effects associated with topical diclofenac. Minor skin reactions (mostly skin dryness) at the application site were reported by 42% of patients. A few reported halitosis and taste changes, which the researchers attribute to the metabolism of dimethyl sulfoxide into a volatile gas.

The diclofenac solution has been approved for use in Canada, the United Kingdom, Italy, and several other countries. It's currently being reviewed by the FDA.

Source: *Arch Intern Med.* 2004;164:2017–2023.

A New View on Cluster Headache Treatment

It's possible to treat cluster headaches without vasoconstrictors, say researchers from the Institute of Neurology, Queen Square and Hammersmith and Charing Cross Hospitals, London, England. In their randomized, controlled, crossover study, 24 (52%) of 46 attacks treated with the somatostatin analog octreotide resolved within 30 minutes, compared with 16 (36%) of 45 attacks treated with placebo—a significant difference.

Octreotide was well tolerated, with eight patients (17%) experiencing short-lived, mild gastrointestinal upset. Similar symptoms were reported by four patients (9%) taking placebo. This makes octreotide an attractive agent when repeated doses will be required over a relatively short period, the researchers say. They note that gallstones have been a concern with long-term octreotide treatment but say the risk is extremely low.

Aside from offering a new option to patients in whom other cluster headache treatments are contraindicated or not practical, the researchers believe their findings shed light on fundamental differences between cluster headaches and migraines. In a previous trial, they found octreotide to be ineffective against migraine, despite some earlier research that suggested a benefit. And the two disorders apparently are associated with disparate patterns of brain activation: In cluster headache, the activity is in the posterior hypothalamus, whereas both episodic and chronic migraine show activity in the brainstem, without hypothalamic activation. The researchers say this is in keeping with greater prominence of a somatostatinergic mechanism in cluster headache. If so, their study would be the first substantial evidence for a pharmacologically based difference in the acute treatment of the two disorders.

Source: *Ann Neurol*. 2004; 56:488–494.

Lamivudine for Advanced Hepatitis B

Continuous treatment with lamivudine can delay clinical progression of chronic hepatitis B in patients with advanced fibrosis or cirrhosis, say researchers from the Cirrhosis Asian Lamivudine Multicentre Study Group. In their randomized, double-blind, placebo-controlled trial, lamivudine reduced disease progression by approximately 50%.

Of 651 patients, 436 were assigned to lamivudine 100 mg/day and 215 were assigned to placebo. None of the patients had evidence of hepatocellular carcinoma and none were coinfected with hepatitis C, hepatitis D, or HIV. The primary end point was time to disease progression, defined as development of hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, or bleeding gastroesophageal varices—or death related to liver disease.

The study was stopped after the second interim analysis because of the large, significant difference between the treatment groups. After a median of 32 months, 17.7% of the placebo patients had reached a primary end point, compared with 7.8% of the lamivudine patients. The incidence and nature of adverse events were similar between the two groups.

The main reservation about long-term lamivudine use in patients with chronic hepatitis B is the emergence of genotypic resistance tyrosine-methionine-aspartate-aspartate (YMDD) mutations, which have been associated with severe and even fatal flares of hepatitis, say the researchers. And in fact, 49% of patients taking lamivudine developed YMDD mutations, compared with 5% of those taking placebo. Hepatitis B virus DNA breakthrough was detected in 62% of patients with the mutations in the lamivudine group, compared with only 5% of patients without the mutations. Nevertheless, the incidence of clinical progression among patients with the mutations was still lower than it was among placebo patients. The researchers conclude, therefore, that lamivudine's benefits were not negated by the emergence of these mutations.

Source: *N Engl J Med.* 2004;351:1521–1531.

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Chemotherapy for Advanced Head and Neck Cancer

The optimal neoadjuvant chemotherapy regimen for advanced, unresectable, squamous cell head and neck cancer is unclear. Researchers from Chang Gung Memorial Hospital, Taipei, Taiwan, however, report encouraging efficacy and relatively low toxicity with a combination of biweekly paclitaxel and cisplatin and daily tegafur and leucovorin.

They administered this regimen in 14-day cycles to 21 patients with stage IV disease. Patients who had at least a partial tumor response after three cycles received up to three more cycles, followed by locoregional therapy.

Overall, 17 patients (81%) responded—six (29%) completely and 11 (52%) partially. Of the 18 patients with neck lymph node metastases, four (22%) achieved a complete response and 11 (61%) had a partial response.

Three patients discontinued the chemotherapy early: two who developed severe neuropathy and one who died of aspiration pneumonia. Treatment was delayed in 11 patients due to renal insufficiency, stomatitis, asthenia, or myelosuppression. The most common grade 3 or 4 toxicities were leukopenia, emesis, asthenia, mucositis, and neuropathy.

Source: *Cancer*. 2004; 101:1818–1823.

Helping Diabetic Patients Lose Weight

Overweight and obesity make it more difficult to control type 2 diabetes and prevent complications. But results from a study of 86 patients at the General Hospital of Mexico, Mexico City, suggest that the serotonin and norepinephrine reuptake inhibitor sibutramine can help.

The patients, who all had a body mass index (BMI) above 27 kg/m^2 and had been taking glibenclamide for type 2 diabetes for at least two weeks, were randomly assigned to receive oral sibutramine 10 mg/day or placebo. A total of 24 sibutramine patients and 23 placebo patients completed the trial.

After 12 months of sibutramine, patients' mean weight dropped by 4.1 kg, BMI fell by 1.7 kg/m^2, and waist circumference decreased by 4.1 cm. Fasting blood glucose and glycosylated hemoglobin (HbA_{1C}) both declined—from 140.4 to 114.2 mg/dL and from 8.9% to 8.3%, respectively. By contrast, placebo patients lost only 1.4 kg in weight, 0.6 kg/m^2 in BMI, and 1.3 cm in waist circumference. And while their fasting blood glucose dropped from 140.7 to 123.9 mg/dL, their HbA_{1C} rose from 9% to 9.1%.

Source: *Clin Ther*. 2004; 26:1427–1435.