In summary, epidural anesthesia provided sufficient anesthesia for a patient with esophageal cancer and a TEF who underwent colon interposition and cervical esophagostomy.

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Vicodin-induced Fulminant Hepatic Failure

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ANESTHESIOLOGISTS in greater numbers are participating in the management of postoperative pain. On cessation of patient-controlled analgesia, or discontinuation of epidural opioids, anesthesiologists on pain-management teams are often called upon to prescribe oral analgesics. Vicodin, a combination of 5 mg hydrocodone and 500 mg acetaminophen, is often prescribed in this setting. We report on the cases of three patients in whom the use of Vicodin resulted in fulminant hepatic failure because of acetaminophen hepatotoxicity.

Case 1

This patient was a 19-yr-old woman with a long history of ulcerative colitis. She underwent an uncomplicated ileostomy closure, but was readmitted to an outside hospital 9 days later with small bowel obstruction. She required exploratory laparotomy and lysis of adhesions. On postoperative day 2, after she was able to take clear liquids, her parenteral opioids were discontinued, and she was prescribed Vicodin 1 or 2 tablets every 4 h as needed for pain. Over the next 4 days, she received approximately 40 Vicodin tablets, as prescribed.

On postoperative day 6, she became obtunded. A physical examination revealed tachypnea and hypotension. Laboratory studies revealed hypoglycemia (blood glucose, 23 mg/dl) and severe metabolic acidosis: arterial blood gas, with $F_{I_{O_2}}$ 1.0, was *p*H 7.12; P_{CO_2} was 18 mmHg; P_{O_2} was 522 mmHg; and base deficit was −21. Liver function tests revealed total bilirubin of 2.6 mg/dl, aspartate aminotransferase (SGOT) of 5,940 U/l, alanine aminotransferase (SGPT) of 1,730 U/l, prothrombin time (PT) of > 100 s, and partial thromboplastin time (PTT) of > 120 s. Her acetaminophen level was 47 μg/ml (therapeutic levels 0.25–0.64 mg/dL), and she was treated with N-acetylcysteine. Progressive deterioration in mental status necessitated tracheal intubation and ventilatory support. Dopamine was administered for profound hypotension.

She was transferred to University of California, San Francisco Moffitt-Long Hospitals with a diagnosis of fulminant hepatic failure. Her course was complicated by recurrent gastrointestinal bleeding, consumptive coagulopathy, acute renal failure, candida sepsis, adult respiratory distress syndrome, and cerebral edema. Because of her multiorgan failure, she was not considered a suitable candidate for liver transplantation, and she died on the 55th posttransfer day.

Case 2

This patient was a 29-yr-old woman with a history of seizures, chronic low back pain, and depression. Her medication regimen included phenytoin, phenobarbital, lorazepam, amitryptilene, Soma (carisoprodol and aspirin), furosemide, verapamil, nonsteroidal antiinflammatory agents, codeine, acetaminophen, and Vicodin. On the

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day of admission, the patient was found unresponsive on the floor of her home. She was taken to the emergency room of an outside hospital. Family members reported that, over the prior month, the patient exhibited a progressively unsteady gait. In the emergency room, her blood acetaminophen level was 22 μg/ml, and she was treated with N-acetylcysteine. Dilantin and phenobarbital levels were within therapeutic ranges. Other laboratory studies revealed total bilirubin of 2.6 mg/dl, SGOT of 6,709 U/l, SGPT of 2,980 U/l, lactic dehydrogenase (LDH) of 27,185 U/l, PT of 24.3 s, and PTT of 66.5 s. Hypoglycemia and metabolic acidosis were treated in the emergency room.

Because of obtundation, the patient required tracheal intubation and mechanical ventilation. Eight hours after emergency room admission, she was transferred to the University of California, San Francisco Medical Center for liver transplantation. Over the next several hours, her neurologic status deteriorated, despite hyperventilation, mannitol, and steroids given to treat cerebral edema. Profound hypotension was treated with dopamine, norepinephrine, and phenylephrine. Before transplantation, within a day of transfer, the patient died.

Case 3

The patient, a 32-yr-old man with chronic low back pain and a history of several lumbar surgical procedures experienced exacerbation of severe back pain 3 days before admission. During that day, he took approximately 30 Vicodin tablets. In addition, the patient may have ingested an unknown quantity of Tylenol #4 (300 mg acetaminophen, 60 mg codeine). He was transferred to the University of California, Los Angeles Medical Center from a local emergency room, with a diagnosis of fulminant hepatic failure.

On arrival in the intensive care unit, the patient's trachea was intubated, and he had spontaneous bleeding from the nose, mouth, and puncture sites. He was hypotensive, with systolic blood pressures of 60–80 mmHg, despite receiving high-dose dopamine. He had intermittent episodes of atrial fibrillation, and no urine output. The patient was unresponsive to painful stimuli, but had some spontaneous movement.

Laboratory studies revealed a metabolic acidosis: *p*H of 7.2, P_{CO_2} of 33 mmHg, and P_{O_2} of 334 mmHg. The patient's creatinine was 3.6 mg/dl, SGOT was 12,309 U/l, SGPT was 7,386 U/l, PT was > 30 s, fibrinogen was 21 mg/dl, and fibrin degradation products were present. His head CT showed no cerebral edema.

A donor liver became available shortly after transfer. The patient was taken to the operating room, where an orthotopic liver transplantation was performed, using intracranial pressure monitoring. The grafted liver functioned well in the immediate postoperative period, and the patient regained full neurologic function over the course of a week.

Discussion

Vicodin, a combination of a synthetic opioid and an antipyretic-analgesic, is often prescribed after surgery. The opioid component, hydrocodone, is six to eight times more potent than codeine, because of its relatively high oral bioavailability. In addition, Vicodin is a schedule III controlled drug, and does not require a triplicate form, an advantage in ease of prescribing. Acetaminophen, when used as an analgesic, exhibits a ceiling effect; the difference in pain relief between 600 and 1,000 mg is not significant.[1] Acetaminophen-induced liver toxicity, however, is dose-related.[2]

Most reported cases of acetaminophen-related hepatotoxicity, which was first recognized in 1966,[3] have been associated with acute ingestion of the drug, usually in doses over 15 g.[4] Liver toxicity from chronic ingestion of therapeutic doses of acetaminophen is much rarer, but has been reported with doses of about 3 g/day, well within therapeutic guidelines.[5,6] Of the few patients reported to have liver disease from therapeutic use of acetaminophen, most developed chronic liver dysfunction. Withdrawal of the drug has been reported to improve this chronic liver disease in most, but not all, patients.[7] Our cases are unusual in that an acetaminophen-containing drug (without intentional overdose) caused fulminant hepatic failure (FHF), as opposed to chronic liver disease.

FHF is acute hepatic necrosis in a patient without chronic liver disease, in whom encephalopathy develops within 8 weeks of the onset of disease.[8] Fulminant hepatic failure is not likely to lead to chronic disease. As in other forms of FHF (viral and other toxins), the vast majority of patients who survive FHF caused by acetaminophen do so with normal hepatic function.[9] However, mortality from FHF is high. In one retrospective review of 150 patients with acetaminophen-induced FHF, mortality was 48%.[10] In these patients, the major cause of death is neurologic, because of intracranial hypertension and cerebral edema.[8]

Normally, most acetaminophen is excreted after hepatic conjugation with glucuronic acid, sulfuric acid, and cysteine.[11] After ingestion of a large dose of acetaminophen, metabolism by P450 enzyme systems leads to the formation of a highly reactive arylating metabolite that is toxic to the liver.[1] The toxic metabolite requires hepatic glutathione for detoxification.

Chronic alcohol ingestion is associated with an increased risk of acetaminophen-induced liver damage from chronic ingestion of the drug.[5] Alcoholics may be predisposed to acetaminophen toxicity because of decreased glutathione stores,[12] or because of the induction of P450 enzymes.[13] Anticonvulsant medications that increase P450 activity, such as phenytoin and phenobarbital, may also predispose patients to acetaminophen-related hepatotoxicity.[14] Isoniazid therapy may also potentiate liver damage in the setting of acute acetaminophen intoxication.[15] In a mouse model of

acetaminophen poisoning, some opioids were shown to deplete hepatic glutathione stores, and, thereby, to worsen acetaminophen hepatotoxicity. Morphine, hydromorphone, ethylmorphone, 1-α-acetyl-methadol, and meperidine all decreased hepatic glutathione concentrations, but codeine, methadone, butorphanol, nalbuphine, and pentazocine did not.[16]

Certain viral illnesses associated with hepatic dysfunction, such as measles[17] or mononucleosis,[18] may increase the likelihood of liver damage from acetaminophen ingestion.

In addition to hepatotoxicity, acetaminophen overdose may cause acute renal failure, with or without liver failure.[19] Acute cardiac toxicity has also been reported.[20]

The treatment of choice for acute acetaminophen overdose is N-acetylcysteine. N-acetylcysteine acts as a glutathione analog that binds and inactivates toxic acetaminophen metabolites.‡ Although originally given as an intravenous preparation,[21] the standard therapy is now given orally, 140 mg/kg for the first dose, then 70 mg/kg every 4 h for 17 doses. The therapeutic efficacy of N-acetylcysteine is related to the promptness of administration, but the treatment is considered appropriate if given within 24 h of an overdose.[22] There are no guidelines available in the literature for N-acetylcysteine therapy in the setting of liver damage caused by chronic ingestion of acetaminophen, in part because the diagnosis often goes unrecognized.[23] Patients with fulminant hepatic failure caused by acetaminophen overdose who do not respond to antidote and supportive therapy may require emergency liver transplantation.[24]

In retrospect, all three patients reported here were at increased risk for acetaminophen-induced liver toxicity. All three patients had a history of chronic pain requiring opioids. In such circumstances, in which tolerance may develop, it is not surprising that the patients required large amounts of Vicodin for adequate postoperative pain relief. In fact, whenever the Vicodin dose is escalated for pain relief, careful consideration must be given to the total amount of acetaminophen that the patient will receive. The second patient was at further risk for acetaminophen-induced hepatic toxicity because she was also taking antiseizure medications.[25] Furthermore, two of the three patients were prescribed, or receiving, plain acetaminophen, in addition to the prescribed acetaminophen-containing Vicodin. These patients were apparently never instructed about the dangers of taking these medicines simultaneously.

In summary, we present three cases of fulminant hepatic failure attributable to the acetaminophen in Vicodin. These cases highlight the need for caution in prescribing Vicodin to patients who may be at increased risk for acetaminophen toxicity. A history of chronic alcohol consumption, or the concurrent use of anticonvulsants, isoniazid, or acetaminophen, warrant caution in prescribing this combination drug. Patients should be specifically instructed as to the maximum safe dosage.

Furthermore, physicians who treat chronic pain syndromes should be alert to the potentially fatal consequences of large doses of acetaminophen in Vicodin.

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