**TABLE 430-4 UNSAFE DRUGS IN PORPHYRIA (*CONTINUED*)**

| Documented Porphyrinogenic | Probably Porphyrinogenic | Possibly Porphyrinogenic |
|---|---|---|
| | Tramadol | Naltrexone |
| | Trimegestone + estrogen | Nateglinide |
| | Verapamil | Nilutamide |
| | Voriconazole | Noscapine |
| | Zidovudine/AZT | Omeprazole |
| | | Oxybutynin |
| | | Oxycodone |
| | | Pantoprazole |
| | | Papaverine |

***Note:*** Based on list in "Patient's and Doctor's Guide to Medication in Acute Porphyria," Swedish Porphyria Association and Porphyria Centre Sweden. Also see the website Drug Database for Acute Porphyrias (*www.drugs-porphyria.com*) for a searchable list of safe and unsafe drugs.

retention are characteristic. Tachycardia, hypertension, restlessness, tremors, and excess sweating are due to sympathetic overactivity.

The peripheral neuropathy is due to axonal degeneration (rather than demyelinization) and primarily affects motor neurons. Significant neuropathy does not occur with all acute attacks; abdominal symptoms are usually more prominent. Motor neuropathy affects the proximal muscles initially, more often in the shoulders and arms. The course and degree of involvement are variable and sometimes may be focal and involve cranial nerves. Deep tendon reflexes initially may be normal or hyperactive but become decreased or absent as the neuropathy advances. Sensory changes such as paresthesia and loss of sensation are less prominent. Progression to respiratory and bulbar paralysis and death occurs especially when the diagnosis and treatment are delayed. Sudden death may result from sympathetic overactivity and cardiac arrhythmia.

Mental symptoms such as anxiety, insomnia, depression, disorientation, hallucinations, and paranoia can occur in acute attacks. Seizures can be due to neurologic effects or to hyponatremia. Treatment of seizures is difficult because most antiseizure drugs can exacerbate AIP (clonazepam may be safer than phenytoin or barbiturates). Hyponatremia results from hypothalamic involvement and inappropriate vasopressin secretion or from electrolyte depletion due to vomiting, diarrhea, poor intake, or excess renal sodium loss. Persistent hypertension and impaired renal function may occur. When an attack resolves, abdominal pain may disappear within hours, and paresis begins to improve within days and may continue to improve over several years.

Homozygous dominant AIP is a rare form of AIP in which patients inherit *HMBS* mutations from each of their heterozygous parents and, therefore, have very low (<2%) enzyme activity. The disease has been described in a Dutch girl, two young British siblings, and a Spanish boy. In these homozygous affected patients, the disease presented in infancy with failure to thrive, developmental delay, bilateral cataracts, and/or hepatosplenomegaly. Urinary ALA and PBG concentrations were markedly elevated. All of these patients' *HMBS* mutations (R167W, R167Q, and R172Q) were in exon 10 within five bases of each other. Studies of the brain magnetic resonance images (MRIs) of children with homozygous AIP have suggested damage primarily in white matter that was myelinated postnatally, while tracks that myelinated prenatally were normal. Most children with homozygous AIP die at an early age.

**Diagnosis** ALA and PBG levels are substantially increased in plasma and urine, especially during acute attacks, and become normal only after prolonged latency. For example, urinary PBG excretion during an attack is usually 50–200 mg/24 h (220–880 μmol/24 h) (normal, 0–4 mg/24 h, [0–18 μmol/24 h]), and urinary ALA excretion is 20–100 mg/24 h (150–760 μmol/24 h) (normal, 1–7 mg/24 h [8–53 μmol/24 h]). Because levels often remain high after symptoms resolve, the diagnosis of an acute attack in a patient with biochemically proven AIP is based primarily on clinical features. Excretion of ALA and PBG decreases over a few days after intravenous hemin administration. A normal urinary PBG level before hemin effectively excludes AIP as a cause for current symptoms. Fecal porphyrins are usually normal or minimally increased in AIP, in contrast to HCP and VP. Most AIP heterozygotes with no history of symptoms have normal urinary excretion of ALA and PBG. Therefore, the detection of the family's *HMBS* mutation will diagnose asymptomatic family members.

Patients with *HMBS* mutations in the initiation of translation codon in exon 1 and in the intron 15′-splice donor site have normal enzyme levels in erythrocytes and deficient activity only in nonerythroid tissues. This occurs because the erythroid and housekeeping forms of HMB synthase are encoded by a single gene, which has two promoters. Thus, the enzyme assay may not be diagnostic, and genetic testing should be used to confirm the diagnosis.

More than 390 *HMBS* mutations have been identified in AIP, including missense, nonsense, and splicing mutations and insertions and deletions, with most mutations found in only one or a few families (Human Gene Mutation Database, *www.hgmd.org*). The prenatal diagnosis of a fetus at risk can be made with cultured amniotic cells or chorionic villi. However, this is seldom done, because the prognosis of individuals with *HMBS* mutations is generally favorable.

## TREATMENT ACUTE INTERMITTENT PORPHYRIA

During acute attacks, narcotic analgesics may be required for abdominal pain, and phenothiazines are useful for nausea, vomiting, anxiety, and restlessness. Chloral hydrate can be given for insomnia, and benzodiazepines are probably safe in low doses if a minor tranquilizer is required. Carbohydrate loading, usually with intravenous glucose (at least 300 g daily), may be effective in milder acute attacks of porphyria (without paresis, hyponatremia, etc.) if hemin is not available. Intravenous hemin is more effective and should be used as first-line therapy for all acute attacks. The standard regimen is 3–4 mg/kg of heme, in the form of lyophilized hematin (Recordati Pharmaceuticals), heme albumin (hematin reconstituted with human albumin), or heme arginate (Orphan Europe), infused daily for 4 days. Heme arginate and heme albumin are chemically stable and are less likely than hematin to produce phlebitis or an anticoagulant effect. Recovery depends on the degree of neuronal damage and usually is rapid if therapy is started early. Recovery from severe motor neuropathy may require months or years. Identification and avoidance of inciting factors can hasten recovery from an attack and prevent future attacks. Inciting factors are usually multiple, and removal of one or more hastens recovery and helps prevent future attacks. Frequent attacks that occur during the luteal phase of the menstrual cycle may be prevented with a gonadotropin-releasing hormone analogue, which prevents ovulation and progesterone production, or by prophylactic hematin administration.

The long-term risk of hypertension and chronic renal disease is increased in AIP; a number of patients have undergone successful renal transplantation. Chronic, low-grade abnormalities in liver function tests are common, and the risk of hepatocellular carcinoma is increased. Hepatic imaging is recommended at least yearly for early detection of these tumors.

An allogeneic liver transplant was performed on a 19-year-old female AIP heterozygote who had 37 acute attacks in the 29 months