12 - 29.12 Calcium Channel Blockers

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reach peak plasma levels for about 6 hours. The half-life of verapamil after the first dose is 2 to 8 hours; the half-life increases to 5 to 12 hours after the first few days of therapy. The half-lives of the other CCBs range from 1 to 2 hours for nimodipine and isradipine to 30 to 50 hours for amlodipine (Table 29.12-1). Table 29.12-1 Half-lives, Dosages, and Effectiveness of Selected Calcium Channel Inhibitors

in Psychiatric Disorders The primary mechanism of action of CCBs in bipolar illness is not known. The calcium channel inhibitors discussed in this section inhibit the influx of calcium into neurons through L-type (long-acting) voltage-dependent calcium channels. THERAPEUTIC INDICATIONS Bipolar Disorder Nimodipine and verapamil have been demonstrated to be effective as maintenance therapy in persons with bipolar illness. Patients who respond to lithium appear to also respond to treatment with verapamil. Nimodipine may be useful for ultradian cycling and recurrent brief depression. The clinician should begin treatment with a short-acting drug such as nimodipine or isradipine, beginning with a low dosage and increasing the dosage every 4 to 5 days until a clinical response is seen or adverse effects appear. When symptoms are controlled, a longer acting drug, such as amlodipine, can be substituted as maintenance therapy. Failure to respond to verapamil does not exclude a favorable response to one of the other drugs. Verapamil has been shown to prevent antidepressant-induced mania. The CCBs can be combined with other agents, such as carbamazepine, in patients who are partial responders to monotherapy. Depression None of the CCBs is effective as treatment for depression and may in fact prevent response to antidepressants. Other Psychiatric Indications Nifedipine is used to treat hypertensive crises associated with the use of MAOIs. Isradipine may reduce the subjective response to methamphetamine. Calcium channel inhibitors may be beneficial in Tourette’s disorder, Huntington’s disease, panic disorder, intermittent explosive disorder, and tardive dyskinesia. Other Medical Uses These drugs have been used to treat medical conditions such as angina, hypertension,

migraine headaches, Raynaud’s phenomenon, esophageal spasm, premature labor, and headache. Verapamil has antiarrhythmic activity and has been used to treat superventricular arrhythmias. PRECAUTIONS AND ADVERSE REACTIONS The most common adverse effects associated with calcium channel inhibitors are those attributable to vasodilation: dizziness, headache, tachycardia, nausea, dysesthesias, and peripheral edema. Verapamil and diltiazem (Cardizem) in particular can cause hypotension, bradycardia, and atrioventricular heart block, which necessitate close monitoring and sometimes discontinuation of the drugs. In all patients with cardiovascular disease, the drugs should be used with caution. Other common adverse effects include constipation, fatigue, rash, coughing, and wheezing. Adverse effects noted with diltiazem include hyperactivity, akathisia, and parkinsonism; with verapamil, delirium, hyperprolactinemia, and galactorrhea; with nimodipine, subjective sense of chest tightness and skin flushing; and with nifedipine, depression. The drugs have not been evaluated for safety in pregnant women and are best avoided. Because the drugs are secreted in breast milk, nursing mothers should also avoid the drugs. DRUG INTERACTIONS All CCBs have a potential for drug–drug interactions. The types and risks of these interactions vary by compound. Verapamil raises serum levels of carbamazepine, digoxin, and other CYP3A4 substrates. Verapamil and diltiazem but not nifedipine have been reported to precipitate carbamazepine-induced neurotoxicity. Calcium channel inhibitors should not be used by persons taking β-adrenergic receptor antagonists, hypotensives (e.g., diuretics, vasodilators, and angiotensin-converting enzyme inhibitors), or antiarrhythmic drugs (e.g., quinidine and digoxin) without consultation with an internist or cardiologist. Cimetidine (Tagamet) has been reported to

increase plasma concentrations of nifedipine and diltiazem. Some patients who are treated with lithium and calcium channel inhibitors concurrently may be at increased risk for the signs and symptoms of neurotoxicity, and deaths have occurred. LABORATORY INTERFERENCES No known laboratory interferences are associated with the use of calcium channel inhibitors. DOSAGE AND CLINICAL GUIDELINES Verapamil is available in 40-, 80-, and 120-mg tablets; 120-, 180-, and 240-mg sustained-release tablets; and 100-, 120-, 180-, 200-, 240-, 300-, and 360-mg sustainedrelease capsules. The starting dosage is 40 mg orally three times a day and can be increased in increments every 4 to 5 days up to 80 to 120 mg three times a day. The patient’s blood pressure, pulse, and electrocardiogram (in patients older than 40 years

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