Primary Biliary Cirrhosis and Sarcoidosis

To the Editor:

In a recent review of primary biliary cirrhosis (PBC), the possible association of this disease with sarcoidosis is not mentioned.1

Although most patients with sarcoidosis have no clinical evidence of liver disease, hepatic granulomas occur in 60 percent of patients with this disease.2 Rarely, patients with sarcoidosis may develop chronic intrahepatic cholestasis, which may progress to biliary cirrhosis and liver failure. Since many patients with PBC show chronic intrahepatic cholestasis were described more than 25 years ago. In 1969, Karlish et al.3 reported the case of a 47-year-old woman with enlarged hilar and paraaortic lymph nodes, a positive Kveim test, circulating antimitochondrial antibodies and progressive cholestatic liver disease. Maddrey et al.,4 in a study of 20 patients with sarcoidosis and chronic hepatic disease, described two patients who had features of PBC: they subsequently described two other patients with pulmonary granulomas and progressive cholestatic liver disease.5 Antimitochondrial antibodies were positive in one of two patients tested in this group of four. Stanley et al.6 described two middle-aged women with pruritus, liver findings compatible with PBC, and positive antimitochondrial antibodies. Both patients had pulmonary infiltrates; after they died from liver disease, autopsy showed pulmonary granulomas. Rudzki et al.7 described a series of five young men who had evidence of systemic granulomatous disease with clinical and biochemical data similar to those of PBC. Antimitochondrial antibodies were not found; survival exceeded the usual survival of patients with PBC and the authors considered sarcoidosis as the most likely diagnosis. Fagan et al.8 described four women with high titers of antimitochondrial antibodies and hepatic granulomas, in addition to prominent pulmonary signs and symptoms. Kveim test was positive in one of the three patients tested; all patients had abnormal chest radiographs and three of them had lung granulomas on biopsy. The authors stressed that their patients' disorders were not discrete entities, but had clinical, serologic and histologic findings that overlapped those of Sjögren's syndrome, celiac disease and mixed connective disease as well as sarcoidosis and PBC. About 95 percent of patients with PBC have positive antimitochondrial antibody tests, as opposed to 1 percent of patients with sarcoidosis. It therefore seems reasonable to use this finding as a defining characteristic for PBC. The absence of antimitochondrial antibodies would identify patients with chronic intrahepatic cholestasis complicating sarcoidosis. Patients with chronic intrahepatic cholestasis, extrahepatic granulomas and circulating antimitochondrial antibodies would be considered to have both sarcoidosis and PBC. Sarcoidosis should be added to the list of diseases that may be associated with PBC.

REFERENCES
1 Pratter MB, Irwin RS. Usefulness and safety of pharmacological bronchoprovocation challenge in evaluating patients with normal spirometric tests who are suspected of having asthma. Chest 1988; 93:999-990

Interaction of Rifampin and Glyburide

To the Editor:

Numerous clinically significant drug interactions have been reported with the use of rifampin, including the sulfonylureas, tolbutamide and chlorpropamide.9,10 We recently observed a case suggestive of an effect of rifampin on serum glyburide concentrations. To our knowledge, this is the first report of this interaction in the literature.

A 67-year-old woman was diagnosed with renal tuberculosis in March, 1988 on the basis of a urine test positive for acid-fast bacilli and positive urine cultures for Mycobacterium tuberculosis. On March 10, therapy was begun using rifampin (600 mg daily), isoniazid (300 mg daily), and pyridoxine (50 mg daily). The patient's past medical history included adult onset diabetes mellitus, hypertension, gout, and mild renal insufficiency. Medications for these problems included allopurinol (100 mg daily), glyburide (5 mg daily), pentoxifylline (400 mg three times daily), furosemide (120 mg in the morning and 80 mg in the evening), nifedipine (20 mg three times daily) and methyldopa (250 mg twice daily). Glyburide dosage was increased to 10 mg in the morning and 5 mg in the evening in July, 1988. In August, insulin therapy (10 units in the morning and 5 units in the evening) was added to help control serum glucose levels. Insulin dosage was further increased in October, 1988 to 15 units in the morning and 5 units in the evening. In October, 1988, furosemide was replaced with metolazone (5 mg daily).

Using a modification (unpublished) of the method of Adams et al., serum glyburide concentrations were determined twice before rifampin therapy was discontinued on December 10 and then three times after rifampin was stopped. Morning trough glyburide serum concentration rose dramatically upon discontinuation of rifampin therapy (Fig 1). Renal and hepatic function remained stable throughout this period.

This case is strongly suggestive of a glyburide and rifampin...
interaction. The other drugs which this patient was receiving have not been reported to interact with glyburide or other sulfonylureas. As with most rifampin interactions, the probable mechanism is the induction of hepatic drug metabolizing enzymes by rifampin causing stimulation of glyburide metabolism. Glyburide undergoes oxidation by the liver. Despite the great increase in glyburide serum concentrations following rifampin discontinuation, blood glucose concentrations did not change appreciably (240 mg/dl December 5, 318 mg/dl December 16, 245 mg/dl December 30). This observation is consistent with studies showing a lack of correlation between serum glyburide concentration and blood glucose concentration. In some patients, however, it is possible that such dramatic increases in glyburide concentrations could result in hypoglycemia.

Timothy H. Self, Pharm. D.,
Professor of Clinical Pharmacy;
Sandra J. Tetsu, Pharm. D.,
William F. Boud Hospital;
Department of Pharmacy Services, and
John W. Fowler, Jr., M.D.
Assistant Professor of Medicine,
University of Tennessee,
Memphis

ACKNOWLEDGMENT: The authors express appreciation to Edward Antal, Ph.D. of the Upjohn Company for providing the glyburide assays.

REFERENCES
1 Bacieiwicz AM, Self TH. Rifampin drug interactions. Arch Intern Med 1984; 144:1667-71
2 Bacieiwicz AM, Self TH, Bekemeyer WB. Update on rifampin drug interactions. Arch Intern Med 1987; 147:565-68

Dosages for Labetalol

To the Editor:

We read with interest the report by Gonzalez and Ramí on the treatment of hypertensive urgencies and emergencies. However, we have some concerns regarding the dosing guidelines they offered for labetalol.

According to the product information for labetalol HCl injection (Trandate, Glaxo; Normodyne, Schering), either a continuous infusion administered at an initial rate of 2 mg/min or intermittent injections of 40 or 80 mg at 10 min intervals following an initial 20 mg injection are recommended. None of the alternative dosages suggested by the authors can be recommended at this time. Maximum cumulative dose used in US clinical trials for this indication was 300 mg; rather than the 150 mg maximum noted in the report. Finally, maximum blood pressure response following intermittent injections is usually observed within 5 min, not 15 min. Although the response is more gradual using a continuous infusion, it does not require six hours to achieve a maximum effect.

Dan Mitchell, Pharm. D., and
Mark Sirgo, Pharm. D.,
Glaxo Inc.,
Research Triangle Park, NC

REFERENCES

To the Editor:

I am appreciative of the clarification offered by Drs. Mitchell and Sirgo regarding the dosage of labetalol injection. Generally, an acceptable therapeutic response can be achieved at 150 mg dosage although a higher dosage (300 mg) has been recommended. Maximal blood pressure response to bolus injections occurs between five and 15 mins, while the response to continuous infusion is more gradual.

C. Venkata S. Ram, M.D., F.C.C.P.,
Associate Professor, Internal Medicine,
University of Texas
Southwestern Medical Center,
Dallas