Acute Cardiac Failure and Hepatic Ischemia Induced by Disopyramide Phosphate

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Two patients abruptly developed congestive heart failure and elevations in serum transaminase levels when given disopyramide phosphate; enzyme abnormalities and hemodynamic status corrected upon withdrawal of the drug. Both patients had underlying ischemic cardiomyopathy. Myocardial infarction, pulmonary embolism, and viral hepatitis were ruled out in both patients. One patient had a liver biopsy documenting central hepatic necrosis with congestion, consistent with hepatic ischemia and not toxic hepatitis. In the other patient, cardiac decompensation and hepatocellular enzyme elevation were reproduced on rechallenge with the drug. Disopyramide should be used with caution in patients with heart failure.

Disopyramide phosphate (DP) is an antiarrhythmic drug that resembles quinidine in its electrophysiologic properties. Because it spares the patient many of the gastrointestinal side effects of quinidine, DP is becoming widely used [1]. However, DP has been shown to have a myocardial depressant effect which may be especially pronounced in patients with underlying heart failure [1-4]. Two cases are reported here in which transient but marked elevations in hepatocellular enzymes had a clear temporal relation to cardiac decompensation induced by DP in patients with ischemic cardiomyopathy.

CASE REPORTS

Case 1

A 62-year-old man was admitted to Yale-New Haven Hospital with congestive heart failure and ventricular ectopy. His past history included hypertension, coronary artery disease with inferior wall myocardial infarction, chronic obstructive lung disease, and transient ischemic attacks successfully treated by right carotid endarterectomy. He was taking furosemide, prazosin, and digoxin for heart failure, and was also taking allopurinol. Quinidine was started for ventricular ectopy but had to be stopped when abdominal cramps, nausea, and vomiting developed; these symptoms then resolved. He had no prior history of liver disease, took alcohol rarely, and had no exposure to known hepatotoxins.

On admission he was afebrile, in mild respiratory discomfort with 24 respiations per minute, a pulse of 100, and a blood pressure of 160/80. He had jugular venous distention, bilateral carotid bruits, bibasilar pulmonic rales, and a left ventricular lift.

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A II/VI early systolic murmur was heard at the apex, with a normally split S₂ and an S₄ gallop. The liver was estimated to be 13 cm in span by percussion; he had trace peripheral edema. Chest X-ray showed cardiomegaly with redistribution of pulmonary flow to the upper lobes. His electrocardiogram showed sinus rhythm with a PR interval of 0.16 sec, a QRS interval of 0.11 sec with a left ventricular conduction delay, inferior Q waves, and lateral ST segment depressions. Serum potassium, SGOT, LDH, bilirubin, alkaline phosphatase, creatine kinase, and prothrombin time were normal. The only serum abnormality was a BUN of 32.

On the morning following admission (day 2) the patient was given DP 250 mg orally followed by 150 mg orally four times a day. That evening he complained of anxiety and dyspnea. ECG was unchanged from that of admission. By the next morning, however, his PR interval had lengthened to 0.20 sec, his BUN was 47, and his SGOT rose to 98 units (normal less than 35). The SGOT peaked at 4780 units on day 4. On day 5 the right upper abdomen was tender. Digoxin was held when his serum level was found to be 3.2 ng/ml (therapeutic 0.5 to 2.0). The PR interval on that day was 0.22 sec and his QRS had widened to 0.13 sec with a left bundle branch block pattern. DP was discontinued after ten doses, and his ectopy was treated with lidocaine. A ventilation/perfusion lung scan was interpreted as showing a low probability of pulmonary embolism. Serial creatine kinase measurements revealed 0 percent MB (cardiac) fraction. The ECG changes resolved by day 7.

The SGOT fell after discontinuation of DP (see Fig. 1). LDH peaked at 10,000 units (normal below 600) on day 4 and fell to normal by day 9. Bilirubin was mildly elevated with total 2.1 mg percent and direct 0.7 mg percent. Alkaline phosphatase remained normal, and titers for hepatitis B surface antigen, cytomegalovirus, toxoplasma, and antinuclear antibody were all negative. Nucleated red blood cells were seen for several days on the peripheral blood smear. By day 7 the liver was non-tender. On day 8 a percutaneous liver biopsy was performed. The specimen showed

![Patient #1](image)

**FIG. 1.** Rise in SGOT in patient 1 after administration of disopyramide phosphate. SGOT = Serum glutamic-oxaloacetic transaminase. DP = Disopyramide phosphate.
central hepatic necrosis with congestion. This picture was felt to be consistent with hepatic ischemia but not with drug toxicity.

On day 12 DP was restarted with one oral dose of 300 mg followed six hours later by 150 mg orally. That evening the patient again complained of anxiety and dyspnea. His arterial oxygen tension had not fallen. DP was discontinued, and dyspnea resolved. He was subsequently treated with procainamide, which he has tolerated well. Liver function tests remain normal.

Case 2

This 61-year-old man was admitted to the West Haven Veterans Administration Hospital with hypotension and chest pain following an oral dose of DP. His past history included colon carcinoma resected nine years earlier, with no evidence of recurrence; low-grade transitional cell bladder cancer for six years; coronary artery disease with two myocardial infarctions and a successful two-vessel coronary artery bypass graft for unstable angina; and a cerebral embolus following conversion from atrial fibrillation. After this episode he was in sinus rhythm with digoxin and quinidine. Congestive heart failure was treated with digoxin, furosemide, triamterene, and sorbitrate. Three months before admission the patient had been evaluated for hepatic fullness. Liver function tests were normal except for a bilirubin of 2 mg percent and a prothrombin time of 14 sec with a control of 12 sec. Radiocolloid scan of the liver and abdominal ultrasound examination both revealed hepatomegaly without filling defects. Because the liver size and discomfort decreased with diuresis this was felt to represent chronic passive hepatic congestion.

The patient had been seen earlier on the day of admission complaining of nausea and a rash. His blood pressure was 150/100, scant bibasilar rales were heard, a holosystolic murmur and an S3 were present, the liver span was 8 cm by percussion, and 1+ peripheral edema was present. These findings were consistent with previous examinations. A maculopapular rash was now evident on the trunk and arms. Electrocardiogram showed a sinus rhythm with a PR interval of 0.20 sec, QRS interval 0.10 sec with a left ventricular conduction delay unchanged from previous tracings. Chest radiograph showed his heart failure to be somewhat better than on previous films. Serum digoxin concentration was within therapeutic range. A quinidine level, drawn five hours after the previous dose, was 4.6 ng/ml (therapeutic 2–6). Since the nausea and rash were presumed to be caused by quinidine, he was given DP 300 mg orally with a prescription for further doses, and was instructed to stop his quinidine.

He returned four hours later complaining of substernal chest pain and dyspnea. He was diaphoretic, with a pulse of 70, blood pressure 100/70, respiratory rate 26 per minute, with rales halfway up both lung bases. The S3 and systolic murmur were still audible. His liver was non-tender and normal in span, he had 1+ edema, and his rash was improved. Chest X-ray showed pulmonary edema. The ECG now revealed no p waves and a new complete left bundle branch block, with QRS interval 0.20 sec. The rhythm was regular at a rate of 70 per minute. BUN has risen from 14 to 28 in four hours. Serum potassium was normal.

A transvenous pacemaker was inserted. During passage through the right atrium no atrial activity could be recorded. A Swan-Ganz catheter was placed in the pulmonary artery. Pulmonary artery pressure was 70/30 with a pulmonary capillary wedge pressure of 32. The patient was treated with diuretics, and dopamine and nitroprusside infusions. Within 24 hours his cardiac rhythm and QRS complexes had
returned to baseline, pulmonary artery diastolic pressure had fallen to 20, and systemic blood pressure was normal. An echocardiogram showed severe LV and LA dilatation. Ventilation/perfusion lung scan was consistent with a low probability for pulmonary embolism. Frequent creatine kinase determinations were all normal. SGOT peaked that evening at 620 units and subsequently fell (see Fig. 2). SGPT rose exactly in parallel, and LDH rose to 2½ times normal on the evening of admission. Alkaline phosphatase remained normal.

The patient did well for several days. Ectopy was treated with lidocaine. Rechallenge with a single dose of quinidine reproduced the rash. Because of multifocal ventricular ectopy and runs of ventricular tachycardia, the patient was restarted on DP 150 mg orally every six hours, on day 6. On day 7 he reported nausea and dyspnea, and on day 8 he was returned to the coronary care unit with angina. On the morning of day 9, two hours after his DP dose, he became hypotensive, with chest pain, left bundle branch block, and atrial standstill. DP was discontinued. A pacemaker and Swan-Ganz catheter were again inserted; elevated filling pressures were again found, and responded to diuresis. Within twelve hours the hemodynamic and ECG changes had all resolved. Myocardial infarction was ruled out. Again, LDH, SGOT, and SGPT rose strikingly, in concert, until day 12, and then fell. The highest measured SGOT was 1495 units on day 12, and LDH on that day peaked at seven times normal. Alkaline phosphatase rose to less than twice normal. Hepatitis antigen was negative. Liver enzymes returned to normal.

The patient is now doing well with his ventricular ectopy controlled on procainamide.

DISCUSSION

Left ventricular failure can result in ischemic hepatic injury with symptoms and chemical findings resembling acute hepatitis [5]. This can occur with or without the
clinical syndrome of chronic passive hepatic congestion due to right heart failure [5,6] and need not follow an identifiable hypotensive episode [5].

Disopyramide has been shown in dogs to have a more pronounced negative inotropic effect than quinidine, and to do so in lower doses. The effect with DP is dose-related [7]. In man, DP given intravenously significantly reduces cardiac output and stroke volume in patients whose filling pressures were already elevated [2]. The reduction in cardiac output is in the range of 18 percent with intravenous administration of 2 mg/kg in humans [3]. Clinical congestive heart failure occurs in a significant proportion of patients treated with DP [4]. One case of cardiogenic shock has been reported previously in a patient on chronic oral therapy with DP [8].

Patient 2, with chronic passive congestion, elevated his hepatocellular enzymes in the setting of cardiogenic shock which was not the result of acute myocardial infarction and which resolved on withholding DP. The duplication of this scenario on rechallenge with DP strongly implicates this drug as the cause. Patient 1 did not become hypotensive, though his rise in BUN was felt to represent hypoperfusion. His liver biopsy confirmed ischemic liver damage. Furthermore, the finding of nucleated RBCs in his peripheral blood is consistent with tissue hypoxia which can be seen in patients with the shock liver syndrome [9,10].

Both patients developed conduction disturbances. Patient 1 had first degree A-V block, which could have been related either to his elevated digoxin level or to DP, but this widened QRS interval could not be explained by digitalis excess. In the second patient, atrial standstill and widening of the QRS may have been due to DP or to hypotension with resultant myocardial ischemia. Conduction disturbances can reflect DP toxicity, especially in patients with underlying conduction disease [1].

In a recent study, 16 of 100 patients placed on DP developed congestive heart failure; 12 of these patients had a history of cardiac decompensation. Remarkably, among the 38 patients receiving chronic DP therapy, 12 of the 13 patients with any history of congestive failure suffered cardiac decompensation on DP [4]. Hepatic injury has not been recorded with the use of DP, other than isolated reports of intrahepatic cholestasis [11,12].

Both patients reported here, despite underlying cardiomyopathy, were able to tolerate quinidine, lidocaine, and procainamide without adverse hemodynamic consequences, but could not tolerate DP. In such patients, "loading doses" of DP should probably be avoided, and lower initial doses should be chosen. Maintenance requirements can be guided by serum levels. The presence of passive hepatic congestion may constitute a relative contraindication to the use of DP, and the drug should be used with caution in any patient with a history of congestive heart failure.

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