# BONE MARROW DEPRESSION ASSOCIATED WITH ACUTE COLCHICINE TOXICITY IN THE PRESENCE OF HEPATIC DYSFUNCTION

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**A case of carcinoma of the pancreas with obstructive jaundice and chronic tophaceous gout is presented. During an 11-day period 14 mg of colchicine were administered as a prophylactic measure. Gastro-intestinal and neurologic symptoms, hypoplasia of the bone marrow, prostration and death resulted. It is suggested that there may be delayed excretion and cumulative toxicity of the drug in patients with hepatic dysfunction.**

A FATAL CASE OF AGRANULOCYTOSIS AND thrombocytopenia with marrow hypoplasia following the prophylactic use of colchicine in recommended therapeutic doses is reported in this paper. It is suggested that the presence of obstructive jaundice may have altered the metabolism of the drug, thereby enhancing its toxicity.

Serious side effects are unusual following the administration of colchicine in the treatment and prophylaxis of acute gouty arthritis.[11] Rarely, severe gastro-intestinal and neurologic symptoms and even death have followed the use of therapeutic doses of the drug.[8, 10] Hematologic abnormalities are known to occur when toxic doses are administered.[1, 3-7, 9, 13] However, even small doses of colchicine may cause bone marrow depression.[1, 9]

## CASE REPORT

A 69-year-old Caucasian male was admitted to the hospital of the University of Pennsylvania for the first time in September 1964 because of the recent onset of painless jaundice, light stools, dark urine and a 15-pound weight loss. He had a 32-year history of chronic tophaceous gout with intermittent exacerbations, treated periodically with colchicine, Co-Benamid, Butazolidin† and prednisone. No colchicine had been administered in the previous 6 months. In 1940 a left nephrectomy had been performed for calculus disease.

The patient was a mildly dehydrated icteric male with evidence of recent weight loss. Oral temperature was 98°F; radial pulse was 96 per minute and regular; blood pressure was 124/74. Numerous large tophi were present in the extremities and helix of the ear. The hands and knees had a deforming arthritis. Examination of the chest and heart was unremarkable except for a sinus tachycardia. A blunt nontender liver edge was felt 4 cm below the right costal margin; the gall bladder was palpable. No other abnormalities were noted.

The hemoglobin was 11.0 Gm per 100 ml; white blood cell count was 7,100 per $mm^3$ (Polymorphonuclears—68%; eosinophils—5%; lymphocytes—15%; monocytes—12%). The blood urea nitrogen was 18 mg per 100 ml; fasting blood sugar was 161 mg per 100 ml; total bilirubin was 11.6 mg per 100 ml (6.8 direct); alkaline phosphatase was 23 Shinowara units; serum amylase was normal; SGOT was 144 units; cephalin flocculation was zero. Uric acid was 6.8 mg per 100 ml; the serological test for syphilis was nonreactive. A prothrombin time was 56% rising to 92% after intramuscular Aquamephyton.* The urine was positive for bile but otherwise normal. Chest roentgenogram and the electrocardiogram were unremarkable. Upper gastro-

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The author is indebted to Dr. George Evans of the Department of Pathology, who performed the bone marrow examination, and to Dr. Robert G. Ravdin on whose service the patient was admitted.

Received for publication July 14, 1965.

† Phenylbutazone, Geigy Pharmaceuticals, Yonkers, N.Y.

* Phytonadione, Merck Sharp and Dohme, West Point, Pa.

intestinal series, barium enema and sigmoidoscopic examination were normal.

During the 5 days prior to operation the patient received 1,000 cc of whole blood, one mg colchicine orally daily and small doses of regular insulin. At operation a large fixed mass in the head of the pancreas was found to obstruct the common bile duct; the gall bladder was tense and distended and contained multiple calculi. The liver was free of metastases. An uneventful cholecystojejunostomy was performed.

Postoperatively the patient received intravenous colchicine, 0.5 mg, 3 times daily for 3 days; thereafter the same dose was given orally. No antibiotics were administered. His initial progress was satisfactory with decreasing jaundice. On the sixth postoperative day, after a total dose of 14 mg of colchicine, he developed nausea, vomiting and increasing glycosuria. Colchicine therapy was stopped. Eighteen hours later his rectal temperature rose to 103 degrees and there were signs of a right lower lobe pneumonia. At this time his hemoglobin was 13 gm per 100 ml.; white blood cell count was 500 per $mm^3$ and platelet count was 18,000 per $mm.^3$ Treatment was begun with intravenous fluids and transfusions of fresh whole blood, antibiotics, gamma globulin and steroids. However, his condition progressively deteriorated with the development of recurrent vomiting and diarrhea, agitation followed by deepening coma, generalized twitching, advancing pneumonia and profound prostration. His serum sodium was 133 mEq per liter, serum magnesium 1.7 mEq per liter, serum calcium 8.0 mg per 100 ml. His blood ammonia was normal and the blood urea nitrogen had risen to 68 mg per 100 ml with a creatinine of 2.4 mg per 100 ml. The arterial pH was 7.53. All blood cultures were negative; urine cultures grew out coliform organisms in significant number. The acid-base imbalance was corrected and calcium and magnesium were administered. The twitching gradually subsided; there were no seizures.

The patient's white blood cell count gradually returned to 5,000 per $mm^3$ over a 4-day period, but the platelet count remained below 20,000 per $mm^3$. Prostration increased; his blood pressure became difficult to maintain and he expired on the twelfth postoperative day. Examination of a bone marrow specimen obtained shortly before death showed a hypocellular marrow with a marked decrease in number of megakaryocytes, platelets and of both granulopoietic and erythropoietic elements. The M/E ratio was high at approximately 14:1. There was a pronounced left shift in the granulopoietic series. Lymphocytes, plasma cells and reticuloendothelial cells showed a relative increase. No abnormal cells were present and cells in mitotic arrest were not demonstrated. Postmortem examination was denied.

## DISCUSSION

Many papers have stressed the efficacy and safety of colchicine in the treatment and prophylaxis of acute gouty arthritis. In one large series[11] a daily prophylactic dose of 0.5 to 2.0 mg was administered from 2 to 10 years without serious consequences. However, severe complications and deaths have occurred following the use of colchicine in ordinary therapeutic doses. Macleod and Phillips report a patient who died after receiving only 7 mg over a 4-day period. "The main symptoms are nausea, vomiting, abdominal colic, diarrhea, oliguria, shock, confusion, coma and death."[8] No mention was made of bone marrow suppression or alterations in the peripheral blood.

In other reports of acute colchicine toxicity there has been a similar clinical picture. However, in these cases hematologic abnormalities were a prominent feature. Seed et al. described a patient who died after receiving 12 mg in 4 days as cancer chemotherapy.[1, 9] Gastrointestinal and neurologic symptoms with hypoplasia of the bone marrow followed. Similar circumstances have occurred incident to the use of known toxic doses of colchicine suicidally or as cancer therapy.[5, 7, 9, 13]

The present case appears to represent an example of colchicine toxicity with bone marrow depression. The patient had received colchicine in the past although the amount is unknown. Its toxicity at this time may have been related to the concomitant hepatic dysfunction or an individual idiosyncrasy to the drug.

Relatively little is known about colchicine metabolism. The available data indicates that the orally administered drug is absorbed in the gastro-intestinal tract and subsequently is excreted by the liver via the bile into the small intestine. To a lesser extent it also is eliminated by the kidneys, and is excreted directly into the small intestine.[2, 5, 12] In the presence of obstructive jaundice and impaired hepatic

function the possibility of delayed excretion and cumulative toxicity of the drug exists. Under these circumstances doses in the therapeutic range might be responsible for acute intoxication.

Considering the extensive use of colchicine and the rarity of serious toxicity the drug may be considered safe when used in therapeutic dosage. In some sensitive patients and when ordinary doses are exceeded there is danger of colchicine intoxication and bone marrow depression. It is suggested that the drug be used with caution and accompanied by frequent blood studies in the presence of hepatic dysfunction until additional clinical and experimental information is available.

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