

JAUNDICE AND THE SULFONAMIDE DRUGS

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IT IS NOW well established that jaundice is one of the toxic manifestations of sulfonamide chemotherapy. Although it is usually possible to recognize this complication, sulfonamide-induced jaundice may be difficult to differentiate from toxic hepatitis occurring as a complication of the infectious process itself as well as from sporadic instances of infectious hepatitis and serum jaundice. Since the sulfonamide drugs are widely used in medical practice, it is perhaps of some interest to review the distinguishing characteristics of toxic hepatitis caused by these compounds. The establishment of a definite diagnosis in jaundiced patients is important because all sulfonamides should be discontinued immediately if this form of chemotherapy appears to be responsible for the toxic complication. In individuals with jaundice due to other causes, sulfonamide medication, especially sulfadiazine, may be given without causing further damage to the liver parenchyma.¹

In general, three forms of jaundice may accompany the use of the sulfonamide drugs. They may be classified as immediate, intermediate and delayed, depending upon the time of appearance of toxic symptoms, including icterus, following the initiation of therapy.

IMMEDIATE JAUNDICE

The immediate form of toxic hepatitis secondary to sulfonamide medication is usually readily recognized. Within a period of one to three days from the time chemotherapy is started, jaundice appears. Prior to this, however, and usually within a few hours after the initial dose of sulfonamide, other toxic symptoms appear. These include nausea, vomiting, headache, chills, fever, burning of the eyes, and skin rashes. As the drug is continued the skin may become icteric and the urine dark with bile. Examination usually reveals an enlarged tender liver as well as various forms of skin rashes. The erythrocyte count and hemoglobin concentration are usually normal and the reticulocyte count is not elevated. The leukocyte count may be elevated or normal.

These patients give a history of previous ingestion of one of the sulfonamide drugs, and usually state that toxic symptoms occurred at that time.² An example of this form of hepatitis is reported below.

CASE REPORT

A 45 year old married woman entered the Evans Memorial, Massachusetts Memorial Hospitals, on September 14, 1940, because of chills, fever, and nausea of three days' duration.* About eight months prior to admission she noticed that her afternoon oral temperature occasionally reached as high as 99.6 F.

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* I am indebted to Dr. Chester S. Keefer for permission to report this case.

and, because of accompanying weakness, she reported to her physician. A diagnosis of endocervicitis was made and she was advised to enter the hospital for study. On July 28, 1940, she was admitted to another hospital where a blood culture revealed *Staphylococcus albus*. She was given sulfathiazole, 1 gram every 4 hours, beginning on August 10, 1940. The hospital record shows that the blood cultures became sterile and she was discharged on August 17. She continued to take sulfathiazole and, on August 24, two weeks after the institution of chemotherapy, she complained of photophobia, lacrimation, and soreness and redness in several old scars around the left shoulder. Later a rash developed around the eyes and over the legs. Because of these findings the drug was discontinued by her physician with subsequent disappearance of all symptoms.

Because she continued to exhibit a low fever of about 99.2 F., on September 11, 1940, her physician again started sulfathiazole therapy. At 10 a.m., and 2 p.m. she took 1 gram. At 4 p.m. she developed a chill with a subsequent rise in temperature to 103 F. No further sulfathiazole was ingested until the following day when the dosage was increased to 1.5 grams. Again she took the drug at 10 a.m. and 2 p.m., but after the latter dose she developed a rigor, the temperature rising to 104 F. The next day she complained of a severe headache, aching in the joints, nausea, and vomiting, and noticed that her urine had become quite dark in color. She was hospitalized because it was thought she had developed hematuria.

The patient gave a history of tonsillitis in 1936 for which she had received sulfanilamide without the development of toxic symptoms.

On admission to the hospital the oral temperature was 100 F. There was a definite icteric tint to the skin and sclerae. There were no petechiae and no rash. The vessels of the conjunctivae and sclerae were injected. The nasal and pharyngeal mucous membranes appeared normal. The lungs were clear to percussion and auscultation. The heart was normal in size; no murmurs were heard. The liver edge was tender and extended 2 centimeters below the costal margin. The spleen was not felt.

Laboratory examinations included a total erythrocyte count of 4,000,000 per cubic millimeter, a hemoglobin of 71 per cent, and 4,200 leukocytes per cubic millimeter. The differential count on the blood smear showed 68 per cent neutrophils, 21 per cent lymphocytes, 2 per cent monocytes and 9 per cent eosinophils. There was bile in the urine as well as a trace of albumin.

Clinical course. The patient improved rapidly during the period of hospitalization. The icterus index which was 25 on September 16, 1940, had fallen to 4 on September 24. Bile was not detected in the urine after the third day in the hospital and the urobilinogen, which was present in a 1:20 dilution, decreased so that it was found only in undiluted urine. The reticulocyte count was 0.6 per cent on September 18 and the erythrocyte count and hemoglobin concentration did not change significantly. The Takata-Ara test was positive and there was a slight depression in the hippuric acid excretion test.

Because it was felt that this patient's illness was caused by sulfathiazole, she was given 0.5 gram on September 24, 1940. One hour later she developed a rigor, the vessels of the conjunctivae and sclerae became congested, she vomited twice, and complained of headache and soreness in the scars on the left shoulder. Four hours after the ingestion of the test dose of sulfathiazole the temperature reached 105 F. She was then given an intravenous infusion of 2000 milliliters of saline and the temperature rapidly returned to normal. No bile was detected in any of the urine specimens, but the icteric index gradually increased to 10 during the subsequent 24 hours. Urobilinogen was found again in dilutions of 1:20.

To summarize this case, the patient received an initial course of sulfathiazole and developed toxic symptoms two weeks later. These symptoms included nausea, vomiting, episcleritis, chills, fever, and skin rash. The drug was discontinued for approximately seventeen days and upon its resumption immediate toxic effects were exhibited. From the history it appears that jaundice developed two days after the first dose of the second course of sulfathiazole. When she had recovered, a test dose of 0.5 gram of sulfathiazole was administered. Again she developed fever, nausea, vomiting, and episcleritis. The icterus index rose from 4 to 10 and remained elevated for forty eight hours. This patient's illness is an example of immediate jaundice due to previous sensitization to the sulfonamide drugs. There was little

evidence of hemolytic anemia although, from the studies recorded, it is not possible to state that some increase in the rate of destruction of the erythrocytes did not occur.

INTERMEDIATE JAUNDICE

This form of jaundice is associated with a mortality rate of 5 to 10 per cent³ and is readily diagnosed as sulfonamide-induced since it is secondary to acute hemolytic anemia as well as to toxic hepatitis. The anemia usually becomes prominent enough to cause pallor, weakness, dyspnea, and nausea and vomiting in about two to five days after the institution of therapy,⁴ although occasionally it may occur later.^{5, 6} Soon after the development of the acute hemolytic anemia, jaundice may appear. This is believed to be due not only to the very great destruction of erythrocytes, but also to some direct action on the liver cells.⁷

The clinical features of this form of jaundice are readily recognized. The patient invariably becomes critically ill during a period of a few hours; pallor is marked; the liver and spleen may be enlarged, and fever is usually present. Hemoglobin may appear in the urine. Later biliuria and urobilinogenuria are observed. The erythrocyte count and hemoglobin concentration are low, and a smear of the blood may show nucleated erythrocytes as well as variations in the size and shape of the cells. The reticulocyte count becomes markedly elevated. There may be spherocytosis and an increased hypotonic fragility during the acute phase of the disease.³

The total leukocyte count is usually markedly elevated, counts of 100,000 per cubic millimeter not being unusual. Immature cells are observed, as well as an increased number of eosinophils. The blood usually contains free hemoglobin as well as increased amounts of bilirubin.

It is apparent from this description that this form of sulfonamide jaundice should be easily recognized. It occurs most frequently following sulfanilamide medication although sulfathiazole, sulfapyridine and sulfadiazine occasionally cause acute hemolytic anemia and jaundice. When such toxic reactions occur, the drug must be stopped immediately and treatment, including blood transfusion, instituted.

DELAYED JAUNDICE

Jaundice may appear ten or more days after the institution of sulfonamide treatment. Under these circumstances, the diagnosis of sulfonamide hepatitis may be difficult since jaundice may develop during the same period as a complication of the infectious process itself. Generally, however, in those patients whose jaundice is secondary to chemotherapy there are other associated toxic symptoms and physical signs.⁸

It is the usual experience that this form of hepatitis develops at about the time clinical improvement is anticipated. The temperature, which may have been normal or somewhat elevated, suddenly increases. In some instances it may be septic in type and associated with severe chills. Nausea, vomiting and epigastric discomfort may be prominent. Other symptoms of toxicity include headache, dizziness, photophobia, and aching of the joints. A distinctive feature which is of considerable aid in the establishment of the correct diagnosis is the appearance of

a rash which may be erythematous or, at times, exfoliative in character. Erythema nodosum is not infrequently observed in patients treated with the thiazole derivatives of the sulfonamides. Jaundice develops within a few hours or days after these other toxic symptoms have become manifest.

The physical signs and abnormalities in the laboratory examinations are similar to those found in patients developing the immediate form of jaundice. The liver and spleen may be enlarged and occasionally ascites may develop.² There may be a moderate anemia, especially if the reaction occurs after the ingestion of sulfanilamide. Usually there is an increase in the total leukocyte count, which may be marked when there is an extensive rash, and occasionally there may be leukopenia. The bilirubin content of the blood is increased and urobilinogen and bile are found in the urine. Impairment of liver function may be demonstrated by several tests.

Although most patients receiving sulfonamide therapy and developing the delayed form of jaundice conform to the above description, there are a few in whom the diagnosis is difficult. Toxic hepatitis apparently may develop several weeks after the cessation of chemotherapy. Garvin² reports an instance where jaundice and exfoliative dermatitis developed forty-three days after all sulfonamide medication had been stopped. In some patients jaundice appears as the only toxic manifestation of chemotherapy. One patient² developed jaundice sixteen days after sulfanilamide therapy was instituted and no other symptoms were recorded. In this instance the patient was being treated for chronic prostatitis, so that it would appear improbable that the hepatitis was secondary to the infectious process.

DISCUSSION AND SUMMARY

It is apparent from a review of the reported cases of hepatitis associated with sulfonamide therapy that it is usually possible to recognize this toxic manifestation. This is of considerable practical importance since, in every instance in which the sulfonamide is responsible for the jaundice, treatment with the drug should be discontinued and some other form of therapy, such as the antibiotics, instituted. If the jaundice is not secondary to the sulfonamide, therapy may be continued even in the presence of hepatitis secondary to the infection.¹

Jaundice which appears during the first week of chemotherapy is usually associated with a previous history of ingestion of sulfonamides and accompanying signs of toxicity (immediate sulfonamide jaundice) or with acute hemolytic anemia and jaundice (intermediate jaundice). In either instance the diagnosis is not difficult because the clinical and laboratory abnormalities are characteristic. Finally, jaundice which occurs after ten days of chemotherapy is usually associated with other toxic manifestations, especially fever and various forms of rashes (delayed jaundice). Occasionally jaundice may be the only toxic manifestation of sulfonamide therapy and, in such patients, a definite diagnosis may be difficult.

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