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HEPATOSENSITIZATION CAUSED BY PROPIONYL ERYTHROMYCIN LAURYL SULFATE*

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ERYTHROMYCIN, isolated in 1952 by McGuire et al., has had wide clinical use. Untoward reactions have been quite uncommon. It has, in fact, been claimed that erythromycin is the safest antibiotic used today. Likewise, the various salts and esters of erythromycin have not appeared to produce reactions of different types or degrees than erythromycin base. These include the lactobionate, ethyl carbonate, ethyl succinate, glucoheptonate, stearate, etc.

In 1958, erythromycin propionate was introduced. This compound was shown to produce significantly higher and more prolonged serum levels of antibacterial activity when given in the fasting state than erythromycin base or other salts of erythromycin. The bitter taste of erythromycin propionate lead to the development of propionyl erythromycin lauryl sulfate, a tasteless ester. In addition, because of the greater acid stability of this ester, the same high and prolonged blood levels occurred even when it was given after meals. Kuder in a study of over 20,000 cases, indicated that these two compounds had no more side effects than erythromycin base. Recently, however, a number of case reports have appeared describing intrahepatic cholestasis due to propionyl erythromycin lauryl sulfate. In these reports, the hepatic injury was thought to be of an allergic nature and similar to other recognized and documented reactions occurring with chlorpromazine, norethandronolone, arsphenamine, carbasone methyltestosterone, PAS, chlorthiazide, sulfadiazine, thiouracil, chlorpropamide, etc.

Five cases of hepatosensitization caused by propionyl erythromycin lauryl sulfate observed at this hospital in the past year are the subject of this report.

CASE 1 (F.R.) — A 63 year old white male was admitted to the hospital on November 3, 1961, for treatment of retinal detachment of the left eye. He was also found to have mild diabetes and hypertension.

Eye surgery was performed on November 5th and the patient was placed on propionyl erythromycin lauryl sulfate.* 250 mg. four times daily and a trisulfa preparation,** 500 mg. four times a day. On November 15th (11 days later), he developed shaking chills and the temperature rose to 103°F. Physical examination was unrevealing. A drug reaction was

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*Ilosone, Eli Lilly and Co., Indianapolis, Indiana.
**Terfonyl (Squibb & Sons).
suspected and on November 16th (12th day of therapy), both erythromycin and sulfonamides were discontinued. On November 18th, the patient was afebrile but dark urine was noted. The sclerae were slightly icteric and the liver was palpable 2 centimeters below the costal margin. Serum bilirubin was 4.2 mg. per cent total and 1.6 mg. per cent direct.

During the next few days the serum bilirubin rose to 9.93 mg. per cent total and 5.76 mg. per cent direct. The alkaline phosphatase reached 8.1 Bodansky Units (normal 1.5—4 BU) and the serum glutamic oxalacetic transaminase (SGOT) 100 units. Note was made of an eosinophilia of 16 per cent with a normal white blood count.

He left the hospital against medical advice on October 25th. At that time the total serum bilirubin was 4.2 mg. per cent total, 1.9 mg. per cent direct. The SGOT was 108 units and the alkaline phosphatase 8.9 Bodansky Units.

CASE 2 (M.K.) — A 67 year old white female, was admitted on August 12, 1961, with acute cellulitis and possible thrombophlebitis of the left leg. She was placed on propionyl erythromycin lauryl sulfate 250 mg. four times daily and anticoagulants.**

Fever promptly subsided and the patient remained afebrile until August 23rd (12th day of therapy), when she suddenly developed chills, fever (100.2°F) and right lower anterior chest pain suggestive of pulmonary infarction. Chest x-ray and electrocardiogram were negative for findings of pulmonary embolism. The serum glutamic oxalacetic transaminase (SGOT) was 49 units and the lactic dehydrogenase (LDH) 800 units. Erythromycin was discontinued the following day and the patient progressively became asymptomatic over the next 72 hours.

On August 28th, (17th day), the SGOT was 324 units, LDH 880 units, total bilirubin 0.32 mg. percent, cephalin flocculation 2 plus, thymol turbidity 6 units, thymol flocculation 1 plus, and alkaline phosphatase 5.3 Bodansky Units. On September 5th, (35th day), the SGOT was 60 units and the alkaline phosphatase 3.8 Bodansky Units.

CASE 3: (R.P.) — A 51 year old white female was admitted on October 27, 1961, for treatment of a felon of two weeks duration.

On October 15th, she received two doses of 250 mg. of propionyl erythromycin lauryl sulfate. The next day, this was changed to oral penicillin G 250 mg. every 8 hours for four days. She then received chloramphenicol 250 mg. every 6 hours for three days from October 20th through October 22nd. As a result of bacterial culture and sensitivity test she was restarted on erythromycin 250 mg. four times daily on October 23rd and this therapy was continued after admission to the hospital on October 27th. Surgical incision drainage of the felon was carried out on October 27th.

On November 3rd (twelfth day of continuous erythromycin therapy) she suddenly developed acute epigastric and retrosternal pain aggravated by deep breathing and accompanied by chilly sensations, anorexia and a rise in temperature to 100.6°F. The electrocardiogram, chest x-ray, white blood count and serum amylase were normal. The following morning, because of progression in symptomatology, she was considered to have pulmonary infarction and started on anticoagulants.**

On November 5th, (fourteenth day of erythromycin therapy), the physical examination revealed a slightly enlarged and tender liver. The serum bilirubin was 1.75 mg. per cent total and 0.8 mg. per cent direct, the cephalin flocculation negative and alkaline phosphatase 8.6 Bodansky Units. Erythromycin and anticoagulants were discontinued on that date.

Forty-eight hours later, the patient became afebrile and the symptoms of anorexia and liver tenderness progressively subsided over the next six days. On November 13th, 18 days after stopping erythromycin, the SGOT was 42 units and the total bilirubin 0.96 mg. per cent.

CASE 4: (G.A.) — A 37 year old white male was admitted on August 25, 1960 for treatment of furunculosis of four months duration and ulcerative cellulitis over the left tibial area.

He was known to be allergic to penicillin and sulfonamides. Chloromycetin had been given by his physician without any improvement. Propionyl erythromycin lauryl sulfate 500 mg. every six hours was started on August 27th.

The low grade fever present on admission disappeared within a few days. A split thickness graft was placed over the ulcer crater on the left tibia on September 8th. On
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September 12th (16th day of erythromycin therapy), the patient developed chilly sensations, sweating and diarrhea. The temperature rose to 104°F. Erythromycin was discontinued on that date. The temperature returned to normal in three days and the epigastric distress along with flatulence and anorexia also disappeared progressively. He was discharged asymptomatic on September 17th.

The patient was seen for a single follow-up in the Outpatient Department on September 24th complaining about a pustular eruption in the groin area. On examination, he was found to be jaundiced. He admitted pale stools and dark urine of recent onset. The serum bilirubin was 4.1 per cent total and 1.19 mg. per cent direct. The urine contained bile. He refused admission and was lost to follow-up.

It was subsequently learned that he was admitted to another hospital and treated symptomatically with good responses. In November, 1961, he took propionyl erythromycin lauryl sulfate and within two days became jaundiced. On that occasion he was admitted to another hospital where a liver biopsy revealed cholestatic hepatitis.*

CASE 5: (C.M.) — A 72 year old white female was admitted May 23, 1962, for bilateral cataract extraction. This was carried out on May 24th (O.D.) and May 30th (O.S.). On May 24th, she was placed on a trisulfa preparation,* 500 mg. four times daily and erythromycin lauryl sulfate 250 mg. four times daily. On May 30th, the sulfonamide was discontinued and on May 31st, demethylchlortetracycline** 150 mg. four times daily was started.

On June 2nd, she complained of abdominal distress which continued the next four days. On June 6th (14th day of treatment she suddenly developed chills, sweating and malaise, the temperature rose to 101.8°F.

Physical examination on that date revealed the liver to be slightly enlarged and tender. No jaundice was observed. A drug reaction was suspected and all drugs were discontinued (erythromycin, demethylchlortetracycline, prochlorperazine, and meprobamate). On June 8th, she was afebrile. A bromsulphalein test (BSP) showed retention of 24 per cent. The alkaline phosphatase was 4.5 Bodansky Units. The serum glutamic oxalacetic transaminase (SGOT) 216 units. The diagnosis of "erythromycin hepatitis" was entertained. On June 12th, the serum bilirubin was 0.64 mg. per cent total and 0.32 mg. per cent direct. Alkaline phosphatase was 3.1 Bodansky Units and the (SGOT) 18 units. The cephalin-cholesterol flocculation was 3 plus, thymol turbidity 3 units and thymol flocculation negative. The BSP test was repeated on June 15th and was normal, (4 per cent).

DISCUSSION

Drug induced hepatic injury has been reported extensively in the literature. However, even when complete liver studies are available, including biopsy, it is not always possible to rule out definitely other underlying causes such as a concomitant hepatitis (infectious or serum type) or tumor. Drugs generally incriminated may produce hepatocellular damage resembling viral hepatitis (iproniazide, cincomphen, sulfamethoxypyridazine) or intrahepatic cholestasis which resembles extrahepatic obstruction (chlorpromazine, norethandrolone, methyl testosterone, para-aminosalicyclic acid, chlorthiazide, sulfadiazine, thiouracil, chlorpropamide).

The pathogenesis of the drug toxicity has not been explained in each instance. Animal experimentations have not always been conclusive. Probably the most extensively studied cases of cholestasis jaundice are those due to chlorpromazine. Histologically, in these instances, the features are those of bile stasis predominantly in the center of lobule zone, mononuclear infiltration of the edematous portal tract with varying

*Personal communication, Lloyd L. Paul, M.D., case to be published.
*Terfonyl, Squibb & Sons.
**Declomycin, Lederle Laboratories.
++Compazine, Smith, Kline and French Laboratories.
+++Equanil, Wyeth Laboratories, Inc.

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admixture of eosinophils and focal necrosis of liver cells with replacement by mononuclear cells.\textsuperscript{13}

It is interesting to note that cases of liver toxicity secondary to erythromycin propionate lauryl sulfate have been reported only recently after the drug has been used for several years. Have many cases gone by unnoticed? This seems improbable.\textsuperscript{4,11,14,15}

The clinical picture of hepatic involvement due to propionyl erythromycin lauryl sulfate is variable and may simulate gallbladder disease or pancreatitis.\textsuperscript{8} In our cases the diagnosis of pulmonary embolus, myocardial infarction, and infectious hepatitis were entertained. Usually, the symptoms appear after a period of 11 to 16 days, as in the cases reported here, and quickly disappear when the drug is stopped. However, recurrence may be noted if the patient is again challenged with the drug as in Case 4 and as reported by others.\textsuperscript{11,15}

Laboratory tests in reported cases and as noted in our patients have shown an elevation of transaminase and bilirubin with little or no change in flocculation tests. Occasionally, as exemplified by Case 4, eosinophilia is noted.\textsuperscript{15} The alkaline phosphatase was slightly to moderately elevated in our cases but has been found to be normal by other authors.\textsuperscript{15}

The mechanism of erythromycin hepatic involvement is thought to be a hypersensitivity reaction.\textsuperscript{11} The offending agent could be the lauryl sulfate ion but this assumption is somewhat speculative since this compound has been used for many years as a wetting agent in toothpastes, shampoos and household detergents\textsuperscript{11} without reported toxicity. The final answer awaits careful studies of challenges with the other forms of the drug and all the constituents of propionyl erythromycin lauryl sulfate.

**SUMMARY**

Five cases of hepatosensitization apparently due to propionyl erythromycin lauryl sulfate have been observed at the Henry Ford Hospital. One patient had a recurrence one year later on again receiving this antibiotic.

Pulmonary infarction, myocardial infarction and hepatitis were suspected in these cases before the correct diagnosis was made.

Other medications could not be excluded completely as the cause of the hepatic injury in all cases. The similarity of the clinical and laboratory findings to those reported by others and the clearing of the process on discontinuing the erythromycin strongly supports hepatosensitization to propionyl erythromycin lauryl sulfate as the cause of the observed hepatic dysfunction.

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