Clinical Research

Clinical Research *fuses indistinguishably into quality improvement. It is increasingly necessary because new medications and techniques are pouring down on us, with their potential for great harm as well as good. Dr Gilbert believed that every reflective health worker would constantly undertake research/quality control if she or he were not overwhelmed by a crowded practice, and that part of the difficulty lies in being too busy to consider how it could be improved. Discovery, he believed, consists of seeing what everybody sees and thinking what nobody has thought. But it takes time to contemplate, and reinvent.*

***Single case studies**, such as this 1962 analysis of Ilosone as a cause of hepatitis, remain an important type of research that can be carried out by any thoughtful physician as part of the routine practice of medicine. Dr Gilbert's report almost single-handedly stopped the indiscriminate use of a new antibiotic.*

Cholestatic Hepatitis Caused by Esters of Erythromycin and Oleandomycin

Fred I. Gilbert, Jr, MD

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Erythromycin is derived from a strain of Streptomyces and belongs to the macrolide family of antibiotics which include triacetyloleandomycin. Erythromycin was introduced in 1952.[1] Erythromycin propionate was introduced in September, 1958. Its lauryl sulfate salt has been named erythromycin estolate. The manufacturer estimates that some 15 million courses of therapy with this drug have been given since its introduction, with only 33 cases of jaundice having been reported as directly or indirectly attributable to the drug.[2]

Kuder, in reviewing 20,525 cases, noted that erythromycin propionate caused some type of gastrointestinal symptomatology in 5.7% of patients, whereas the lauryl sulfate salt of this drug (erythromycin estolate) caused only 2% to have gastrointestinal symptoms constituted the major side effects, with nausea leading the list. No jaundice or hepatitis was reported in this series. He also observed that of 69 patients less than one month of age receiving the antibiotic, there were no side effects except for loose stools in 2. Reichelderfer and associates[4] also observed that giving large amounts of erythromycin estolate to premature and newborn infants resulted in no significant side effects after several days of treatment.

More recently, Kohlstaedt[2] has received reports from physicians noting hepatitis in 13 patients treated with erythromycin estolate. In the more carefully studied patients, it appeared to be hypersensitivity rather than a toxic reaction. The initial symptoms of hepatitis appeared between the 10th and 21st day of continuous therapy or after repeated courses of the drug.

Robinson[5] also noted similar hypersensitivity with hepatitis in approximately 12% of the patients who received triacetyloleandomycin or erythromycin estolate for longer than 14 days. This reaction mimics viral hepatitis, cholecystitis, or pancreatitis, with midepigastric pain, vomiting, transaminase elevation, increased direct-reacting bilirubin, and a negative or weakly positive turbidity test. In some instances, serum alkaline phosphatase was elevated. Liver biopsy in one patient showed periportal infiltration with lymphocytes, a few polymorphonuclear leukocytes, and many eosinophils. Peripheral eosinophilia has been noted. It is of interest that hepatitis with jaundice had been previously reported in 3 of 82 patients receiving triacetyloleandomycin.[6]

Report of a Case

A 46-year-old physician was seen on September 13, 1961, after having taken 750 mg of erythromycin estolate during the previous 12 hours. When examined at about midnight, she was acutely ill, with severe epigastric pain radiating through to the back and both shoulders. She believed she was experiencing a myocardial infarction, while I considered biliary colic or pancreatitis as the cause of the upper abdominal pain, vomiting, and right upper quadrant tenderness. Subsequent events proved us both wrong: her serum amylase, gallbladder visualization, and electrocardiogram were all normal. The packed cell volume (PCV) was 43 ml%; hemoglobin 13.5 gm; white blood cell count 6,600 with 76% polymorphonuclear leukocytes, 18% lymphocytes, 2% eosinophils, 3% monocytes, and 1% stab cells. Urinalysis was normal.The serum glutamic oxalacetic transaminase (SGOT) was moderately elevated to 350 units (normal 40 to 80 units), but the thymol turbidity was normal at 2.5 units. For the first 4 days of hospitalization, the patient was miserable with persistent upper abdominal pain, vomiting, and anorexia. The afebrile course was interrupted on the third day of the illness by a fever of 102°F (39° C). This fever subsided within 24 hours, and she was discharged 9 days after admission, free of symptoms except for mild epigastric distress after meals and residual tenderness in the right upper quadrant on deep inspiration.

Further history disclosed that hives had developed after the patient had received penicillin several years before, but that she had taken erythromycin sterate for 4 days in May, 1961, without incident. Three erythromycin estolate capsules had been taken on September 13, because of a tooth extraction that day. There was no other history of drug sensitivity, asthma, hay fever, or other know allergy (Fig 1).

On October 31, 1961, she came into the office desperately ill, with fever of 104°F (40° C), chills, nausea, vomiting, and abdominal pain so severe that she could not tolerate abdominal palpatation until after injection of 100 mg of meperidine hydrochloride. This time she had taken one 25-mg capsule of erythromycin estolate after further dental work and had noted abdominal pain at 3 hours, chills and fever at 8 hours, and vomiting at

10 hours after the single dose. She was extremely sick and noted a peculiar disturbance of color vision, with red, yellow, and green vertical bars, on closing her eyes. There was also an unusual sensation of tumbling vertigo, and for several days there was
persistent yellow tinting of the central visual field. She had continuous headache, upper abdominal pain, and repeated attacks of vomiting for the past 3 days. During this period, intravenous fluids were required. Thirty-six hours after the onset, she became afebrile and remained so until discharge on November 4, 1961 (Fig 1).

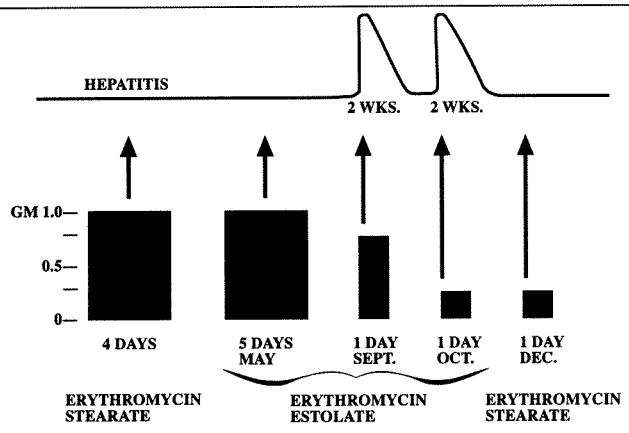

Fig 1.—Patient's response to administration of erythromycin estolate.

Laboratory studies performed during this second episode showed increased serum bilirubin, with total bilirubin of 2.4 mg%, 1.1 mg% direct-reacting. The SGOT was elevated to 91 units. There was a slight increase in the serum alkaline phosphatase to 4.7 Bodansky units. Blood studies revealed a drop in the hemoglobin, PCV, and (except for eosinophils) granulocyte, as compared to the values obtained 2 weeks previously (PCV 35 ml%,; hemoglobin 11.9 gm; white blood cell count 4,700 with 52% polymorphonuclear leukocytes, 33% lymphocytes, 6% eosinophils, and 9% monocytes). A radio-rose bengal test done 4 days after onset of acute symptoms indicated moderate liver dysfunction without biliary tract obstruction. The radio dye flowed into the intestine readily. Urinalysis, including qualitative tests for bile and urobilinogen, was normal. The thymol turbidity was 2 units.

By November 7, 1961, one week after taking the capsule, the patient was asymptomatic except for acute iritis of the left eye and epigastric distress after meals. On November 18, she had no symptoms. Scratch tests with erythromycin as the base, stearate, estolate, and controls were negative at 1, 24, and 72 hours. The SGOT, serum bilirubin, and blood cell count were normal. The PCV was 38 mil% white blood cell count 5,600, with 56% polymorphonuclear leukocytes, 37% lymphocytes, and 7% eosinophils, and the radio-rose bengal test continued to indicate very slight liver dysfunction with 56% retention in 20 min.

On December 5, 1961, after having taken a small test dose of less than one-quarter of a 250-mg tablet of erythromycin sterate the night before, the patient took the remaining portion of the tablet. No unusual signs or symptoms developed and 24 hours later, all laboratory studies, including SGOT, and radio-rose bengal, were within normal limits.

Comment

This 46-year-old physician tolerated a 4-day course of erythromycin sterate in 1957 and a 5-day course of erythromycin estolate in May, 1961. Neither of these courses of treatment caused symptoms, but the latter almost certainly sensitized her, so that a challenge dose of the same preparation administered on 2 subsequent occasions cause symptoms and signs of hepatitis within 12 hours of erythromycin ingestion. Her second challenge of only 250 mg of erythromycin estolate caused a much more severe illness than the first challenge of 750 mg. A final challenge of 250 mg of erythromycin sterate resulted in no clinical or laboratory evidence of hepatitis.

This case is similar in most respects to the one recently reported by Johnson and Hall.[7] In their patient, cholestatic hepatitis developed after 12 days of erythromycin estolate. Three challenges with the estolate reactivated signs and symptoms of hepatitis. A final challenge with erythromycin base failed to produce hepatitis. They concluded that drug allergy was the cause of the hepatitis.

Although clinical jaundice develops in less than 5% of patients receiving macrolide ester antibiotics, routine sulfobromophatalein (BSP) and SGOT determinations carried out on patients receiving triacetyloleandomycin for longer than 10

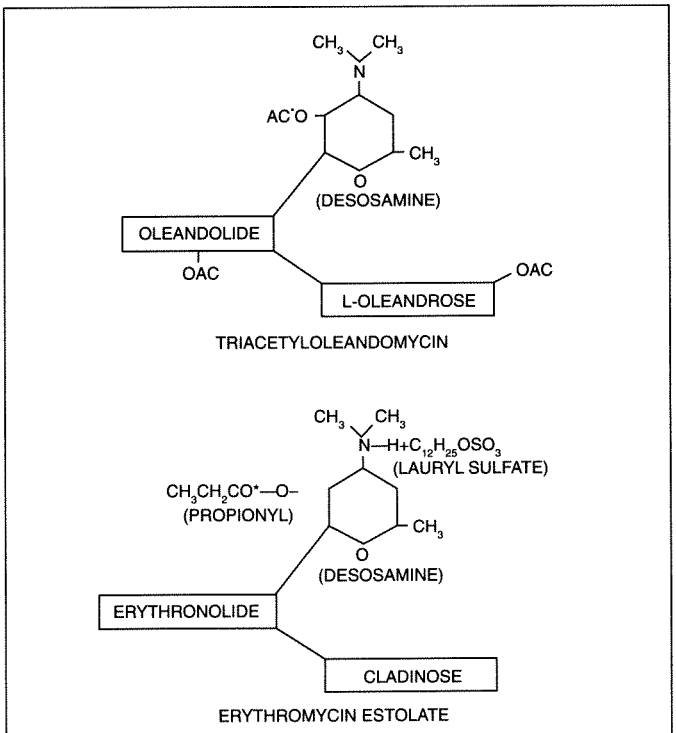

Fig 2.—Comparison of formulas of erythromycin estolate and triacetyloleandomycin. Asterisks indicate position of desosamine OH group in both antibiotics.

days indicate that subclinical hepatitis develops in approximately 50% of patients receiving the drug. In 3 of 4 patients with abnormal liver function tests, elevated SGOT and elevated BSP values developed within 24 hours of a challenge dose of triacetyloleandomycin. These results were sufficient to cause 2 drug companies reporting this high incidence of occult hepatitis to revise their brochures and suggest that their products not be used for longer than 10 days.[8,9] The significance of the challenge

dose producing hepatitis within 24 hours of administration has been almost overlooked, for there is no word of caution regarding a second course of the antibiotic. As yet, no comparable studies with erythromycin estolate have been reported, but it is anticipated that the results will be similar. The appearance of cholestatic hepatitis in patients receiving the macrolide antibiotics, triacetyloleandomycin and erythromycin estolate, is too much to expect coincidence. The parent molecules, oleandomycin phosphate and erythromycin, have not produced hepatitis. Triacetylation of oleandomycin phosphate and propionylation of erythromycin results in preparations that are more effective antibiotics. At the same time, the new compound acquires the capacity to cause hepatitis.

On turning to the chemical formulas[10-12] (Fig 2) in an attempt to explain the sensitization property (Fig 2) of the esterified molecules, it is observed that erythromycin and oleandomycin phosphate differ as to their macrocyclic lactone nuclei and one of their side-chain sugars. The second side-chain "sugar," desosamine, is the same in both antibiotics. When the molecular position marked with an asterisk is represented by a simple OH group in either antibiotic, hepatitis does not occur; nor does it occur when stearate is added proximal to the single nitrogen atom in desoamine.

Only when the OH at the positions marked by asterisks is replaced by the propionyl radical in erythromycin and by the acetyl radical in oleandomycin phosphate do these macrolide antibiotics acquire the capacity to cause hepatitis. In all probability, other acids similarly linked to macrolide desosamine would provoke similar hypersensitivity and hepatitis, but with the specificity of the immune response residing in the specific acid radical.[13]

It has been suggested[14] that esterification at the molecular position indicated confers the properties of a haptene on the macrolide molecule. This chemical alteration may permit the antibiotic to become antigenic by enabling it to conjugate with the necessary body protein, or more likely provides the signal by which the individual's cellular clones recognize the antibiotic as "not self." In any event, administration of the esterified antibiotic to a susceptible individual starts the chain of events that may lead to the hypersensitivity response. Once this occurs, all that is now necessary to produce cholestatic hepatitis is a properly timed triggering dose of the antibiotic in the primed hypersensitive individual.

Summary

The macrolide antibiotics erythromycin and oleandomycin, incapable of causing hepatitis in their basic form, apparently acquire this capacity by esterification of their desosamine side chains.

Although abnormal liver function developed in approximately 50% of patients receiving triacetyloleandomycin for longer than 10 days, clinical jaundice developed in less than 5%. Because of the high incidence of liver function abnormalities following the use of triacetyloleandomycin, 2 drug firms have advised that this product not be used for longer than 10 days. It appears advisable to observe similar precautions in the use of erythromycin estolate until appropriate investigation has excluded the possibility of high incidence of subclinical hepatitis. It is also suggested that a second course of either of these macrolide esters be used with extreme caution, if at all.

I am grateful to my patient, Dr Emiko Sakurai Hirschy, who recognized the potential hazard of reexposure to the antibiotics studied, yet deliberately accepted the risk in order to gain more information about this hepatosensitivity.

Generic and Trade Names of Drugs

Triacetyloleandomycin - Cyclamycin, Tao.
Erythromycin estolate - Ilosone.
Erythromycin stearate - Erythocin Stearate.
Meperidine hydrochloride - Demerol Hydrochloride.
Oleandomycin phosphate - Matronycin.
Erythromycin - Erythromycin, Ilotycin.

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Combining patient information. *The step beyond single case reports is to combine information from many patients in one or more practices. This is especially important if the answers vary in different practices, laboratories, or (so common in Hawaii) ethnic groups. The next papers describe the outcomes from some of the innumerable questions that cry out for solution, that would improve the health of our patients if known, and that can best be answered by ourselves.*

Dr Lynn Madanay tells this story about the following article: Several recent publications suggested that prostate-specific antigen (PSA) gradually increases with age in men without prostate cancer, and therefore laboratories should report age-adjusted normal limits. Pressure was put on Lynn to consider changing the standards in his laboratory. He and Fred Gilbert were discussing whether to make those changes when Fred suggested that they find out whether the age-adjustments obtained from mostly Whites at Mayo applied to our own laboratory and to our own ethnic populations. In three days Fred dropped on his desk a 16-page proposal, budget and all, ready for signature. A week later funds were available, and within three months the analysis was made, paper written, and presentation given at the American College of Physicians' Annual Scientific Meeting in April, 1995.