

THE EXCRETION AND CONCENTRATION OF TERRAMYCIN IN THE ABNORMAL HUMAN BILIARY TRACT*

JERRY ZASLOW, M.D. AND AARON ROSENTHAL, M.D.

PHILADELPHIA, PA.

FROM THE ALBERT EINSTEIN MEDICAL CENTER, PHILADELPHIA, PA.

THE EXCRETION and concentration of the sulfonamides, penicillin, streptomycin and aureomycin, in the abnormal human biliary tract has been reported in previous communications.²⁻⁶ While the results found for one antibiotic are generally applicable to what may be expected pharmacologically of other antibiotics, the true state of affairs can only be determined by a thorough investigation of each agent. Therefore, the study of the excretion and concentration of terramycin into the abnormal human biliary tract was undertaken. The results and conclusions are summarized in the following paragraphs.

PART I. GALLBLADDER METHOD OF INVESTIGATION

A series of patients who were to be subjected to cholecystectomy was selected for the study. Each patient was given a single dose of either 250 mg. or 500 mg. of terramycin sometime before operation. Nothing orally was permitted once the drug was ingested. The time interval elapsing between ingestion of the drug and the clamping of the cystic duct at the time of operation was observed in each case. A note was made as to the pathologic state of the gallbladder, and as to the patency of the cystic duct as observed at operation. The level of terramycin in the gallbladder bile

was determined in each case according to the method of Whitlock, Hunt and Tashman,¹ using the Oregon-J strain of *Staphylococcus aureus*, American culture type 9801. (All levels were determined by Sylvia G. Tashman, M.A., modified by her to measure specifically levels in bile.)

RESULTS OF INVESTIGATION (TABLE I)

All the gallbladders in this study contained stones.

In seven patients no terramycin could be demonstrated to be present in the gallbladder bile. The time intervals elapsing between ingestion of the drug and clamping of the cystic duct at operation varied in these patients from two and a half to ten hours. In each of these patients the cystic duct was obstructed by a stone. In four of them the gallbladder was acutely inflamed. In the remaining three in this group the gallbladder was the site of chronic disease, and in one of these the organ was hydropic.

Terramycin could be recovered in the gallbladder bile of the remaining 18 patients. The levels in these varied from 0.74 gamma per ml. to 36.8 gammas per ml. The time intervals between ingestion and clamping of the cystic duct varied from three and a half hours to 16 hours. In each the cystic duct was determined to be patent at the time of operation. All of them showed chronic inflammatory changes.

In general, the levels of terramycin in the gallbladder bile were generally higher in those patients who received 500 mg. of

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terramycin. In none of these was a level below 2.5 gammas per ml. obtained. On the other hand, in most of the patients who received the 250 mg. dose the level was less than 1.0 gamma per ml. It was interesting to observe that the single highest level, 36.8 gammas per ml., was obtained in a patient who received the smaller dose.

TABLE I. Levels of Terramycin in Bile From Gallbladders Following Oral Administration of the Drug.
(All gallbladders contained stones)

Type of Gallbladder	Concentration of Terramycin (gamma per ml.)	Time after ingestion (hours)	Obstructed cystic duct
acute suppurative...	0	2½	yes
Acute hydroptic.....	0	10	yes
Acute gangrenous...	0	9	yes
#Acute suppurative...	0	8	yes
#Chronic hydroptic...	0	8	yes
Chronic.....	0	5	yes
#Chronic.....	0	5	yes
Chronic.....	2.5	7	no
Chronic.....	2.9	9	no
Chronic.....	11.2	9	no
Chronic.....	12.0	16	no
Chronic.....	7.8	6½	no
Chronic.....	8.0	11	no
Chronic.....	2.8	12	no
Chronic.....	8.8	4½	no
Chronic.....	10.0	9	no
Chronic.....	11.2	9	no
Chronic.....	20.0	8½	no
Chronic.....	12.0	5½	no
#Chronic.....	36.8	13	no
#Chronic.....	0.94	11	no
#Chronic.....	5.0	3½	no
#Chronic.....	6.1	10	no
#Chronic.....	0.74	10	no
#Chronic.....	0.94	8	no

#—indicates that the dose given was 250 mg. of terramycin. All others received a single dose of 500 mg.

PART II. HEPATIC DUCT BILE
METHOD OF INVESTIGATION

Eight patients in whom T-tubes were inserted into the common duct at the time of biliary tract operation were selected for the study. A single dose of 250 mg. of terramycin was given intravenously over 30 minutes in 100 ml. of normal saline, either on the day of operation or within a three-day period thereafter. Specimens of bile

were collected from the T-tube at 30, 60, 120 and 180 minutes. The concentration of terramycin was determined in each of the specimens according to the method used in the gallbladder study. In each of the patients the study was repeated in an identical manner at various times in the postoperative period. Several liver function tests were done in the preoperative period and were repeated in some of the patients in the postoperative period on one or more occasions. The data for these eight patients are summarized in Table I, and are presented in more detail in the following paragraphs.

RESULTS OF INVESTIGATION (TABLE II)

Five of the eight patients were jaundiced at the time of operation or in the immediate preoperative period (Patients 1, 2, 3, 7 and 8).

Patient #1. This patient was a 54-year-old white female who was admitted to the hospital with an acute attack of biliary colic and jaundice. The jaundice had been mild, and had been persistent for about 3 days. On the day of operation the serum bilirubin level which had been 3.6 mg. per 100 ml. had returned to normal. No stones were found in the common duct at the time of operation. A calculous gallbladder was removed. All liver functions tests performed in the immediate preoperative period were within normal limits. The initial excretion study was done on the third postoperative day. The highest level of excretion was 2.5 gamma per ml. The excretion was repeated again on the eighth postoperative day and the highest level of excretion was 7.1 gamma per ml.

While the excretion on the eighth postoperative day was somewhat better than on the third day, at no time did the level of terramycin in common duct bile reach what we could consider a normal level of at least 20 gammas per ml. The latter level was determined in subsequent patients to be the lowest level to be expected in a patient who has normal liver function and an obstructed biliary tree. It may very well be that had the study been repeated again at a later date, the level of excretion would have been higher. In any event, it can be stated with certainty that for at least the first week after operation the ability of the liver in this patient to excrete the terramycin

TABLE II. Excretion of Terramycin in Hepatic Bile After the Intravenous Injection of 250 mg. (Pertinent Data of 8 Cases.)

Case No.	Jaundice Duration in days	C. F.	T. T.	P.	B. S.	S. B.	Excretion of Terramycin (gamma/ml.)— time after injection in minutes.				Postop. Day
							30	60	120	180	
1.	3#	N.	N.	80	N.	N.					3
							7.1	3.0	1.7	2.1	8
2.	170 ###	N.	4	100	N.	11.5	2.6	4.0	10.0	4.0	0
				100		21.8	4.1	2.8	2.8	2.8	4
						20.6	2.6	2.8	4.6	3.0	8
3.	7##	N.	N.	60	N.	6.0	12.6	7.7	4.0	6.2	0
				100		2.0	2.4	4.0	3.4	5.0	3
						2.0	3.4	6.2	1.9	4.1	6
						7.1	30.4	30.4	20.0	2	
4.	0	N.	N.	100	N.	N.	3.4	.78	3.4	7.7	0
5.	0			100	N.	N.	14.4	16.0	34.0		4
6.	0	N.	N.	70	N.	N.	1.4	1.8	7.4	5.2	0
							2.5	3.2	26.4	13.6	11
							.6	2.3	5.8	10.4	
7.	5	N.	N.	90	N.	2.0	.53	.45	2.5	2.8	0
						N.	25.6	44.8	48.8	17.6	4
8.	7	N.	N.	100	N.	6.8	0	1.0	3.1	2.9	0
						N.	12.0	5.2	7.4	7.4	5
						N.	14.2	20.6	24.0	30.0	8

C. F.—Cephalin Ficculation Test.
 T. T.—Thymol Turbidity Test.
 P.—Prothrombin Time in Percent.
 B. S.—Bromsulfalein excretion.
 S. B.—Serum bilirubin in mg% (total).
 N.—Normal result.

#—Jaundice gone at time of initial study of terramycin excretion.
 ##—Jaundice decreasing at time of initial study of terramycin excretion.
 ###—Patient with hepatogenous jaundice with liver function tests indicating obstructive jaundice.

was definitely impaired. This may have been the result of the obstruction which may have been of sufficient intensity to affect this particular function of the liver.

Patient #2. A 45-year-old white female, was admitted to the hospital with persistent jaundice of 170 days. There had been very little fluctuation observed in the intensity of the icterus. Except for the markedly elevated serum bilirubin, all the liver function tests performed appeared to be within normal limits. The preoperative diagnosis was obstructive, rather than hepatogenous, jaundice. This was based entirely on the fact that the liver function tests were within normal limits. At the time of operation it was observed that the common duct was completely patent. The gallbladder was normal. Excretion of terramycin was measured several hours after operation was completed. The highest level obtained was 10 gammas per ml. On the fourth postoperative day the serum bilirubin had risen from 11.5 to 21.8 mg. per 100 ml. and the highest level of excretion was 4.1 gammas

per ml. In a repeat study done on the eighth post-operative day, when the serum bilirubin level was the same as on the fourth day, the highest level of excretion again was only 4.6 gammas per ml.

It has been observed on previous occasions that it is often impossible to differentiate hepatogenous from obstructive jaundice from the laboratory standpoint alone, and that patients with hepatogenous jaundice may exhibit all the laboratory evidence which is said to be diagnostic of an obstructive jaundice. This type of patient has been classified as one with "cholangiolitic" type of hepatitis. In spite of the fact that the liver function tests performed in this patient were within normal limits, the excretion of terramycin was markedly impaired. It has been observed for other antibiotics that the excretion of these agents is a sensitive index of liver function. It would appear in this patient, as in the preceding one, that this phenomenon is also true in the case of terramycin. It must also be noted that whereas the other antibiotics and chemotherapeutic agents studied were usually

not excreted at all when intense jaundice was present, in the case of terramycin at least some of the drug was able to get through into the extra-hepatic biliary tree.

Patient #3. The patient, a 42-year-old white male, was admitted to the hospital with jaundice of 7 days' duration. At the time of operation the jaundice appeared to be diminishing. The usual liver function tests performed were within normal limits. Stones were removed from the common duct and a T-tube placed into its lumen. Initial terramycin excretion studies done on the day of operation revealed the highest level to be 12.6 gammas per ml. On the third postoperative day, when the serum bilirubin had fallen to a level of 2.0 mg. per 100 ml., the highest level of terramycin excretion was again only 5.0 gammas per ml. A repeat study on the sixth day yielded almost identical findings.

As was true in Patient #2, although liver function tests were within normal range, except for the slightly elevated serum bilirubin, there was definite impairment of the excretion of terramycin from the liver. Although the stones in the common duct had been removed, the serum bilirubin level was still elevated as late as the sixth postoperative day. At this time there was also marked impairment of excretion of terramycin.

Patient #7. The patient was admitted with a history of jaundice persisting for 5 days prior to admission. All liver function tests done the day before operation were within normal limits. The serum bilirubin was slightly elevated, 2.0 mg. per 100 ml., and appeared to be stationary. Several stones were recovered from the common duct at the time of operation. An initial excretion study done on the day of operation revealed the highest level to be 2.8 gammas per ml. A repeated study done on the fourth day when the serum bilirubin level had returned to normal revealed the highest level of excretion to be 48.8 gammas per ml.

Patient #8. This patient had been jaundiced for about 7 days prior to admission. The level of serum bilirubin at the time of operation was 6.8 mg. per 100 ml. Other liver function tests were normal. Excretion studies done on the day of operation revealed the highest level of terramycin to be 2.9 gammas per ml. A repeat study done on the fifth postoperative day when the serum bilirubin level had returned to normal revealed the highest level of excretion to be 12 gammas per ml., and on the eighth day, 30 gammas per ml.

While patients #7 and #8 had been jaundiced at the time of operation, in each case the level of excretion of terramycin had reached very high

levels when the serum bilirubin level had returned to normal.

Patients #4, 5, 6. None of these patients were jaundiced at the time of operation. In each, the liver function tests performed before operation were within normal limits. An excretion study done in Patient #4 showed the highest level on the second postoperative day to be 30.4 gammas per ml. In Patient #5 the level of excretion was low the day of operation, 3.4 gammas per ml., but had reached a level of 34.0 gammas per ml. on the fourth postoperative day. Patient #6 is interesting insofar as two operations were performed during the hospital stay, both for non-obstructing common duct stones. On the day of the first operation a terramycin level of 7.4 gamma per ml. was obtained and on the eleventh day a level of 26.4 gamma per ml. The patient was reoperated upon on the 22nd postoperative day because of a large stone which was visualized by cholangiography in the distal end of the common duct. It is interesting to note that whereas the excretion level previously had been as high as 26.4 gammas per ml., the highest level on the day of reoperation was only 10.4 gammas per ml. Further excretion studies in this patient could not be performed because the patient died three days later as a result of a massive pulmonary embolus. This case demonstrates clearly that operation and anesthesia itself may effect one or more of the functions of the liver.

GENERAL DISCUSSION GALLBLADDER

As has been found when the sulfonamides and other antibiotics were studied as to their concentration and excretion in the abnormal human biliary tract, the patency of the cystic duct was observed to be the single most important factor in terramycin reaching the gallbladder lumen, provided it is normally excreted from the liver. In none of these cases where the cystic duct was obstructed by stone was any antibiotic recovered in the gallbladder bile. On the other hand, in all other cases where the cystic duct was patent various concentrations of the drug could be recovered from the gallbladder contents. Acute inflammation of the gallbladder wall did not in any way appear to affect the mode of entrance of the drug into its lumen. In none of the cases where there was acute

suppuration and where the cystic duct was obstructed was any antibiotic recovered in the gallbladder contents, proving that the drug does not enter the gallbladder lumen by excretion through its wall. It was observed that the concentration of the drug in the gallbladder lumen varied considerably in different patients, even though the time elapsing between ingestion of the drug and clamping of the cystic duct was practically identical. This may have been due to one of several factors. It may very well have been that in one case the gallbladder contained much more bile than in another, and therefore the drug was diluted that much more. It may also be that the rate of excretion varied in individual patients, depending upon the ability of the liver to excrete the drug at that particular moment. However, it was also observed that once the drug reached the gallbladder lumen it remained there in fairly high concentration for long periods of time, in one case as long as 16 hours in a concentration of 12.0 gammas per ml.

As far as dosage is concerned, it would appear that the single dose of 500 mg. produces a much higher concentration of the drug in the gallbladder bile, and would probably be the desired dose if oral medication is indicated in any particular case.

HEPATIC DUCT

It would appear that following a single intravenous injection of 250 mg., terramycin is excreted in high concentration from the liver into the extrahepatic biliary tree. It also appears that in the presence of either obstructive or hepatogenous jaundice the excretion of the drug is impaired to a greater or lesser degree. In none of the patients who were jaundiced at the time of operation was the initial excretion level high, and in many of them, even after the jaundice subsided postoperatively, the level of excretion was still lower than what we considered to be normal. In the single

patient with hepatogenous jaundice (Patient #2) the level of excretion at no time exceeded 10 gammas per ml., and as the jaundice became more intense the level was even lower. This phenomenon was observed when other antibiotics were studied. However, in a patient with jaundice as intense as that present in this one, there usually was no excretion of the antibiotics previously studied from the liver into the bile ducts. In all of the patients studied in the present investigation some terramycin was excreted, regardless of the degree of jaundice present. This would appear to make terramycin a somewhat more desirable agent than the others.

All of the patients were operated upon under general anesthesia, various anesthetics being employed. Whenever an excretion study was done on the day of operation and repeated a few days later, other factors being equal, the level of excretion was always lower on the day of operation. This is due to the fact that two factors are operating, namely, the trauma of operation and the effect of the anesthetics. This was dramatically demonstrated in Patient #6. In this patient the level of excretion fell dramatically on the day of reoperation from a high level several days before.

When obstructive jaundice had been overcome and the liver was not too severely injured, the levels of excretion increased as the serum bilirubin levels fell and subsequently returned to normal. In those patients who were not jaundiced in the immediate preoperative period, levels of excretion were high once the initial effects of the operation and anesthesia had disappeared.

It appears that the usual liver function tests performed cannot be used as an accurate index as to whether or not terramycin will be excreted from the liver in normal concentrations. As previously mentioned, in the presence of active common bile duct obstruction or in the presence of hepatitis

with normal liver function tests, the ability of the liver to excrete the drug into the bile ducts is impaired. The ability of the liver to excrete the drug is apparently an independent function of the liver itself, and may be impaired when other excretory functions are normal.

While not shown in the table, it was demonstrated that the normal level of terramycin in bile is six to ten times that in the blood serum.

SUMMARY

1. Terramycin appears in the gallbladder bile after oral ingestion of the drug when the liver is able to excrete the agents and when the cystic duct is patent.

2. When the cystic duct is obstructed by stone, no terramycin appears in the gallbladder lumen.

3. Acute inflammation of the gallbladder does not in any way alter the mode of entrance of terramycin into the gallbladder lumen.

4. Higher levels of terramycin in gallbladder bile are usually obtained when a large dose of the drug is given orally.

5. When the liver function is normal and when the common duct is unobstructed, terramycin is excreted into the hepatic duct from the liver in high concentration.

6. When there is impairment of liver function and/or the common bile duct is

obstructed, the ability of the liver to excrete terramycin is impaired.

7. When liver function improves and common duct obstruction is overcome, the organ is better able to excrete the drug.

8. No matter how intense the jaundice, in no case in this series was there complete inhibition of excretion of the drug. This may be a distinct advantage of terramycin over the other antibiotics previously studied.

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