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Research Article

THE ELIMINATION OF CHOLIC ACIDS. IV. IN PATIENTS WITH LIVER DISEASES [1]

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This investigation was undertaken to study the rate of elimination of injected bile salts from the blood of patients with different types of liver disease.

In normal human subjects Josephson and Larsson (13) found that intravenously injected cholate disappeared from the blood very rapidly. Five minutes after the injection only a small part of the injected amount could be found in the blood and after thirty minutes the cholate concentration in the blood was normal again. In one hour most of the injected cholate had been excreted by the liver.

Corresponding results with normal animals had been previously reported by several investigators. This literature was briefly reviewed by Josephson, Jungner, and Rydin (11). On the other hand, Snell, Greene, and Rowntree (22) found that in animals with experimental obstructive jaundice disappearance of injected bile salts from the blood was very much delayed. Similar results were obtained later by Bollman and Mann (3) and by Chabrol, Cottet, and Sallet (6). Jungner, Rydin, and Josephson (14) studied the elimination from the blood of sodium cholate injected intravenously into animals with different experimental liver injuries. They found that the rate of disappearance was different in various kinds of jaundice. The elevation of the blood concentration after a cholate injection was, as one would expect, much greater in experimental jaundice than in normals. In most cases, however, the subsequent decrease was rather rapid in obstructive jaundice, but delayed in toxic hepatitis. The present investigation was carried out in order to determine whether corresponding results could be found in patients with liver diseases.

The spontaneous cholic acid concentration in the blood of patients with liver diseases has been the subject of many investigations (2, 5, 15, 16, 17, 21). All these workers used different methods and their results do not correspond. Usually cases of obstructive jaundice seem to have shown a high cholate concentration while cases with hepatitis and cirrhosis have given widely varying results. For this reason, determinations of the bile salt concentration in the blood have never been of clinical use.

Nakagawa, Simuro, and Suzuki (19) have tried to get a bile acid tolerance test by giving patients an injection of sodium dehydrocholate with subsequent analyses of the urine on substances precipitable by acetic acid. Their method, however, is not sufficiently specific to yield accurate data concerning bile acid excretion.

METHODS

The experiments were carried out on 62 patients in both medical departments of the Serafimer Hospital. They were divided into two groups. The first includes all cases with evidence of liver or bile duct involvement. The second group consists of control cases who had diseases in which liver involvement usually does not occur.

In the elimination tests pure sodium cholate was used. Ten ml. of a 0.52 per cent solution corresponding to 0.5 gram cholic acid, was injected into a cubital vein. The solution also contained 25 per cent glucose which prevents the pain usually caused by an intravenous injection of a pure cholate solution. No pains or symptoms were ever observed in connection with the injections. One blood sample for cholate analysis was taken before the injection. The subsequent samples were taken 5, 30, and 60 minutes after the injection in a vein on the opposite side than that where the injection was made. The cholic acid analyses were carried out with the method of Josephson (10) [2] as modified by Josephson and Larsson (13).

[1] This investigation was aided by a grant from the Foundation, "Therese och Johan Anderssons minne."

[2] This method has been criticized by Jenke (9) who has claimed that it would be nonspecific at low concentrations

The tests were carried out between 9 and 12 a.m. and all subjects were in the postabsorptive state. At the same time as the first blood sample for cholate analysis was taken other samples were drawn for the analysis of bilirubin (Jendrassik and Csike) and of the icterus index (Meulengracht). In addition to the routine tests on bile pigments and urobilin in the urine and feces and the Hay test in the urine, the galactose test (Brauer) was carried out in most cases and frequently also the Takata test. Other liver and blood tests of interest are not reported in the tables as they were carried out only occasionally.

RESULTS

A brief summary of the results obtained from the 27 control cases is given in Table I, showing that there was no marked difference between the

TABLE I

Patients without liver diseases. Concentration of cholic acids in blood before and after injection of 0.5 gram of cholic acid

	Cholate concentration in blood				Difference between concentrations *		
		Minutes after injection					
	I Before injection	5	30	60			
		II	III	IV	II–I	II–III	III–I
	mgm. per 100 ml.	*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*			
Average.....	2.23	4.40	2.47	2.47	2.06	1.93	0.21
σ.....	0.84				1.23	1.19	0.65
Maximum...	4.0	6.7	4.7	4.6	4.8	4.2	+1.8
Minimum...	0.9	2.2	0.9	0.2	0.4	0.2	−1.0

* The sums of and differences between the different averages do not correspond correctly as one value is missing in a few series.

and erroneous at high. According to Josephson's studies (10), it is very probable that the method is specific for cholic acids in blood, but it may be admitted that this is not definitely proved. In this investigation and those of Josephson and collaborators, a nonspecific reaction has no influence on the results, as they deal with comparisons of the concentration over a short period of time in single individuals after addition of pure cholates. For higher concentrations of a degree occurring in jaundice before and after cholate injections, the method has been shown by Josephson to give very satisfactory results. This has been confirmed in this laboratory.

elimination rate in these cases and that in normal cases receiving twice this amount of cholate, as described by Josephson and Larsson (13). The elevation of the blood cholates 5 minutes after the injection was much less than would be expected by dilution in the total volume of the blood. The rate of disappearance of the cholates was more rapid than that of other liver active substances, *e.g.*, bromsulphalein (18). As the 5-minute samples were taken during the rapid decrease of the blood cholates it was quite natural that the concentrations found, and the differences between these and other values should show great variations. After 30 minutes the cholate concentration was normal again.

Three of these cases showing values within the normal limits were treated for severe thyrotoxicosis. This may be of interest in connection with an investigation by Schmidt (20) showing that in rabbits treated with thyroxin, the elimination of injected cholates was considerably delayed. It is also well known that other liver function tests often give pathological values in cases of hyperthyroidism (literature reviewed by Bartels (1)).

The results from the patients with liver symptoms are shown in Tables II to V.

To some degree the original cholate concentration in the blood of these patients corresponded to the degree of jaundice, but there were several exceptions. No difference could be found between the concentration in different kinds of jaundice. In the cases with carcinoma, cirrhosis, or congestion of the liver without jaundice there was no elevation. The concentration was also normal in a few cases with jaundice. The tests in Cases 14, 15, and 20 with hepatitis were carried out during the recovery periods which explains the normal values.

The elevation of the cholates after the injection varied widely but was increased in jaundice and highest in the most jaundiced cases.

The subsequent decrease showed interesting characteristics. In cases with liver tumors the decrease was nearly as rapid as in normals. As a rule, the difference between the 5-minute and the 30-minute values was above 2.2 mgm. per 100 ml. There were two exceptions. Case 1, in addition to the obstructive jaundice, had an acute cholangeitis with multiple abscesses and extensive destruction of the liver parenchyma; and Case 4 had no

TABLE II

Cholic acids elimination in patients with tumors in the liver or bile ducts

Case number	Patient number	Sex	Diagnosis	Age	Diagnosis verified†	Skin jaundice	Liver enlargement	Serum bilirubin	Icterus index	Galactose excretion	Takata test	Urine			Feces. Bile pigments	Cholic acids in blood				Difference
												Bile pigments	Hays test	Urobilin		Before injection	Minutes after injection			
																	5	30	60	
																I	II	III	IV	II–III
				years				*mgm. per 100 ml.*		*grams*						*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*
1	375/37	M	Bile duct carcinoma, liver metastases, acute cholecystitis with multiple liver abscesses	66	p.m.	+	++ nodular	4.8	50*	0.9		+++	+	+++	0	4.9	6.2	4.4	5.5	1.8
2	762/37	F	Operated breast carcinoma; liver and lung metastases	59		++	+++ nodular		65			+	+	0	0	5.4	9.2	7.0	6.4	2.2
3	1020/37	F	Carcinoma of the gallbladder and bile ducts, liver metastases																	
			Sept. 3	57	p.m.	+++	++ nodular	20.5	60	1.0		++	+	+++	0	6.4	10.1	7.6	7.1	2.5
			Sept. 21			+++	++ nodular		100	0.2		++	+	+++	0	8.4	12.2	9.3	9.1	2.9
4	1089/37	M	Colon carcinoma, enormous liver metastases	51	p.m.	0	+ nodular	1.3	15	1.3		0	0	0	+	2.4	4.1	2.7	2.2	1.4
5	1212/37	F	Carcinomatosis of liver	43	p.m.	++	+ smooth	12.1	50			+++		0		2.7	8.5	3.2	4.9	5.3
6	1290/37	M	Liver carcinoma, lung metastases, ascites	54	p.m.	0	+++ lobed	0.9	5		Neg.	0	0		+	2.0	5.9	3.0	0.8	2.9
7	524/38	M	Pancreas carcinoma	50	X-rays	+++	±	13.7	45*		++	+	+	+	0	7.7	18.0	14.0	8.3	4.0
8	600/38	F	Bile duct carcinoma, purulent cholangeitis	41	p.m.	+++	+++ smooth			0.5		++	+	++	0	10.4	18.1	15.2	10.0	2.9
9	1176/38	M	Syphilis tertiary, bile duct carcinoma	67		++	++ smooth	13.6	60*	1.4	Neg.	++		+	0	1.9	2.6	0.3		2.3

* Value increasing.
† p.m. = postmortem.

TABLE III

Cholic acids elimination in patients with hepatitis

Case number	Patient number	Sex	Diagnosis	Age	Diagnosis verified†	Skin jaundice	Liver enlargement	Serum bilirubin	Icterus index	Galactose excretion	Takata test	Urine			Feces. Bile pigments	Cholic acids in blood				Difference
												Bile pigments	Hays test	Urobilin		Before injection	Minutes after injection			
																	5	30	60	
																I	II	III	IV	II–III
				years				*mgm. per 100 ml.*		*grams*						*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*
10	747/37	M	Acute hepatitis	28	Recovered	+++	0	10.1	60‡			+	+	++	0	5.7	8.4	8.0	7.5	0.4
11	1031/37	M	Arsphenamine treatment, acute hepatitis	23	Recovered	+	+	4.2	38‡	0.3	Neg.	+	+	±	0	4.6	8.6	7.5	7.2	1.1
12	1139/37	F	Acute hepatitis	22	Recovered	+	+	5.2	40	1.0		+	+	+++	+	8.9	10.8	9.4	9.0	1.4
13	1415/37	M	Acute hepatitis	46	Recovered	+++		18.0	85‡	0.8		+++	+	±	0	4.1	7.1	6.6	5.4	0.5
14	104/38	M	Acute hepatitis	57	Recovered	+	+	10.1	55‡			+	+	+	+	2.2	8.8		3.3	
15	185/38	M	Acute hepatitis	24	Recovered	+	++	10.6	60‡	4.2		+	+	+++		3.0	5.1	5.7	4.6	−0.6
16	447/38	M	Acute hepatitis	42	Recovered	+	0	4.0	15‡		Neg.	+		+	+	4.1	5.3	4.4	7.7	0.9
17	719/38	M	Acute hepatitis	42	Recovered	++	+	21.3	70‡	2.0	Neg.				+	7.7		11.2	9.6	
18	795/38	M	Pernicious anemia, acute hepatitis																	
			July 11	57	Recovered	+++	++	20.1	70*	2.2	Neg.	+++	+	±	0	5.4	8.4	7.9	7.1	0.5
			July 27			+++	++	25.0	90‡	1.1		+++	+	+	0	7.1	10.1	9.4	9.1	0.7
			Oct. 19			0	0	1.0	6			0	0	+	+	3.0	5.1	1.7	1.6	3.4
19	836/38	F	Acute yellow liver atrophy	42	p.m.	+	+	17.2	60		Neg.	+		0	0	6.5	11.4	10.4	11.4	1.0
20		F	Subchronic hepatitis	21		+	0	7.7	25‡	0	++	+		+	+	0.3	6.0	2.9	1.6	3.1
21	1215/38	M	Acute hepatitis	40		++	+	15.6	105*	1.4	Neg.	++		0	+	9.7	10.0	13.2		−3.2

* Values increasing.
† p.m. = postmortem.
‡ Values decreasing.

TABLE IV

Elimination of cholic acids in patients with liver cirrhosis and cholecystitis

Case number	Patient number	Sex	Diagnosis	Age	Diagnosis verified†	Skin jaundice	Liver enlargement	Serum bilirubin	Icterus index	Galactose excretion	Takata test	Urine			Feces. Bile pigments	Cholic acids in blood				Difference
												Bile pigments	Hays test	Urobilin		Before injection	Minutes after injection			
																	5	30	60	
																I	II	III	IV	II–III
				years				*mgm. per 100 ml.*		*grams*						*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*
22	1066/37	M	Chronic ethylism. Hypertrophic liver cirrhosis, gastritis	55		±	+	2.0	12‡	0.7		0	0	+	+	2.6	6.2	3.7	3.9	2.5
23	1317/37	F	Chronic ethylism. Hypertrophic liver cirrhosis	69	Operation	±	+	1.9	7			0	0	+	+	0.4	4.3	1.8	2.1	2.5
24	377/38	M	Hypertrophic liver cirrhosis	45	p.m.	+++	+	10.8	60	0	+++	++	+	+	+	6.7	10.7		11.7	
25	754/38	M	Chronic cholecystitis	45	Operation	0	±	1.2	3			0	0	+	+	3.2	5.3	3.6	2.7	1.7
26	831/38	M	Acute cholecystitis	72	Operation	0	0	1.5	4			0	0	±	+	3.2	5.0	2.8	3.7	2.2
27	843/38	F	Atrophic liver cirrhosis	44	X-ray	0	0	1.5	5		Neg.	0	0	0	+	3.2	6.0	3.1	3.3	2.9
28	1209/38	M	Atrophic liver cirrhosis	39	p.m.	++	0	10.7	90	3.0	++	++	0	0	0	2.9	5.4	5.3	5.2	0.1

† p.m. = postmortem.
‡ values decreasing.

TABLE V

Elimination of cholic acids in patients with secondary liver symptoms

Case number	Patient number	Sex	Diagnosis	Age	Diagnosis verified†	Skin jaundice	Liver enlargement	Serum bilirubin	Icterus index	Galactose excretion	Takata test	Urine			Feces. Bile pigments	Cholic acids in blood				Difference
												Bile pigments	Hays test	Urobilin		Before injection	Minutes after injection			
																	5	30	60	
																I	II	III	IV	II–III
				years				*mgm. per 100 ml.*		*grams*						*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*	*mgm. per 100 ml.*
29	497/37	M	Myeloid leukemia, enormous liver enlargement	77		0	++	0.8	4			0	0	0	+	1.7	2.4	0.9	1.1	1.5
30	1055/37	M	Heart failure, liver enlargement	56		0	++		4			0	0	0	+	2.7	4.9	2.7		2.2
31	172/38	M	Heart failure, liver enlargement	63		0	++					0	0	++	+	1.6	5.1		2.7	
32	442/38	M	Heart failure, liver enlargement	42		0	+			0.4		0	0	0	+	4.9	7.7	4.7		3.0
33	635/38	F	Heart failure, liver enlargement	46		+	+++	2.4	16	0.3		0	0	0	+	3.5	6.5	3.8	1.7	2.7
34	653/38	M	Pyelonephritis, uremia, liver enlargement	49	p.m.	0	+++	0.4	1			0	0	0	+	3.8	5.6	4.2	2.7	1.4
35	766/38	M	Pancreas carcinoma, ascites	67	X-ray	0	0	1.8	9			0	0	0	±	4.3	5.2	4.6	3.6	0.6

† p.m. = postmortem.

signs of biliary obstruction and a normal elimination curve.

In acute hepatitis the decrease was much slower; in Case 11 the difference between the 5-minute and the 30-minute value was 1.1, and in Case 12, 1.4, but in other cases it was not over 0.9 mgm. per 100 ml. Case 20 with subchronic hepatitis later developed a biliary cirrhosis with ascites.

Two cases of cholecystitis and the cases with liver edema showed normal elimination curves. One case of cirrhosis with severe jaundice had an elimination curve of the hepatitis type. Other cases with cirrhosis reacted normally.

The elimination curves did not correspond to the other liver tests.

The sharp difference between the elimination curves in jaundice due to obstruction and in hepatitis corresponds very well to the results of Jungner, Rydin, and Josephson (14). This difference was found even more regularly in human cases of liver diseases than it was in the animals with experimental jaundice. It is possible that the first disappearance from the blood of the major part of the injected cholates was due to adsorption of the bile acids to tissues other than the liver. The subsequent sharp decrease in cases of obstruction could be referred to absorption by a still functioning liver parenchyma, according to Bollman and Mann (4) and Chabrol, Cottet, and Sallet (7). Following this first decrease a slight increase one hour after the injection was observed in some cases. This could be due to a partly maintained circulation of the bile salts by the aid of the lymph vessels of the liver as in experimental obstructive jaundice (12). The existence of such a short circuit of the bile circulation in obstructive jaundice is also supported by the recent experiments of Doubilet (8) who recovered bile pigments in the thoracic lymph of dogs a few minutes after applying slight pressure in the bile ducts. In hepatitis, the absorbing function of the liver is diminished and consequently those bile salts which are not adsorbed by other tissues remain in the blood and the decrease is slow.

SUMMARY

In jaundice, the increase of the cholic acid content in the blood after an injection of sodium cholate is greater than in normals. It is not greater in liver diseases without jaundice. The subsequent decrease is delayed in acute hepatitis, but not in jaundice due to obstruction of the bile ducts. A cholic acid elimination test seems to be valuable in the differential diagnosis between these two kinds of jaundice.

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