Brit. J. Pharmacol. (1949), **4**, 274.

DIMERCAPROL AND THE BILIARY EXCRETION OF LEAD IN RABBITS

BY

MICHAEL GINSBURG* AND MILES WEATHERALL†

From the Department of Pharmacology, University of Edinburgh

(Received June 13, 1949)

Ginsburg and Weatherall (1948) showed that dimercaprol injected intramuscularly in rabbits shortly after lead acetate had been injected intravenously increased the amount of lead in the alimentary canal and particularly in its contents, and decreased the amount in the liver. The concentration of lead in bile obtained from the gall bladder was very variable and did not provide good evidence about the part played by biliary excretion in this redistribution. The present experiments were directed to settling this point.

METHODS

The procedures used in preparing solutions, administering and estimating lead by means of the tracer Ph^{212} (thorium B) have already been described (Ginsburg and Weatherall, 1948).

In order to collect samples of bile, rabbits weighing 2.5–2.9 kg. were anaesthetized with intravenous pentobarbitone or ether and cannulae were tied into the trachea, the internal carotid artery and the common bile duct. The cystic duct was tied. The arterial blood pressure was recorded, and artificial respiration was applied if necessary. Lead acetate (2.07 mg. Pb/kg.) containing about 200 microcuries of thorium B was then given intravenously and bile was collected for the next four periods of one hour, and their content of lead estimated. In some rabbits, dimercaprol (12.5 mg./kg.) in 66 per cent (v/v) aqueous propylene glycol (0.25 mg./kg.) was injected intramuscularly two hours after the lead acetate, and into the rest 66 per cent propylene glycol alone. This dose is one-quarter of that previously used for the initial injection, and has been reduced because it is doubtful whether rabbits already subjected to anaesthesia and operative trauma would tolerate much larger amounts. In one rabbit (No. 355) the dose of dimercaprol was 4 mg./kg. After 4 hours the rabbits were killed with a large dose of pentobarbitone and certain tissues were taken for the estimation of the lead in them.

* Present address—Department of Pharmacology, University of Bristol. † Present address—Department of Pharmacology, London Hospital Medical School.

RESULTS AND DISCUSSION

The results are shown in Table 1 and Fig. 1. When dimercaprol was not administered, the highest

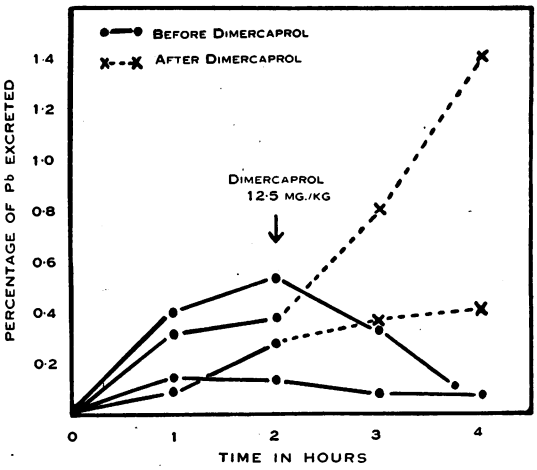

FIG. 1.—The effect of dimercaprol on the excretion of lead in bile. Abscissa: time in hours after the intravenous administration of lead acetate (2.07 mg. Pb/kg.). Ordinate: percentage of administered lead excreted per hour in bile.

concentration of lead in the bile occurred in the second hour and later samples contained less. When dimercaprol was injected after the second hour, even in a dose as small as 4 mg./kg., the concentration continued to rise, except in the rabbit anaesthetized with ether. This rabbit was in poor condition and died before the end of the third hour and it is unlikely that the lack of response was due directly to the different anaesthetic. In all these experiments there was a progressive decline in the blood pressure without striking changes referable to the lead acetate or dimercaprol. There was no indication that the increased excretion after dimercaprol was due to circulatory improvement.

TABLE I

THE EFFECT OF DIMERCAPROL ON THE FATE OF LEAD IN ANAESTHETIZED RABBITS WITH CANNULATED BILE DUCTS, AFTER THE INTRAVENOUS ADMINISTRATION OF LEAD ACETATE (2.07 mg. Pb/kg.)

Rabbit number:—	323†			353			355			317			345			356*		
Weight and sex:—	2.9 kg.♂			2.5 kg♂			2.9 kg.♀			2.6 kg.♂			2.5 kg.♂			2.5 kg.♀		
Anaesthetic:—	Pentobarbitone															Ether		
Dose of dimercaprol mg./kg.	Nil			Nil			4.0			12.5			12.5			12.5		
	Bile vol. (ml.)	% of dose	µg. Pb per ml.	Bile vol. (ml.)	% of dose	µg. Pb per ml.	Bile vol. (ml.)	% of dose	µg. Pb per ml.	Bile vol. (ml.)	% of dose	µg. Pb per ml.	Bile vol. (ml.)	% of dose	µg. Pb per ml.	Bile vol. (ml.)	% of dose	µg. Pb per ml.
Hepatic bile 1st hr. ...	12.0	0.40	2.0	8.7	0.15	0.78	9.3	0.11	0.72	8.1	0.12	0.88	3.6	0.34	4.8	3.6	0.04	0.53
,, ,, 2nd ,, ...	9.0	0.54	3.7	6.5	0.15	1.0	9.2	0.22	1.4	7.2	0.24	1.9	3.8	0.38	5.2	6.0	0.16	1.4
,, ,, 3rd ,, ...	6.9	0.34	3.0	6.3	0.08	0.57	8.2	0.23	1.6	6.3	0.36	3.2	3.7	0.83	11.6	3.3	0.04	0.85
,, ,, 4th ,, ...	2.5	0.08	1.9	6.3	0.08	0.61	8.2	0.38	2.8	3.8	0.41	6.1	3.4	1.4	21	—	—	—
,, ,, Total ...	—	1.36	—	—	0.46	—	—	0.94	—	—	1.13	—	—	2.95	—	—	0.24	—
	% dose	µg. Pb per gm.		% dose	µg. Pb per gm.		% dose	µg. Pb per gm.		% dose	µg. Pb per gm.		% dose	µg. Pb per gm.		% dose	µg. Pb per gm.	
Liver at death	43	31		33	31		53	29		71	67		36	40		32	25	
Small intestine at death ...	2.4	2.0		0.21	0.17		2.0	1.4		0.90	0.88		1.1	1.3		0.74	0.70	
Small intestine contents at death	0.38	—		0.12	0.70		0.49	3.5		0.66	1.5		0.33	1.7		0.09	0.02	
Blood	3.1	—		5.0	1.5		—	0.90		—	—		5.1	1.5		—	—	

† Died 3 hrs. 45 min. after injection of lead.

* Died 2 hrs. 40 min. after injection of lead.

The average amount of lead in the liver was not reduced by dimercaprol in the rabbits and the amount of lead in the small intestine in one of the control animals was much higher than any previously observed by us. As the bile duct was ligated, this suggests that lead is also excreted directly by at least some part of the alimentary canal. The high value was associated with considerably more handling of the gut than usual in the operative procedure and was perhaps due to consequent hyperaemia. The present results for tissues are very variable and cannot be compared with the findings in normal rabbits.

SUMMARY

Dimercaprol increases the excretion of lead in the bile of anaesthetized rabbits.

We are indebted to Miss Irene Munro for technical assistance, and to the Therapeutic Research Corporation for a personal grant to one of us (M.G.), and to the Medical Research Council for a grant for expenses to the other of us (M.W.).

REFERENCE

Ginsburg, M., and Weatherall, M. (1948). *Brit. J. Pharmacol.*, **3**, 223.