Reprinted from THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 96, No. 2, June, 1949

R

725144

STUDIES OF THE METABOLISM OF GALLIUM[1]

H. C. DUDLEY, G. E. MADDOX AND H. C. LA RUE

Naval Medical Research Institute, National Naval Medical Center, Bethesda 14, Maryland

Received for publication January 28, 1949

In a previous report (1) the findings on the toxic properties of gallium have been reviewed. In order to elucidate in part the mode of action of gallium a study of certain biochemical phases of the problem have been carried out. In this report we give results of the following studies, (a) influence of time on the excretion and retention of injected gallium in the rat and rabbit, (b) influence of time and route of administration on blood gallium, and (c) influence of injected gallium on formed elements of the blood.

EXPERIMENTAL. *Influence of time on clearance of gallium in rats.*—The analytical method used in the determination of gallium in tissues and excreta has been given in detail previously (2). It is this method which has been used in the determination of the gallium content of the tissues of rats following a single near-lethal injection of gallium lactate (1, 3). Two or more of these rats were killed at stated intervals from four hours to 180 days following the subcutaneous injection of 100 mgm. Ga/kgm. body weight. Duplicate determinations of gallium content of the liver, kidney and femur from each animal were carried out. In figure 1 are shown the results of the analysis of tissues from rats killed at the indicated intervals. Of particular interest is the rapidity with which gallium enters bone (femur) and is retained there in appreciable quantities for more than 90 days. The liver and kidney while having moderate to high concentrations initially lose much of the gallium by 30 days and are all at a low level after 60 days.

Control animals show no detectable gallium in any tissue with the possible exception of bone. Indications are that normal bone may contain traces of gallium, but of such small magnitude as to be below the threshold of the analytical procedure (<1 ppm).

Rate and route of excretion of gallium by the rabbit.—To determine the rate and route of excretion of gallium in the rabbit, four grown albino rabbits were injected with gallium lactate, 90 to 100 mgm. Ga/kgm. body weight. These animals were individually housed in metabolism cages and the urine and feces collected periodically for a period of ten days.

In table 1 are shown the results of studies of the excretion of injected gallium. In these four rabbits the urine accounts for 96 per cent of the gallium excreted. The balance was found in the feces and it seems probable that even this small amount may be due to contamination of the feces by the urine. As will be seen, the gallium rapidly makes its appearance in the urine at a high level, but the drop

[1] The opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or the endorsement of the Navy Department.

REPOSITORY Records Holding Area Bldg. 499
COLLECTION Protocols - Clinical
BOX No. 4
FOLDER Human Protocols 1950-1963

1176170

is rapid so that after three days the urinary gallium approaches a constant low level, less than 1 mgm. Ga/day, which continues more than ten days.

In view of the retention exhibited by the rats (fig. 1) the retention by the rabbit of injected gallium is also significant. The total subcutaneous dose of gallium lactate was 90 to 100 mgm. Ga/kgm., and by summation of the total excreted in ten days, we find that more than 85 per cent of the original amount of gallium was fixed in tissues ten days following the injection. This confirms the rat findings and indicates probable marked absorption by the skeletal tissues.

Further study of the gallium content in bone of rats and rabbits has shown that both the soft marrow and periosteum contain approximately the same gallium content as muscle (2 to 6 ppm) whereas the hard structure (cortex) contains 50 to 150 ppm. The trabecular bone (spongy) is still richer, containing from 100 to 300 ppm. This deposition occurs in large part within four hours after injection with gallium lactate and is carried to completion within 24 hours.

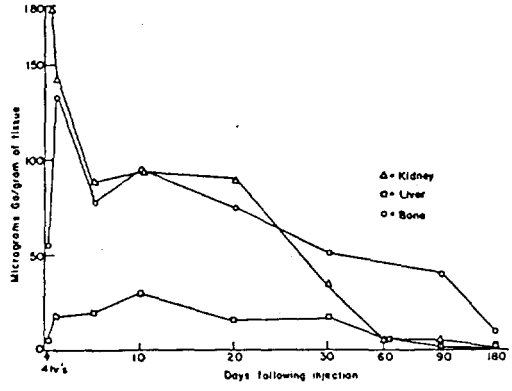

FIG. 1. Ga content of tissues of rats following subcutaneous injection of 100 mgm. Ga/kgm. as gallium lactate.

Gallium in blood.—To determine the influence of gallium on the blood, twelve rabbits were injected with gallium lactate, 20 to 35 mgm. Ga/kgm., and bled periodically by heart puncture and the oxalated blood centrifuged. The cells were washed with 0.9 per cent saline, while plasma was analyzed directly for gallium. Analyses of blood plasma from animals injected subcutaneously were compared with results from the same dose of gallium lactate given intravenously in order to determine the influence of mode of administration on plasma gallium.

In figure 2 are presented data derived from studies of rabbits injected intravenously with the indicated dose of gallium lactate. As will be seen whole blood contains considerably less gallium per cc. than does plasma. By washing the cells with 0.9 per cent saline it was found that while no significant amount of gallium is contained in the cells, all is carried by the plasma. As will be seen the ultimate plasma gallium is not affected by increases in dosage, since the fall is quite rapid and at 24 hours the two dosage levels have yielded plasma levels of 1 to 3 microgm. Ga/cc. plasma. These studies were continued for fourteen days at which time the plasma concentration was approaching a trace level (<0.2 microgm./cc.). From two to fourteen days the plasma levels gradually de-

1176171

creased from about 2 ppm to the 0.2 ppm level. The points shown on the curves in figure 2 are the average of values obtained from three or more animals. Analyses were run in duplicate.

To determine the influence of route of administration on plasma gallium rabbits were injected with gallium lactate, 20 mgm. Ga/kgm., subcutaneously or intravenously. At intervals thereafter blood was taken by heart puncture and the gallium content of the plasma determined. The intravenous results are shown in Curve B of figure 2. The subcutaneous dosage gave values of 10 to 15 microgm. Ga/cc. plasma one hour after injection. There was no further rise in plasma gallium and the concentration slowly fell to 1–3 microgm. Ga/cc. plasma at 24 hours, identical to the intravenously injected animals. This finding is explained by the slower absorption from the subcutaneous tissues since these tissues, at the site of injection, still contain considerable gallium three days after injection of the lactate.

TABLE 1

Excretion of gallium following subcutaneous injection of Ga lactate (mgm. gallium excreted during intervals shown)

RABBIT NO.	TOTAL DOSE OF GA MGM.[1]	EXCRETED IN URINE					EXCRETED IN FECES					% OF TOTAL DOSE EXCRETED IN 10 DAYS
		0–24 hrs.	24–48 hrs.	48–72 hrs.	72–120 hrs.	120–240 hrs.	0–24 hrs.	24–48 hrs.	48–72 hrs.	72–120 hrs.	120–240 hrs.	
1	302	19.1[2]					0.32[2]					
2	272	25.5		3.0	1.1	4.2	0.06		0.31	0.28	0.09	12.8
3	246	20.9	6.0	2.3	1.4	4.8	0.01	0.13	0.12	0.57	0.23	15.2
4	247	8.6	10.3	3.6	1.8	3.9	0.07	0.11	0.04	1.80	0.77	12.5

[1] Dosage 90–100 mgm. Ga./kgm. body weight.
[2] Death followed this period.

Examination of the slopes of the plasma curves in figure 2 will show that at very high plasma gallium levels the combination of excretion and tissue deposition is quite rapid. The slope of the curves from 15 to 24 hours indicates that there is a second fixation process. Therefore the curves as observed seem to be a resultant of two independent processes, the nature of which we have no knowledge at this time.

Influence of gallium lactate on formed elements of blood.—Rabbits, injected with near-lethal, and often lethal quantities of gallium lactate have shown no significant or marked changes in the formed elements of the blood. The rabbits used in these studies were those used in the toxicity determinations and represent a total of twenty animals. These rabbits had received gallium lactate intravenously in excess of 20 mgm. Ga/kgm. or if treated subcutaneously received in excess of 90 mgm. Ga/kgm.

There was often a transitory decrease in the lymphocytes and an increase in segmented cells in 24 to 48 hours after injection, which lasted less than 48 hours. The total white cell count was within normal limits, as were the erythrocytes.

1176172

In terminal stages total white cell counts did increase, however this is considered to result from terminal pneumonia since the animals died of respiratory failure, probably caused by paralysis.

DISCUSSION. From a study of the data presented in this paper, together with the toxicity, and distribution studies reported previously it seems probable that in gallium we have a new tool for the study of bone metabolism, both in the embryonic and post natal stages. By the analytical procedures developed it is possible to determine micro quantities of gallium, so that administration of non-toxic amounts of gallium lactate will occasion no great change in the metabolic economy and will serve to tag bone structures at different stages of development.

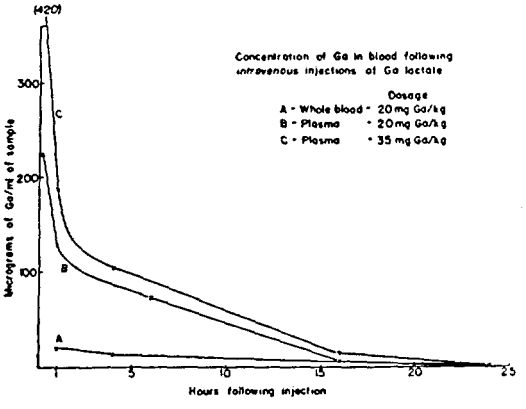

FIG. 2

SUMMARY AND CONCLUSIONS

Excretion of injected gallium is via the urine, with greater than 85 per cent of a near toxic dose retained in the rabbit more than ten days.

The liver and kidney fix appreciable quantities of the gallium where it is retained in part for more than 30 days. Gallium enters the bone rapidly, in less than four hours, and is retained in large degree for more than 90 days.

Gallium is transported wholly by the plasma, but is largely cleared therefrom within 24 hours. The influence of the amount of intravenous gallium is transitory since at 24 hours the plasma has attained a constant level of 1 to 3 microgm./cc. The mode of injection influences markedly the initial plasma gallium levels. Intravenously the plasma gallium is initially high and drops rapidly during the first six hours while subcutaneous injection produces only a moderate plasma concentration, which falls slowly to a constant figure by the end of 24 hours.

No significant changes were observed in the formed elements of the blood by injection of fatal or near-fatal amounts of gallium lactate.

It is suggested that gallium may prove to be a new tool for the study of bone metabolism, both in embryonic and post natal stages of growth.

REFERENCES

1. DUDLEY, H. C., AND LEVINE, M. D.: THIS JOURNAL, (In Press).
2. DUDLEY, H. C.: THIS JOURNAL, (In Press).
3. DUDLEY, H. C., AND GARZOLI, R. F.: J. Amer. Chem. Soc., 70: 3942, 1948.

1176173