The Excretion of Gallamine in the Dog

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The excretion of ^{3}H-gallamine was studied in the dog. Eighty-four per cent of the drug was recovered unchanged from the urine in 24 hours. Following ligation of both renal pedicles a sustained blood gallamine concentration was maintained for 24 hours, producing prolonged paresis. Unlike ^{3}H-*d*-tubocurarine, ^{3}H-gallamine was excreted in the bile in negligible amounts only.

GALLAMINE TRIETHIODIDE (Flaxedil) has been used as a neuromuscular blocking agent in anesthetic practice since 1948. In a study of its pharmacologic properties, Mushin *et al.*[1] reported that 20–80 per cent of the drug was recovered from the urine of rabbits in two hours. The amount of drug was estimated by biological assay. Because of the lack of suitable chemical methods for assaying gallamine, there has been no confirmation of this original work. In spite of the wide variation in the amount of drug recovered reported by these authors, it has become accepted that gallamine is largely excreted unchanged in the urine. Reports of prolonged paresis following the administration of gallamine to patients with renal failure[2, 3, 4] have justified this assumption. Cohen *et al.*[5] demonstrated that *d*-tubocurarine is also largely excreted unchanged in urine, yet there have been relatively few reports of prolonged paresis following the use of this drug in patients with renal failure.[6, 7] Furthermore, in no case has the prolongation of action reported been as great as that found with gallamine. This suggested the possibility that there is a fundamental difference in the way the body excretes the two drugs. The present study was undertaken to ascertain the role of renal excretion in the termination of action of gallamine and the effect of renal failure upon elimination of the drug.

Method

Thirteen mongrel dogs (16.3–23.5 kg) were used for this study. The animals were anesthetized with intravenous sodium pentobarbital, 30 mg/kg. Following intubation, the lungs were artificially ventilated and a stable *p*H, 7.40 to 7.46, was maintained throughout the experiment. An infusion of Ringer's lactate solution was started at a rate of 5.0 ml/kg/hour and maintained at a level sufficient to ensure diuresis. The femoral artery was cannulated for monitoring blood pressure and for withdrawal of blood samples. In three animals, exhaled water was collected by passing the expired gases through a cold trap-condensing system. In ten animals an indwelling catheter permitted collection of total urinary excretion. In three animals renal function was ablated by double ligation of both renal pedicles. In seven animals, the common bile duct was cannulated after prior ligation of the cystic duct to allow collection of the total biliary excretion. All animals received minimal supplementary doses of pentobarbital to ensure unconsciousness.

Each animal received an intravenous injection of 2 mg/kg gallamine containing 100–200 μc ^{3}H-gallamine § diluted with nonradioactive drug. Blood, urine, exhaled water, and bile were sampled periodically and radioactivity

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§ Tritiated gallamine was supplied by Nuclear Chicago, Des Plaines, Ill. The preparation was back-exchanged at 37–40 C, *p*H 7.4 for several days until constant activity was obtained. Purity was confirmed by descending paper radiochromatography. The specific activity of the final product was 365 μC/mg.

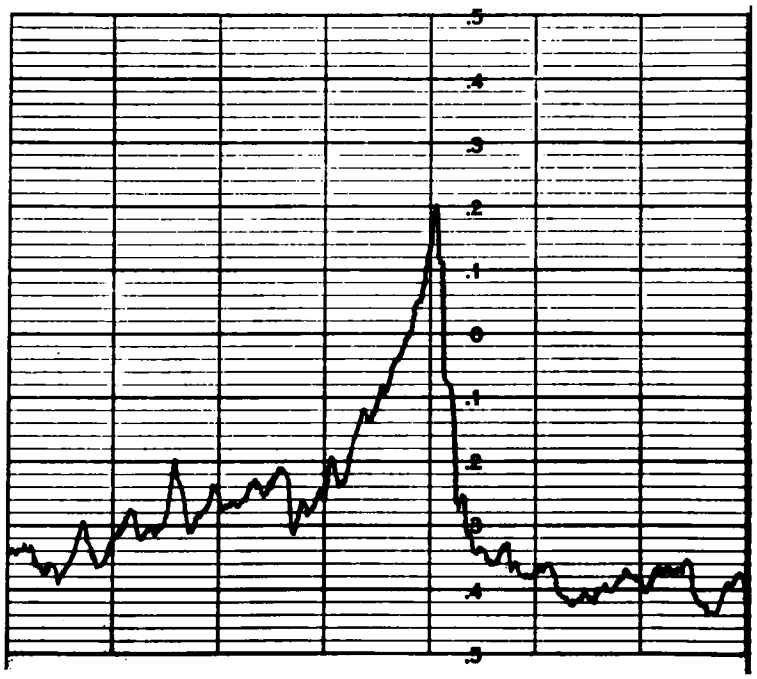

FIG. 1. Descending paper radiochromatogram of urine from a dog that had received ^{3}H-gallamine.

content determined by liquid scintillation counting.¶

Blood samples were withdrawn into heparinized syringes and the plasma separated by centrifugation. 0.1 ml of plasma was mixed with 10 ml dioxane or with toluene x-100 mixture * in a scintillation vial. There was good correlation between the radioactivity of the samples counted by both methods. Where both methods were employed, the mean was used in calculating the results. Samples of urine were counted in a toluene NCS † mixture or toluene x-100 mixture. Acidification of the toluene NCS mixture was required to prevent chemiluminescence. Radioactivity of the bile samples (0.5 ml) was determined following dilution with an equal volume of water. Scintillation counting was in dioxane. Quench suppression factors were determined for each counting system used and for each type of biological sample.

Samples of urine collected during the experiment were concentrated and subjected to descending paper radiochromatography. This procedure confirmed that the tritium activity in the urine was associated with a compound identical to that of the original ^{3}H-gallamine (fig. 1).

The extent to which the presence of red blood cells modified the plasma ^{3}H-gallamine content was studied *in vitro* with both dog and human blood. A known amount of ^{3}H-gallamine was added to blood of known hematocrit and incubated at 37 C for two hours. The difference between the initial plasma ^{3}H-gallamine content and that at equilibration represented loss on to, or into, the red blood cell. The total amount of gallamine in the circulating blood was calculated from the plasma concentration, assuming a red blood cell volume of 40 per cent and a blood volume of 100 ml/kg.

In an additional two experiments, the degree of neuromuscular block was correlated with the blood content of gallamine. The hypoglossal nerve was stimulated supramaximally at a rate of one per sec. The resultant tongue twitch was recorded with a Statham strain-gauge transducer (GI-95021). Gallamine, 2 mg/kg, containing 200 μC ^{3}H-gallamine, was then injected, and blood samples were withdrawn at 15-minute intervals and

¶ Beckman scintillation system.
* Triton x-100 (Beckman No. 161405).
† Nuclear Chicago Solvent.

the radioactivity determined. The degree of neuromuscular block and the effect of tetanus were observed at each interval.

Results

Intact Renal Function

Urine (*Table 1*). The ^{3}H-gallamine was largely excreted by the kidneys. Following a fluid load, 84 ± 3.6 per cent of the drug was recovered from the urine in 24 hours. Excretion was maximal during the first hour, and by the second hour had accounted for 56 ± 7.4 per cent of the drug given (fig. 2).

Bile (*Table 2*). Minimal amounts of ^{3}H-gallamine were recovered from the bile. Within 12 hours only 3.5 ± 1.4 per cent of the drug was present in the bile.

Exhaled Water. Less than 0.1 per cent of the injected tritium was recovered from the exhaled water over a six-hour period. This provides evidence for a lack of back exchange and also suggests that the gallamine is not metabolized to a significant extent in the body.

Table 1. Percentage of Injected ^{3}H-gallamine Excreted in Urine

Time	Cumulative Percentage	
1 hour	37.9	±6.9
2 hours	56.0	±7.4
3 hours	65.0	±8.1
4 hours	67.8	±7.7
6 hours	73.8	±7.0
9 hours	76.7	±7.0
12 hours	78.2	±6.5
21 hours	79.2	±5.3
24 hours	84.3	±3.6

Blood (*Table 3*). The plasma:red blood cell distribution ratio of ^{3}H-gallamine in the dog was 2.5 to 1.0. This differed markedly from the distribution ratio in human blood, which was 1.34 to 1.0.

One minute following injection of ^{3}H-gallamine the blood content was 52.2 ± 6.0 per cent (fig. 3). By five minutes only 25.0 ± 4.5 per cent remained in the circulation, and at 30 minutes the blood contained 12.2 ± 1.5 per

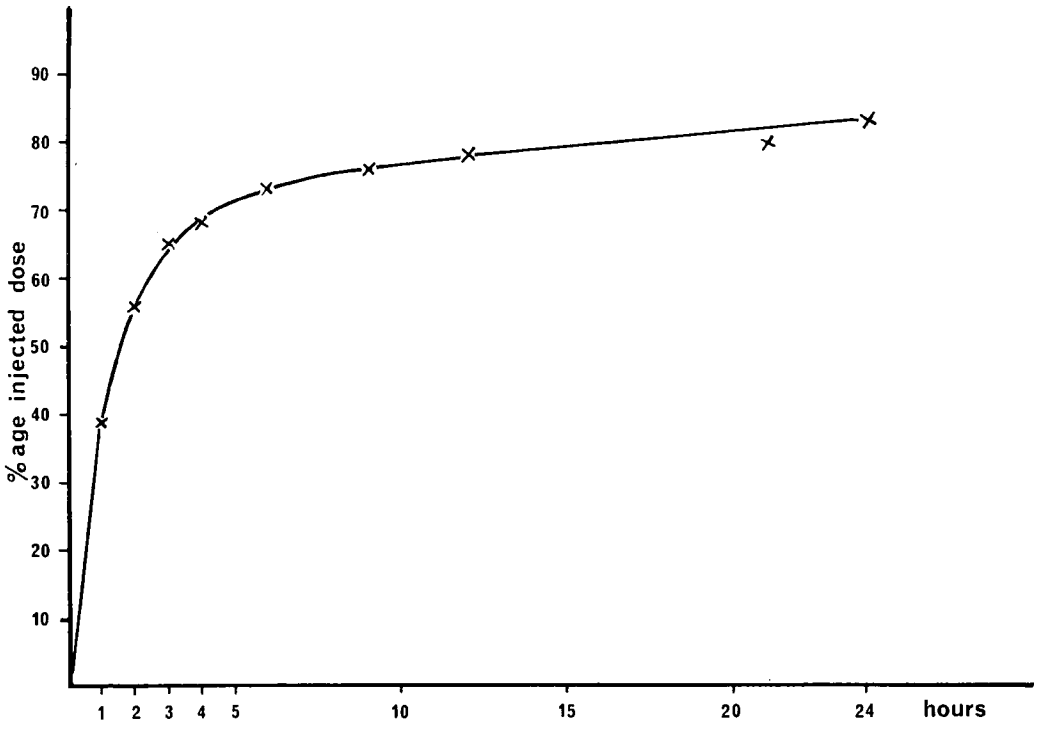

Fig. 2. Urinary excretion of ^{3}H-gallamine.

TABLE 2. Percentage of Injected ^{3}H-gallamine Excreted in Bile

Time	Cumulative Percentage	
1 hour	1.28	±0.8
2 hours	1.31	±1.1
3 hours	2.33	±0.9
4 hours	2.56	±0.8
5 hours	2.74	±1.1
6 hours	2.92	±1.2
9 hours	2.98	±1.2
12 hours	3.50	±1.4

cent of the drug. At this time spontaneous respiratory movement was frequently observed, suggesting this to be a subparalytic concentration. At one hour the blood contained 7.4 ± 0.8 per cent of the original dose of ^{3}H-gallamine.

BILATERAL RENAL PEDICLE LIGATION

Blood (*Table 4*). Figure 3 shows that bilateral renal pedicle ligation resulted in a delayed reduction in the initial ^{3}H-gallamine content of blood and also a considerable delay in the rate of fall of blood gallamine during a 24-hour period. By five minutes 32.2 ± 7.0 per cent of the drug was present in the blood, compared with only 25.0 ± 4.5 per cent in dogs with intact renal circulation. At 30 minutes, 17.5 ± 1.9 per cent of the drug was still present in the circulation, and at 24 hours 9.8 ± 1.2 per cent of the drug still remained in the blood. Twenty-four-hour blood levels in these animals were comparable to those found after 30–60 minutes in dogs with normal renal circulation.

TABLE 3. Percentage of Injected ^{3}H-gallamine in Blood Following Intravenous Injection of 2 mg/kg body weight

Time	Percentage	
1 minute	52.2	±6.0
5 minutes	25.0	±4.5
10 minutes	19.0	±2.2
30 minutes	12.2	±1.5
1 hour	7.4	±0.8
2 hours	4.1	±1.0
3 hours	2.9	±1.1
4 hours	2.3	±0.8
6 hours	1.6	±0.6
9 hours	1.2	±0.7
12 hours	1.4	±0.1
15 hours	1.3	±0.0
18 hours	1.2	±0.0
21 hours	1.2	±0.0
24 hours	1.1	±0.1

Bile (*Table 5*). In spite of the sustained high blood concentrations of ^{3}H-gallamine, there was negligible loss of the drug in the bile. Only 0.9 ± 0.1 per cent of the injected gallamine was recovered from the bile in 24 hours following bilateral renal pedicle ligation. This was actually less than the amount recovered from bile in dogs with normal renal circulation, although in both circumstances the biliary loss of gallamine was negligible.

In the tongue–hypoglossal nerve preparation, complete neuromuscular block was present until the blood gallamine level fell below 13.2 per cent of the injected dose, corresponding to a plasma gallamine concentration of 3.8 μg/ml. Muscle twitch returned to 50 per cent of its resting height when the blood content was 10.8 per cent and some degree of neuromuscular block was present until the blood content fell to 7.0 per cent, representing a plasma gallamine concentration of 1.94 μg/ml. At this plasma concentration no posttetanic facilitation was demonstrable, and tetanus was well maintained.

Discussion

It has been postulated, on the basis of clinical observations, that a combination of redistribution and renal excretion produces a fall in blood gallamine concentration and terminates the action of the drug.[8] This has been confirmed by the present investigation. Even in the absence of renal function, 69 per cent of the injected dose of gallamine leaves the circulation in five minutes. The drug is rapidly distributed in the extracellular-water compartments of the body, especially the lung, liver, spleen, muscle and cartilage.[9] If renal circulation is intact, the drug is concentrated seven- to eightfold in the kidneys prior to excretion.[9] Under these conditions even more of the drug leaves the circulation in the first five minutes. Although further equilibration between tissues and blood continues, it is urinary excretion that plays the final major role in reducing the blood gallamine level to below that which produces neuromuscular block.

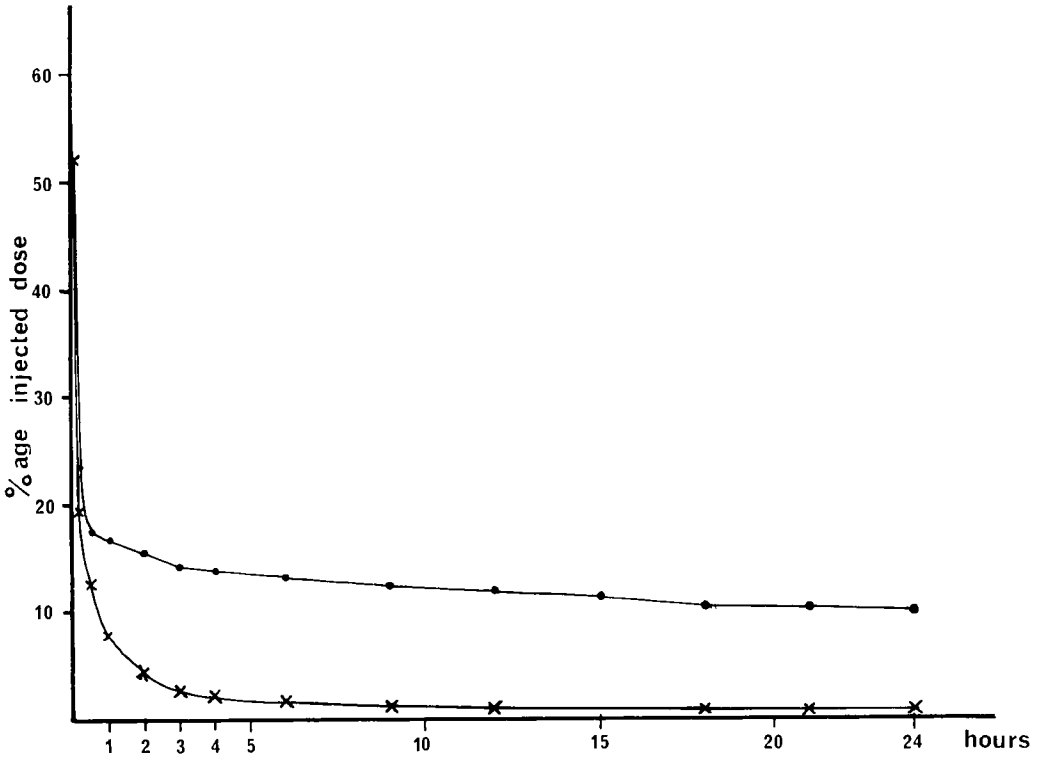

FIG. 3. ^{3}H-gallamine in blood following injection of 2 mg/kg. × = normal renal function; ● = following bilateral renal pedicle ligation.

Assuming that the duration of muscle paralysis depends upon the plasma concentration of gallamine, the first evidence of returning neuromuscular conduction should occur 35 to 45 minutes after the injection of 2 mg/kg. Fifty per cent of twitch would occur at 60 minutes, and full restoration of neuromuscular conduction should be established by 120 minutes. Following administration of the same dose of gallamine to animals with bilateral renal pedicle ligation, paralysis could continue for six to nine hours, and it should take approximately 18 hours for 50 per cent restoration of twitch height. Full recovery of neuromuscular conduction might be delayed several days.

Churchill-Davidson *et al.*[6] reported prolonged paresis following administration of gallamine to patients subjected to bilateral nephrectomy prior to renal transplantation. Although prolonged paralysis was recorded following the use of *d*-tubocurarine, it was less frequent and less prolonged. Strunin[7] used *d*-tubocurarine in patients prior to renal transplantation and reported that only one patient

TABLE 4. Percentage of Injected ^{3}H-gallamine in Blood Following Intravenous Injection of 2 mg/kg Body Weight (Bilateral Renal Pedicle Ligation)

Time	Percentage	
1 minute	56.0	±7.3
5 minutes	31.2	±7.0
10 minutes	23.3	±2.5
30 minutes	17.5	±1.9
1 hour	17.1	±2.1
2 hours	15.7	±1.0
3 hours	14.9	±0.8
4 hours	14.5	±1.5
6 hours	13.5	±2.1
9 hours	12.3	±1.3
12 hours	11.6	±1.9
15 hours	11.1	±2.0
18 hours	10.6	±1.4
21 hours	10.5	±1.3
24 hours	9.8	±1.2

TABLE 5. Percentage of Injected ^{3}H-gallamine Excreted in the Bile Following Intravenous Injection of 2 mg/kg Body Weight (Bilateral Renal Pedicle Ligation)

Time	Cumulative Percentage	
1 hour	0.08	±0.04
2 hours	0.14	±0.01
3 hours	0.20	±0.08
4 hours	0.27	±0.08
6 hours	0.39	±0.10
9 hours	0.52	±0.10
12 hours	0.62	±0.12
15 hours	0.71	±0.10
18 hours	0.83	±0.10
21 hours	0.85	±0.08
24 hours	0.89	±0.10

developed prolonged paresis. Cohen *et al.*[5] demonstrated that 74 per cent of the injected dose of *d*-tubocurarine could be recovered from the urine of dogs in 24 hours. However, when the renal pedicles were ligated, the biliary excretion of *d*-tubocurarine increased, accounting for more than 38 per cent of the injected dose, thereby causing an effective reduction in the blood curare level. From our present results, it would appear probable that the difference in the responses of patients with renal suppression to the two drugs is due to the absence of significant biliary excretion of gallamine and the presence of this alternative method of excretion for *d*-tubocurarine.

Conclusions

The duration of the clinical activity of gallamine is largely limited by redistribution and renal excretion of the drug. In the absence of renal excretion, blood levels of gallamine are sustained. Following a dose of 2 mg/kg, 10.3 per cent of the injected dose is still present in the blood at the end of 24 hours. Biliary excretion of gallamine is very limited and, unlike *d*-tubocurarine, gallamine is not lost in the bile to any significant extent following renal pedicle ligation.

References

1. Mushin, W. W., Wien, R., Mason, D. F., and Langston, G. T.: Curarelike actions of tri (diethylaminoethoxy) benzene triethiodide, Lancet 1: 726, 1949.
2. Montgomery, J. B., and Bennett Jones, W.: Gallamine triethiodide and renal disease, Lancet 2: 1243, 1956.
3. Fairley, H. B.: Prolonged intercostal paralysis due to a relaxant, Brit. Med. J. 2: 986, 1950.
4. Feldman, S. A., and Levi, J. A.: Prolonged paresis following gallamine, Brit. J. Anaesth. 35: 804, 1963.
5. Cohen, E. N., Brewer, W. H., and Smith, D.: The metabolism and elimination of *d*-tubocurarine H^{3}, ANESTHESIOLOGY 28: 309, 1967.
6. Churchill-Davidson, H. C., Way, W. L., and de Jong, R. H.: The muscle relaxants and renal excretion, ANESTHESIOLOGY 28: 540, 1967.
7. Strunin, L.: Some aspects of anaesthesia for renal homotransplantation, Brit. J. Anaesth. 38: 812, 1966.
8. Feldman, S. A.: Effect of changes in electrolytes, hydration and *p*H upon the reactions to muscle relaxants, Brit. J. Anaesth. 35: 546, 1963.
9. Cohen, E. N., Hood, N., and Golling, R.: Use of whole-body autoradiography for determination of uptake and distribution of labelled muscle relaxants in the rat, ANESTHESIOLOGY 29: 987, 1968.