KINETICS OF DISTRIBUTION
OF RADIOACTIVE LABELLED MUSCLE RELAXANTS
IV: URINARY ELIMINATION OF A SINGLE DOSE OF \(^{14}\text{C}\)-GALLAMINE

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SUMMARY

The urinary elimination and the kinetics of distribution of gallamine were investigated in dogs by intravenous administration of a single trace dose of radioactive \(^{14}\text{C}\) labelled gallamine. Although some aspects of the distribution of gallamine remain to be studied, the data of the present study suggest certain general conclusions of practical interest. Gallamine is eliminated in the urine at a higher rate than other muscle relaxants. The molecule of gallamine is eliminated intact. The duration of the muscle-paralyzing effect of gallamine coincides with a rapid distribution and with a limited urinary elimination. The role of urinary elimination becomes important during the phase following the muscular paralysis when the drug slowly disappears from plasma and from the extravascular compartment. Gallamine does not cross the blood-cerebrospinal fluid barrier. However, once injected into the subarachnoid space, it can easily diffuse into blood. Arterial hypotension, shock, hypoxia and hypercapnia decrease urinary elimination of gallamine. Diuresis—as per Ringer-lactate infusion—seems to correct the decreased urinary elimination during generalized arterial hypotension. Renal insufficiency, though probably not affecting the clinical response to a single dose of gallamine, might cause prolonged recovery from subsequent maintenance doses.

The concept that renal excretion per se can influence the duration of action of muscle relaxants is an interesting and an exciting one. Surprisingly enough, very few studies have been made along these lines, even in the experimental animal (Churchill-Davidson, Way and De Jong, 1967). Gallamine* is quoted as the muscle relaxant excreted at a higher rate by the kidneys (Mushin et al., 1949; Dougherty and Wylie, 1951; Foldes, 1957; Koelle, 1965; Dinnick, 1968; Evans and Gray, 1965; Wylie and Churchill-Davidson, 1966). However, convincing demonstration of this occurrence has not been provided, and no studies are available on the simultaneous distribution of gallamine within the body (Churchill-Davidson, Way and De Jong, 1967).

It was therefore felt appropriate to study the urinary elimination of gallamine and to find out if a correlation exists between urinary excretion and kinetics of distribution of the drug.

The investigation was conducted in dogs under normal conditions, and in dogs in which urinary function was directly or indirectly affected by arterial hypotension, haemorrhagic shock, provoked diuresis, hypoxia, hypercapnia, unilateral renal vessel ligation and bilateral ligation of the ureters. Single trace doses of gallamine, labelled with radio-carbon \(^{14}\text{C}\) at the nine ethyl groups were employed.

PROCEDURE

Twenty-five adult mongrel dogs, weighing between 12 and 18 kg, fasted for 12 hours and unpremedicated, were anaesthetized with an initial dose of 20 mg/kg of sodium pentobarbitone (Nembutal) intravenously. When necessary, anaesthesia was maintained with repeated doses of pentobarbitone equal to about half of the initial dose.

* Distributed as Flaxedil by Davis & Geck.
ventilation with air was maintained throughout the experiment with a ventilator set at a rate of 12 cycles/min, and a tidal volume of 300–400 ml through a cuffed endotracheal tube. Arterial blood pressure, lead II of the e.c.g., the e.e.g., as well as arterial pH, Po₂ and Pco₂ were recorded simultaneously at intervals throughout the experiments. Physiological saline solution was infused through an 18-gauge intravenous needle (8–10 drops/min) to maintain blood volume, extravascular fluid and constant urinary output for the duration of the experiments. Both ureters were cannulated and urine samples collected at intervals. After control values were established, a single dose of 50 μC of 14C-gallamine, specific activity 2.86 mc/mM, purity controlled with radiochromatography, labelled at the nine ethyl groups and equivalent to 50 x 10⁶ counts/min, was administered rapidly, intravenously.* Samples (average number, 7) of the following were taken during the 7 hours after injection: (a) 1.5–2.5 ml of arterial blood; (b) 0.5 ml of cerebrospinal fluid from the cisterna magna through an indwelling 22-gauge spinal needle; (c) a few ml of urine.

A parallel study was conducted in 19 dogs in which the following conditions were provoked: (a) arterial hypotension by intravenous infusion of trimetaphan camphor-sulphonate (Arfonad) (3 dogs), and by bleeding (6 dogs); (b) increased urinary elimination by administration of Ringer-lactate solution (1 dog); (c) hypoxia and hypercapnia by reducing the tidal volume (3 dogs); (d) unilateral and bilateral ligation of the ureters at the renal pelvis (6 dogs).

The radioactivity of 14C was determined with a liquid scintillation counting system according to a method previously described (Dal Santo, 1963). The concentrations of the radiolabelled drug in plasma, extravascular space, cerebrospinal fluid and urine, measured in counts/min, were expressed in percent of the radioactivity of the administered compound. Blood and plasma volume were calculated employing the 131I-serum albumin method (Albert, 1963).

### RESULTS

#### Control experiments.

Subsequent to the intravenous administration of a single dose of 14C-labelled gallamine to 25 dogs in the control group, the kinetics of distribution resulted as follows.

(a) **Disappearance from plasma.** In about 15 minutes, 75% of the administered drug, as expressed by the radioactivity of 14C, quickly left the plasma. This fast component of the disappearance curve was followed by a slower 2-hour component, during which only 20% of the radioactivity disappeared. From the third hour to the seventh, the concentration of 14C in plasma slowly decreased from 2% to 0.2% (fig. 1).

#### DISTRIBUTION of 14C-GALLAMINE

**Control dogs'**

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<th>Time in Hours</th>
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**Fig. 1.** Disappearance from plasma, cumulative urinary elimination, and passage into the extravascular space of radiocarbon (14C) following intravenous administration of a single trace dose of 14C-gallamine to control dogs. Qplasm is the amount of 14C in plasma at any time following the administration, Pvoi is the plasma volume in ml, ct is the content of 14C in 1 ml of plasma at time t from administration, A₁ is the amount of 14C in the extravascular space at any time t from injection, Q is the amount of radioactivity administered, Qextr is the amount of 14C excreted in urine at time t, Ceq is the amount of 14C in 1 ml plasma when plasma and extravascular compartment, having both attained a transient equilibrium point at time t0, both contain equal amounts (Ceq) of radioactivity, Gspace is the "total distribution volume" for gallamine. K₂ represents the transfer coefficient governing renal excretion, and K₄ the coefficient related to the passage into the extravascular compartment.

*14C-gallamine was obtained from the New England Nuclear Co., Boston, Massachusetts, 02118.
(b) Passage into the extravascular compartment.*
Coincident with the fast component of the curve of disappearance from plasma, a rapid passage of the labelled drug into the extravascular space occurred (fig. 1). After reaching an equilibrium point (Ceq) at a level equivalent to 45% of the administered dose, the concentration decreased exponentially, reaching the zero value 5 hours following injection.

c) Urinary elimination. Renal excretion was active from the beginning. In 15 minutes, an average of 30% of the radioactive material was eliminated after injection (fig. 1). Total elimination was approached in about 4 hours.

(d) Passage into the cerebrospinal fluid. Subsequent to the intravenous administration of 14C-gallamine, no significant radioactivity was found in the cerebrospinal fluid. However, when injected into the cisterna magna, radioactive material passed into plasma and urine (fig. 2).

(e) Metabolic studies. By using paper radiochromatography of urinary samples taken at various intervals after the intravenous administration of 14C-gallamine, it was possible to show the presence of “peaks” and Rf ratios,† identical to those obtained by scanning the radiochromatograms of the original (non-metabolized) 14C-gallamine (fig. 3). This proved that gallamine was eliminated unchanged.

With these data on hand, the Gspace, i.e. the total distribution volume (“gallamine space”), can be calculated. The formula for the calculation can be seen in figure 1. From the slopes of the components of the curve of disappearance of 14C-gallamine from plasma, the transfer coefficients K1 and K2 (fig. 1) can also be calculated (Solomon, 1949; Dal Santo and Campus, 1956; Dal Santo, 1964). K1 represents the transfer coefficient governing renal excretion, and K2 the coefficient expressing the passage rate into the extravascular compartment.

Experiments during abnormal conditions.
Subsequent to the intravenous administration of a single trace dose of 14C-gallamine to 19 dogs under experimentally provoked pathological conditions, maintained for an average of 5 hours, the results were as follows.

(a) Arterial hypotension. In 3 dogs to whom an infusion of a ganglionic blocking agent (trimetaphan 2 mg/ml) was administered, in order to maintain a sustained arterial systolic pressure of 40–60 mm Hg, the urinary elimination of 14C-gallamine was delayed and decreased (fig. 4). As a consequence, the rate of elimination from plasma was reduced and the passage and permanence in the extravascular space was prolonged. In another trimetaphan-treated dog, in which the rate of elimination of urine was increased above normal by the rapid administration of 1500 ml of Ringer-lactate solution, the distribution pattern was in the normal range (fig. 4).

(b) Bleeding. In 3 dogs, 500 ml of arterial blood was quickly bled. The blood pressure immediately fell to a level of 60/40 mm Hg. The trace dose of 14C-gallamine was then administered intravenously. The blood pressure spontaneously returned to an average of 115/80 mm Hg in 5 minutes, and stabilized around 130/110 thereafter. Whereas the rate of disappearance of the labelled drug from plasma was similar to that of the control animals (fig. 5), urinary elimination was markedly decreased. The permanence of the radioactive material in the extravascular space was prolonged and at higher levels. In 3 other animals, subsequent to an initial bleeding of an average of 500 ml, additional fractional bleedings (50–100 ml) were provoked throughout the 4-hour procedure. The total additional bleeding amounted to ± 200 ml. Under these conditions: (1) the urinary elimination was further
FOLLOWING ADMINISTRATION

Fig. 3. Radiochromatograms of urinary samples, taken at various intervals, subsequent to the intravenous administration of a single trace dose of $^{14}$C-gallamine. Patterns and $R_f$ ratios are identical to those obtained by scanning the radiochromatograms of the original (non-metabolized) $^{14}$C-gallamine.

reduced; (2) the passage into the extravascular space was even more prolonged; (3) the content in the extravascular space remained persistently close to 80% of the administered amount (fig. 5), whereas this amount was only 45% ($C_{eq}$) in the control animals, in whom, also, it was only momentarily maintained.

(c) During hypoxia and hypercapnia, as provoked by reduced ventilation in 3 dogs, maintained for 4 hours at an arterial blood pH of 7.14–7.08, at a $P_{CO_2}$ of 90–96 mm Hg, and at an arterial $P_{O_2}$ of 40–70 mm Hg, the urinary elimination of $^{14}$C-gallamine was reduced to about two-thirds of the control value (fig. 6). The rate of disappearance of

the drug from plasma was within the normal range and its presence in the extravascular compartment was prolonged.

(d) During unilateral ligation of the renal pedicle in 3 dogs, the cumulative urinary elimination decreased to about half of the control values, and the rate of disappearance from plasma was diminished (fig. 7). In 3 other dogs, in whom the ureters were ligated bilaterally at the renal pelvis, the disappearance from plasma was very slow and the drug passed nearly in toto into the extravascular compartment (fig. 7).

DISCUSSION

After intravenous administration to dogs under control conditions of a single radiolabelled dose of gallamine was excreted in the urine. The urinary elimination was active from the beginning: 30% during the first 15 minutes, 80% after 2 hours, approaching 100% 4 hours after injection.

By correlating the curve of urinary elimination of $^{14}$C-gallamine (fig. 1) with the other curves of dis-
DISTRIBUTION OF RADIOACTIVE LABELLED MUSCLE RELAXANTS

**Fig. 5.** Disappearance from plasma, passage into the extravascular space, and urinary elimination of a single intravenous trace dose of $^{14}$C-gallamine administered to dogs subsequent to arterial bleeding.

**Fig. 6.** Disappearance from plasma, passage into the extravascular space, and urinary elimination of a single intravenous injection of a trace dose of $^{14}$C-gallamine to dogs subsequent to hypoxic hypoxia and hypercapnia.

**Fig. 7.** Disappearance from plasma, passage into the extravascular space, and urinary elimination of a single intravenous trace dose of $^{14}$C-gallamine administered to dogs subsequent to unilateral ligation of a renal pedicle and to 3 dogs following bilateral ligation of the ureters at the level of the renal pelvis.

If we compare the kinetics of distribution of $^{14}$C-gallamine in dogs with that of radiolabelled dimethyl tubocurarine (Dal Santo and Petrilli, 1963; Dal Santo, 1964) and suxamethonium (Dal Santo, 1968)* (fig. 8), it can be seen that gallamine is eliminated in the urine at a higher rate, the disappearance from plasma is more rapid, and its permanence in the extravascular space shorter.

So far, we have expressed the kinetics of distribution of gallamine in terms of radioactive carbon.

* In the case of suxamethonium, it must be pointed out that a large percentage of the labelled material in urine represents metabolites of $^{14}$C-succinyldicholine.
The distribution of muscle relaxants (control dogs) in plasma, extravascular space, and urine is illustrated in Figure 8. It shows the disappearance from plasma, passage into the extravascular space, and urinary elimination of single intravenous trace doses of $^{14}$C-gallamine, $^{14}$C-dimethyl tubocurarine, and $^{14}$C-suxamethonium (control dogs). The interdependence of the curves of the distribution of $^{14}$C-gallamine in plasma, extravascular space, and urine in the control animal (Figure 1) may explain why the muscle-paralyzing effect of a single dose of gallamine lasts 15–20 minutes. In fact, this duration coincides remarkably well with the phase of fast disappearance of the drug from plasma, with the phase of rapid diffusion into the extravascular space and with a rather limited urinary elimination. It appears obvious then, that in the absence of metabolism of the drug, rapid distribution more than urinary elimination is responsible for this duration. Furthermore, the peak of the curve of concentration in the extravascular space may reflect the rate at which gallamine diffuses to and from its site of action during the period of full paralyzing effect.

The observation that, at the end of the 15–20 minute muscle-paralyzing effect of an initial single dose of gallamine, an average of 70% of the drug is still in the organism, may suggest that, at this moment, the concentration of the relaxant at the endplate is non-effective and/or that some fraction of the drug may be present in an inactivated form or merely in a depot form. In this last regard, it could be supposed that a sizeable fraction of the drug is bound to plasma and to other proteins of the organism. This was observed to happen with suxamethonium (Dal Santo, 1968). If this is also the case with gallamine, we can anticipate that plasma binding results in the formation of a pharmacologically inactive complex, with no access to sites of action. Furthermore, the protein-drug linkage being a labile one, the possibility exists that the drug is liberated from its labile combinations. Obviously, once released, gallamine could produce delayed muscle-paralyzing effects.

![Distribution of Muscle Relaxants](https://academic.oup.com/bja/article-abstract/44/4/321/268146)

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![Schematic Representation of Kinetics of Distribution](https://academic.oup.com/bja/article-abstract/44/4/321/268146)

A schematic representation of the kinetics of distribution, under normal conditions, of gallamine is shown in Figure 9. It is postulated that gallamine, while being mainly excreted in the urine, may interact with plasma protein and with cells and endplate "receptors". Urinary elimination affects the kinetics of distribution of gallamine more significantly than in the case of tubocurarine (Dal Santo, 1964; Dal Santo and Petrilli, 1963) and suxamethonium (Dal Santo, 1968).

Convincing experimental evidence of a passage into the central nervous system and of central effects of gallamine is not available. That no radioactivity was present in the various compartments (plasma, extravascular space, urine, cerebrospinal fluid). However, convincing evidence that gallamine is not metabolized is provided by the radiochromatographic data of the urinary samples (Figure 3). This is also suggested by the finding that other onium compounds do not undergo biological transformation in the intact animal (Doughty and Wylie, 1951; Dal Santo, 1964, 1968; Levine, 1959; Levine and Clark, 1957; Paton and Zaimis, 1952; Milne and Olesky, 1951; Zaimis, 1950). It can therefore be reasonably concluded that the radioactivity of $^{14}$C traces the kinetics of distribution of the labelled gallamine.

![Schematic Representation of Kinetics of Distribution and Reversible Interactions](https://academic.oup.com/bja/article-abstract/44/4/321/268146)
detected in the cerebrospinal fluid suggests that gallamine does not cross the “blood-to-cerebrospinal fluid barrier” and presumably does not exert central actions when given intravenously. However, when 14C-gallamine is injected directly into the subarachnoid space (cisterna magna), it can easily diffuse into plasma. Both these facts might prove that a “blood-brain barrier” for gallamine is located between arterial blood and cerebrospinal fluid and not between cerebrospinal fluid and brain tissue. This is not necessarily true; in fact, it has been shown that quaternary ammonium compounds may leave the cerebrospinal fluid through the arachnoid villi and the choroid plexuses (Dal Santo, 1968; Schanker et al., 1962; Prockop and Schanker, 1962; Schanker, 1962).

Arterial hypotension, arterial haemorrhage, hypoxic hypoxia, and ligature of one renal pedicle affect in varying degrees the urinary elimination of a single intravenous dose of gallamine. The only exception was the case of arterial hypotension when urinary flow was increased with a higher infusion rate of Ringer-lactate solution. In this case, the urinary elimination of gallamine was within the control range, thereby suggesting that in the presence of a sustained arterial hypotension, an adequate fluid volume at the level of the kidney, as well as an adequate renal blood flow, could maintain urinary elimination of gallamine. This can be expected in view of the compensatory mechanisms for low arterial blood pressure, which can be activated by the renal circulation (Wylie and Churchill-Davidson, 1966). In fact, urinary elimination of gallamine was decreased when, as after bleeding, circulating volume was affected (fig. 5).

The decreased renal elimination of gallamine during arterial hypotension, haemorrhage, hypoxic hypoxia, and hypercapnia, can be attributed to renal damage, as has been reported to occur for other drugs in all these conditions (Corcoran and Page, 1963; Phillips et al., 1946; Van Slyke, 1948; Selkurt, 1946; Schnedorf and Orr, 1941; Toth, 1937; Van Liere et al., 1935; Stickney, Northup and Van Liere, 1946; Selkurt, 1953; Axelrod and Pitts, 1952; Stone et al., 1958; Franklin, McGee and Ullmann, 1951; Kopecky et al., 1952; Brassfield and Behrmann, 1941; Adolph, 1935; Barbour et al., 1953; Barker et al., 1956; Dows, Brickner and Selkurt, 1953; Brazeau and Gillman, 1953; Dorman, Sullivan and Pitts, 1954).

A decreased urinary elimination of gallamine obviously implies a retention of the drug. However, clinical evidence suggests that under the pathological conditions studied, the duration of action of a single dose of gallamine is not affected. This might well be for the reasons discussed above, i.e. that urinary elimination does not condition the duration of the muscle-paralyzing effect of gallamine, but rapid distribution does. Urinary elimination enters the picture when the muscle-paralyzing effect of a single dose is dissipated. It is, therefore, fair to expect that, if renal insufficiency seems not to affect the muscle-relaxant response to a single dose of gallamine, it might cause prolonged recovery from subsequent maintenance doses.

REFERENCES


CINETICA DE LA DISTRIBUCION DE RELAJANTES MUSCULARES MARCADOS RADIOACTIVAMENTE

IV: ELIMINACION URINARIA DE UNA SOLA DOSIS DE 14C-GALLAMINA

RESUMEN

La eliminación urinaria y la cinética de la distribución de gallamina fueron investigadas en perros por medio de la administración intravenosa de una sola dosis trazadora de gallamina marcada radiactivamente con 14C. Aunque quedan por estudiar algunos aspectos de la distribución de la gallamina, los datos del presente estudio permiten ciertas conclusiones generales de interés práctico. La gallamina es eliminada en la orina a una velocidad superior que otros relajantes musculares. La molécula de gallamina es eliminada intacta. La duración del efecto paralizante muscular de la gallamina coincide con una distribución rápida y con una eliminación urinaria limitada. El papel de la eliminación urinaria adquiere importancia durante la fase consiguiente a la parálisis muscular, cuando el medicamento desaparece lentamente del plasma, y del compartimiento extravascular. La gallamina atraviesa la barrera sangre-líquido cerebrospinal. Sin embargo, si es inyectada dentro del espacio subaracnoideo puede difundirse fácilmente por la sangre. La hipotensión arterial, shock, hipoxia e hipercapnia disminuyen la eliminación urinaria durante la hipotensión arterial generalizada. La insuficiencia renal, aunque probablemente no afecta la respuesta clínica a una dosis única de gallamina, pudiera causar una prolongación de la recuperación después de dosis subsiguientes de mantenimiento.

BOOK REVIEWS


This volume is concerned with the production of disease in the respiratory tract of experimental animals and in particular with bronchopulmonary inflammation, cough, asthma and lung oedema.

In contrast to the other sections, that devoted to bronchopulmonary inflammation is written in English. It contains a review of the methods used to induce inflammation and distention of the lung. Emphasis is placed on the choice of experimental animal and on the need for careful assessment of the results, if the methods are to achieve a better understanding of human bronchitis and emphysema, and to serve as a basis for pharmacological study.

Following an elaborate consideration of the procedures which may be used to induce cough in animals, there is a description of the techniques by which cough can be artificially produced in normal human subjects. Since, however, the actions of drugs on artificially induced cough do not correlate with findings at the bedside, in that subjective feelings of the sick person do not come into the picture, the need is emphasized for further study of the methods by which artificial cough may be induced in man.

Bronchial asthma is considered with respect to allergic asthma and the asthma reaction produced by other agents. The condition is discussed with reference to the unanaesthetized and anaesthetized animal. One of the advantages of the anaesthetized animal is that it allows a more detailed analysis of the disturbances of respiratory function. Asthma reactions are also discussed in relation to the isolated lung.

In the review of lung oedema, the author describes briefly what is meant by the condition. Some of the difficulties involved in the differentiation of lung oedema from other conditions are also mentioned. The general aspects of lung oedema are followed by a consideration of factors involved in its production. Attention is devoted not only to methods used to diagnose and assess the degree of oedema in the lungs of the living animal and in animals at postmortem, but also to oedema occurring during lung perfusion. This is followed by a discussion of the methods used to produce lung oedema, for example by changes in respiratory resistance and inhalation of noxious substances.

This comprehensive multi-author book is a mine of information, well illustrated and equipped with a rich supply of experimental details and references. It should prove invaluable to those concerned with the experimental approach to respiratory disease.

H. Wilson


This small book of 129 pages, priced at £1, deals with the unconscious patient and "is written for those who intend to care for patients remaining unconscious or dependent for weeks or months". It is a basic and practical text most appropriate to junior nurses preparing to work in an intensive care unit or a neurosurgical unit. Such readers will find this book helpful in giving the fundamental facts on which they can begin to build the complex structure of knowledge and experience necessary to nurse effectively in such intensive care areas.

D. G. McDowall