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A PRELIMINARY INVESTIGATION OF THE RENAL AND HEPATIC EXCRETION OF GALLAMINE TRIETHIODIDE IN MAN

S. AGOSTON, G. A. VERMEER, U. W. KERSTEN AND A. H. J. SCAF

SUMMARY

The fate of gallamine triethiodide has been investigated in patients undergoing cholecystectomy with choledochostomy (group I), pelvic operations (group II) and orthopaedic operations (group III). Following a single i.v. injection of gallamine 2.5 mg kg^{-1} the disappearance of the drug from the serum occurred in three phases with half-lives of less than 5, 30, 138 min, less than 5, 39, 141 and less than 5, 48, 144 min in the respective groups. Twenty-four hours after injection the renal excretion of the unchanged drug was 53% (15–100%) of the administered dose in group I, 67% (40–90%) in group II and 95% (89–100%) in group III. The biliary excretion of gallamine appeared to be negligible in man. The relationship between renal excretion and duration of action of gallamine, and the influence of some intraoperative factors on drug disposition, are discussed.

It has been accepted generally that gallamine triethiodide is excreted unchanged in the urine. Furthermore, it has been assumed that the renal excretion of gallamine is the prime determinant of the duration of action of this compound (Churchill-Davidson, Way and de Jong, 1967; Anand et al., 1972). As a consequence many clinicians consider the use of gallamine in patients with established or potential renal insufficiency (McLaughlin et al., 1972), or undergoing bilateral nephrectomy (Churchill-Davidson, Way and de Jong, 1967; Singer, Dutton and Way, 1971) to be contraindicated. Prolonged, sometimes fatal postoperative neuromuscular block has been reported after the use of gallamine in such patients (Joske, Ebeling and Stanistreet, 1954; McLaughlin et al., 1972). A different point of view was expressed, however, by White, De Wreed and Dawson (1971). Based on their experience with 17 patients undergoing bilateral nephrectomy, they concluded that gallamine, in relatively low dosage, can be used with safety even in patients with no renal function.

These controversial views and the lack of quantitative data on the fate of gallamine in man prompted us to investigate its disposition and excretion in surgical patients.

PATIENTS AND METHODS

Patients and surgery

Fifteen patients undergoing elective cholecystectomy and choledochostomy, gynaecological pelvic operations or orthopaedic procedures volunteered to participate in this study. Based on the type of surgical procedure, the patients were allocated to three groups (table I). Apart from the pathological conditions requiring surgery, all patients were free of renal, hepatic, neuromuscular, metabolic or other systemic disease, as determined from the clinical history and physical examination.

Anaesthetic procedure

The anaesthetic procedure was similar for all patients. Premedication consisted of atropine 0.5 mg and diazepam 10 mg given i.m. 30 min before induction of anaesthesia. Anaesthesia was induced with thiopentone 200–250 mg and thalamonal 2 ml (droperidol 5 mg and fentanyl 0.05 mg) followed by suxamethonium 40 mg to facilitate introduction of a tracheal tube. Anaesthesia was maintained with nitrous oxide in oxygen and repeated small doses of fentanyl (20–50 μg). After recovery from the neuromuscular effects of suxamethonium, a single dose of gallamine 2.5 mg kg^{-1} was injected i.v. over 30 s. In a pilot study it was found that the cardiovascular effects of gallamine 2.5 mg kg^{-1} were not significantly greater than those observed after moderate doses of $1.0\text{--}1.5 \text{ mg kg}^{-1}$. The larger dose of gallamine was selected because it provided adequate relaxation for the surgical procedures of 60–90 min duration performed on our patients. The use of a smaller initial dose of gallamine, followed by repeated fractional doses, would have complicated our

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TABLE I. Patient characteristics and composition of groups

Patient	Group I (cholecystectomy with choledochostomy)			Group II (pelvic operations with urethral catheter)			Group III (orthopaedic operations without urethral catheter)		
	Age (yr)	Sex	Body wt (kg)	Age (yr)	Sex	Body wt (kg)	Age (yr)	Sex	Body wt (kg)
1	51	F	85	67	F	60	20	M	72
2	49	F	54	48	F	70	52	M	86
3	61	M	70	47	F	64	29	F	60
4	64	F	70	73	F	72	17	F	65
5	22	F	90	49	F	75	32	M	90
Mean	49.4		73.8	56.8		68.2	30.0		74.6
SEM	7.4		6.4	5.5		2.7	6.2		5.8

pharmacokinetic studies. During surgery the patients received a continuous i.v. infusion of 500 ml of 5% glucose in water, 500 ml of 0.9% saline and Haemaccel 500 ml, into an antecubital vein. Gallamine was injected into an antecubital vein in the opposite arm. After operation, in the first 24 h all patients received 5% glucose 1500 ml and 0.9% saline 1000 ml. Drugs given after operation were: prophylactic antibiotics (tetracycline or a combination of penicillin and streptomycin), a narcotic analgesic (piritramide) and a hypnotic (nitrazepam) as required.

Experimental and analytical procedure

Blood samples (6 ml) were removed at 2, 5, 10, 20, 30, 60, 90, 120, 240, 360 and 480 min after the start of the administration of gallamine from a vein in the arm opposite to that in which the infusion was sited. The blood was allowed to clot; thereafter the serum was separated and kept at -30°C until chemical analysis could be performed.

Urine specimens were obtained after each spontaneous micturition from patients in groups I and III. Patients in group II had indwelling urethral catheters and urine specimens were collected at 2-h intervals. Bile samples were obtained from patients with total biliary drainage (group I) at various intervals for up to 12 h.

For the chemical analysis of the samples, a slight modification of the method employed for the determination of pancuronium-like compounds (Kersten, Meijer and Agoston, 1973) was used. This method is based on an ion-pair extraction of pancuronium with rose bengal in chloroform and determination of the fluorescence of the pancuronium dye complex in the organic phase after dilution with acetone.

For the determination of gallamine in serum, eosin was used instead of rose bengal. For the estimation

of gallamine in bile and urine the analytical method was identical with that described for pancuronium (Kersten, Meijer and Agoston, 1973). The lowest concentrations of gallamine that could be determined reliably were: $0.5\text{ }\mu\text{g ml}^{-1}$ in serum, $0.1\text{ }\mu\text{g ml}^{-1}$ in urine and $1.0\text{ }\mu\text{g ml}^{-1}$ in bile. Thin-layer chromatographic identification on silica-gel plates, developed with a 1:1 mixture of acetone and hydrochloric acid and sprayed with iodoplatinate, revealed, in addition to unchanged gallamine, three other compounds showing distinct R_F values. The three compounds in the urine were found also when gallamine powder was dissolved in water or hydrochloric acid $0.1\text{ mol litre}^{-1}$ and in the commercial preparation of gallamine (Flaxedil), in the same proportion. According to the manufacturers, these three compounds represent degradation products related closely to gallamine triethiodide. The serum half-life of gallamine in the successive phases was calculated by plotting the measured values semi-logarithmically against time and correcting the second component of the resulting curve for the third one.

RESULTS

Serum concentration

The mean time-courses of the serum concentrations in the three groups of patients are shown in figure 1.

Assuming that the plasma volume of an adult patient is equivalent to 5% of the body weight, quantities of gallamine in serum can be expressed as a percentage of the injected dose. By 2, 5 and 30 min after the end of the injection of gallamine, about 40, 60 and 80% respectively of the administered dose had disappeared from the serum. Two hours after injection the serum content of gallamine corresponded to about 10% of the administered dose.

FIG. 1. The mean serum concentration of gallamine after the i.v. administration of a single 2.5-mg kg⁻¹ dose.

Semi-logarithmic plots of serum concentrations against time showed that gallamine is eliminated from the serum at progressively slower rates, in three distinct phases. The mean half-lives of the three phases are summarized in table II. No difference could be demonstrated between the groups in the half-lives of the respective phases.

TABLE II. The serum half-life of gallamine (min)

	Serum half-life* of gallamine (min)		
	Group I	Group II	Group III
1st phase	< 5	< 5	< 5
2nd phase	30	39	38
3rd phase	141	144	138

* Mean values of the successive phases.

Renal excretion

The urine output and urinary excretion of gallamine were studied in all the patients for 30 h (figs 2-4). The amounts of gallamine excreted in the urine varied from 15 to 100% approximately of the injected dose in group I (fig. 2). The time-course of urinary excretion was also very variable. In this group there were "low excretors" (patients 1, 2 and 3), who excreted less than 15% of the injected dose of gallamine in 16 h after administration of the drug. Patient 3 had oliguria and excreted only 8% of the

administered dose in 28 h. None of these patients, however, had higher than average serum concentrations of gallamine, or showed any clinical signs of residual neuromuscular block while in the recovery room. The individual variations in the excreted amounts of gallamine in the second and third groups (figs 3 and 4) were much less than in the previous group, ranging from 40 to 90% and from 89 to 100% of the injected dose respectively. In these two groups the time-course of excretion was similar in all patients; they excreted most of the urine load of gallamine within 12-16 h from the time of administration of the drug.

There were considerable differences in the urinary output of the individual patients in all three groups, but only in patients of group I was there even the suggestion of a correlation ($P = 0.95$) between the total volume of urine and the total amount of gallamine excreted both in the first and subsequent urine samples.

Biliary excretion

The biliary excretion of gallamine was studied for the first 12 h after the administration of gallamine in group I. Only very small amounts of gallamine were recovered in the bile. Data on the biliary excretion of gallamine and the biliary flow are summarized in table III.

TABLE III. Biliary flow and excretion of gallamine in Group I. (Bile collected for 12 h in patients 1-4; in patient 5, biliary excretion was not determined)

Patient	Flow (ml)	Gallamine content (%)*
1	137	0.4
2	32	< 0.1
3	312	< 0.1
4	132.5	< 0.1
5	—	—

* Expressed as % of the total dose administered.

DISCUSSION

The initial steep decline of the serum concentration of gallamine may indicate rapid distribution into the extracellular compartment of organs with a high blood flow. Subsequently, the rate of decline of the serum concentration of gallamine becomes slower. During this second phase the drug is probably redistributed to the extracellular fluid of organs with a less abundant blood supply (acceptor tissue depots).

FIG. 2. Group I.

FIG. 3. Group II.

FIG. 4. Group III.

FIGS. 2-4. Cumulative urinary excretion (individual curves) of gallamine after i.v. injection of a single 2.5-mg kg^{-1} dose (solid lines; left scale) and cumulative urinary flow (dashed lines; right scale). Urine samples were obtained separately after each spontaneous micturition from patients in groups I and III (figs 2, 4). Patients in group II (fig. 3) had an indwelling urethral catheter and the samples were collected at regular intervals. The numbers of each curve correspond to the patients' numbers.

In the third phase the elimination of gallamine from a large hypothetical volume of distribution is primarily responsible for the even slower rate of decrease of the serum concentration. The only demonstrated pathway for the excretion of gallamine in

animals is in the kidney (Mushin et al., 1949; Chagas, 1962; Feldman, Cohen and Golling, 1969). The results of the present study show that in man also, gallamine is primarily excreted unchanged in the urine. Only negligible amounts were excreted in the

bile. Our observations (fig. 2; patients 1, 2 and 3) indicate that poor urinary excretion of gallamine will not invariably result in persistent high serum concentrations and prolonged duration of the neuromuscular effects, as far as it could be judged by simple clinical tests including the patient's ability to lift his head off the bed for 5 s, to cough and breathe deeply. Contrary to the widespread clinical assumption of the importance of renal excretion in determining the duration of action of gallamine (Churchill-Davidson, Way and de Jong, 1967; Singer, Dutton and Way, 1971; Anand et al., 1972; McLaughlin et al., 1972), it appears that redistribution from postjunctional receptor sites to non-specific tissue acceptors, rather than renal excretion, limits the duration of action of gallamine particularly after the administration of a single moderate dose (less than 2 mg kg⁻¹). However, after an excessive single dose or after the administration of repeated doses the non-specific acceptor sites may be filled gradually. Consequently, increased concentrations of gallamine, capable of neuromuscular blockade, may persist even in the third phase, during which its disappearance from the serum will proceed at the slowest rate. Thereafter the duration of action of gallamine will depend on the rate of its excretion. Examples supporting this view were described in the frequently cited reports (Fairley, 1950; Joske, Ebeling and Stanistreet, 1954; Jenkins, 1961; Churchill-Davidson, Way and de Jong, 1967; Singer, Dutton and Way, 1971; Anand et al., 1972; McLaughlin et al., 1972) of the prolonged neuromuscular block and "recurarization" observed after the use of gallamine in patients with inadequate kidney function. Although in most of these reports the body weight of the patient was not stated, it is conceivable that absolute or relative overdoses (ranging from 110 to 400 mg) of gallamine were primarily responsible for the prolonged neuromuscular block. In some cases (Feldman and Levi, 1963; Lowenstein, Goldfine and Flacke, 1970) the concomitant administration of antibiotics known to potentiate non-depolarizing muscle relaxants may have been a contributory factor. There are several reports (Fairley, 1950; Montgomery and Bennett-Jones, 1956; Jenkins, 1961; Churchill-Davidson, Way and de Jong, 1967) of patients in whom signs of neuromuscular blockade recurred for as long as 48 h after the use of gallamine despite the repeated administration of anticholinesterases or peritoneal dialysis (Montgomery and Bennett-Jones, 1956). The phenomenon of "recurarization" (to be distinguished from prolonged duration of action) in

most of the cases described in the literature was observed after the use of gallamine and not after other non-depolarizing drugs such as tubocurarine or pancuronium, although both are excreted largely unchanged in the urine (Cohen, Brewer and Smith, 1967; Agoston et al., 1973). It is conceivable, therefore, that gallamine is stored in different tissue depots or that its binding properties to the same depots differ from those of other drugs. That renal disease may change the binding capacity of the acceptors cannot be excluded. This might be the reason why recurarization is not observed in patients with normal renal function.

The most striking finding in the present study is the wide individual variation in the amounts of gallamine excreted, especially in group I, with no corresponding variation in the serum concentration curves over the same period. The observation in patients recovering from biliary tract surgery, pelvic operations and orthopaedic procedures, that 53% (15–100%), 67% (40–90%) and 95% (89–100%) respectively was excreted in the urine in 24–30 h, indicates that not only the underlying pathology and the degree of surgical stress, but also the patient's age, or a combination of these factors, may influence the renal excretion of this compound and of pancuronium (Agoston et al., 1973). Unfortunately, we could not correlate the excretion rate with pre-operative liver or kidney function because no function tests were performed. There was no indication of disturbed hepatic or renal function in the case histories. It is highly unlikely that the age of the patient influenced the excretion rate of gallamine in this study, since no correlation could be found between these factors (table I and figs 2–4).

Other factors such as incomplete collection of urine specimens, although unlikely, might have contributed to the wide variations in the total amounts of gallamine recovered from the urine.

In a similar study with pancuronium (Agoston et al., 1973) the disappearance of the drug from the plasma proceeded in three phases with half-lives of 5 min, 7–13 min and 108–147 min.

Thirty hours after injection, the total recovery of the bisquaternary steroids amounted to 37–44% of the injected dose in the urine and 11% in the bile, indicating that, for pancuronium, renal excretion represents the major route of elimination in man. As in the case with gallamine in this study, wide individual variations with irregular patterns were seen in the renal excretion of pancuronium in patients

undergoing cholecystectomy, in contrast to those undergoing pelvic operations.

Of the three metabolites of pancuronium, known from animal experiments only one, the 3-OH derivative, could be identified in the urine and bile, accounting in total for about 20% of the administered dose.

Since pancuronium is both metabolized and excreted in the bile and urine, no definite conclusions could be drawn with regard to the underlying mechanisms (metabolism, distribution, biliary excretion or a combination of these) responsible for the variations observed (Agoston et al., 1973). Gallamine, however, is neither metabolized nor excreted in the bile to any appreciable extent. Thus, differences in redistribution into inactive tissue depots remain the only explanation for the irregular pattern of renal elimination seen in some patients. This view is supported by the lack of any difference in the half-lives of the respective phases between the investigated groups (table II).

There is reason to speculate that, in patients who underwent biliary tract surgery, hepato-renal factors possibly attributable to transient hepatic dysfunction (Clarke, Daggart and Lavery, 1976) and increased blood concentrations of aldosterone (Wolff, Bette and Blaise, 1966), might also be responsible for the decreased urinary excretion of gallamine and pancuronium (Agoston et al., 1973). The findings of this and our earlier studies (Agoston et al., 1973) permit us to speculate that the disposition of, and thus the pharmacological effects of, neuromuscular blocking agents may be influenced significantly, not only by species variation and pathological conditions, but also by altered metabolic or excretory functions, or both, caused by the stress of certain types of surgery. Further studies of the effects of disease and surgery upon the excretory patterns of neuromuscular blocking drugs are needed.

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RECHERCHES PRELIMINAIRES EFFECTUEES SUR L'EXCRETION RENALE ET HEPATIQUE DE GALLAMINE TRIETHIODIDE CHEZ L'HOMME

RESUME

On a fait des recherches sur le sort réservé à la gallamine triéthiodide sur des malades ayant subi une cholécystostomie avec cholédochostomie (Groupe I), des opérations pelviennes (Groupe II) et des interventions chirurgicales

orthopédiques (Groupe III). Après une seule injection intra-veineuse de gallamine à raison de $2,5 \text{ mg kg}^{-1}$, la disparition de ce médicament du sérum s'est produite en trois phases avec demi-vies respectives de moins de 5, 30, 138 min, de moins de 5, 39, 141 min et de moins de 5, 48, 144 min pour chacun de ces groupes. Vingt-quatre heures après l'injection, l'excrétion rénale du médicament inchangé a été de 53% (15–100%) de la dose administrée dans le Groupe I, de 67% (40–90%) dans le Groupe II et de 95% (89–100%) dans le Groupe III. L'excrétion biliaire de gallamine semble être négligeable chez l'homme. On expose dans cet article la relation qui existe entre l'excrétion rénale et la durée de l'action de la gallamine, ainsi que l'influence de certains facteurs intra-opératoires sur la disparition du médicament.

Injektion betrug die renale Ausscheidung der unveränderten Droge 53% (15–100%) der verabreichten Dosis in Gruppe I, 67% (40–90%) in Gruppe II und 95% (89–100%) in Gruppe III. Die Gallenwegausscheidung von Gallamin scheint beim Menschen kaum der Rede wert zu sein. Die Beziehung zwischen renaler Ausscheidung und der Wirkungsdauer von Gallamin, sowie der Einflüsse einiger innerer Faktoren auf das Verhalten der Droge werden diskutiert.

UNA INVESTIGACION PRELIMINAR DE LA EXCRETION RENAL Y HEPATICA DE GALAMINA TRIETIODIDA EN EL HOMBRE

SUMARIO

Se ha investigado la suerte de galamina trietiodida en pacientes sometidos a colecistectomía con coledocostomía (grupo I), operaciones pélvicas (grupo II) y operaciones ortopédicas (grupo III). Tras una sola inyección intravenosa de galamina $2,5 \text{ mg kg}^{-1}$, la desaparición de la droga del suero se produjo en tres fases de vida media inferiores a 5, 30, 138 min, 5, 39, 141 min y 5, 48, 144 min en los respectivos grupos. Veinticuatro horas después de la inyección, la excreción renal de la droga no transformada fue de 53% (15–100%) de la dosis administrada en el grupo I, 67% (40–90%) en el grupo II y 95% (89–100%) en el grupo III. La excreción biliar de galamina pareció ser despreciable en el hombre. Se discute la relación entre la excreción renal y la duración de la acción de la galamina, y la influencia que ejercen algunos factores interoperatorios sobre la disposición de la droga.

EINE VORLÄUFIGE UNTERSUCHUNG ÜBER NIEREN- UND LEBERAUSSCHIEDUNG VON GALLAMIN TRIÄTHIODID BEIM MENSCHEN

ZUSAMMENFASSUNG

Der Verbleib von Gallamin Triäthiodid wurde bei Menschen untersucht, die einer Cholezystektomie mit Choledochostomie (Gruppe I), einer Beckenoperation (Gruppe II) und orthopädischen Operationen (Gruppe III) unterzogen wurden. Nach einer einzelnen intravenösen Injektion von $2,5 \text{ mg kg}^{-1}$ Gallamin ereignete sich das Verschwinden der Droge aus dem Serum in drei Phasen mit Halbwertszeiten von 5, 30 und 138 min, 5, 39 und 141 min, bzw. von 5, 48 und 144 min in den jeweiligen Gruppen I bis III. Vierundzwanzig Stunden nach der