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Passage of gallamine from blood into the liquor space in man and in dog

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Summary

1. Patients receiving an intravenous injection of 2–3·8 mg/kg gallamine showed gallamine-like activity in their lumbar c.s.f. collected 15 and 70–100 min after the injection. The activity assayed on acetylcholine contractions of frog rectus muscle was equivalent to between 0·1 and 0·75 μg/ml gallamine.

2. In anaesthetized dogs an intravenous injection as well as an intravenous infusion of gallamine led to the appearance of gallamine-like activity in the cisternal c.s.f. and, on perfusion of the cerebral ventricles, in the effluent collected from the cisterna magna.

3. After an intravenous injection of 1 mg/kg the activity in the cisternal c.s.f. corresponded to between 0·2 and 1 μg/ml and in the effluent to between 130 and 175 ng/min during the first 15 min perfusion and then declined.

4. On intravenous infusion of gallamine at a rate of 10 (μg/kg)/min for 2 h the cisternal c.s.f. showed a uniform gallamine-like activity corresponding to between 0·4 and 0·67 μg/ml during the infusion. In the cisternal effluent the gallamine-like activity rose initially to between 20 and 90 ng/min but declined before the infusion was ended.

5. The intravenous injection of gallamine caused respiratory paralysis but did not affect arterial blood pressure; its intravenous infusion caused no respiratory paralysis and did not affect arterial blood pressure.

Introduction

Muscle relaxants like tubocurarine and gallamine, which are quaternary ammonium compounds, are expected either not to pass from blood into cerebrospinal fluid (c.s.f.) or to do so with difficulty. Previous reports on the passage of muscle relaxants from blood into c.s.f. have been contradictory. The passage of tubocurarine into c.s.f. was reported by Mahfouz (1949) and Dal Santo (1964). But Cohen (1963) did not detect tubocurarine in the c.s.f. in animal and human experiments after intravenous administration of tubocurarine. Recently definite evidence was obtained in man and dog for its passage into the liquor space. The lumbar c.s.f. of patients who had received an intravenous injection of tubocurarine was found to exert tubocurarine-like activity when assayed on the frog rectus muscle contracted by acetylcholine. Similarly, tubocurarine-like activity was detected in the cisternal c.s.f. as well as in the effluent collected during perfusion of different parts of the liquor space after an intravenous injection and during an intravenous infusion of tubocurarine (Devasankaraiah, Haranath & Krishnamurty, 1973). On

the other hand, Dal Santo (1972) who studied the urinary excretion and the distribution of labelled [^{14}C]-gallamine injected intravenously into anaesthetized dogs, found no significant radioactivity in the c.s.f.

In the present experiments the passage of gallamine from blood into the liquor space was studied in man and dogs with the methods used by Devasankaraiah *et al.* (1973) in their experiments with tubocurarine. In patients, lumbar c.s.f. was examined for gallamine-like activity after intravenous injection of gallamine, and in anaesthetized dogs cisternal c.s.f. and cisternal effluent collected during perfusion of the cerebral ventricles were examined for such activity after intravenous injection or during intravenous infusion of gallamine.

Methods

Clinical procedures

Six male patients (33·1 to 50 kg), who were scheduled for surgery, were given atropine 0·6 mg as preanaesthetic medication. Anaesthesia was induced by intravenous thiopentobarbitone sodium (150 to 250 mg). Gallamine (2 to 3·8 mg/kg) was then injected intravenously. As it produced immediate respiratory arrest the trachea was intubated, connected to a Boyle's apparatus and controlled respiration was applied. Anaesthesia was maintained with nitrous oxide and oxygen. Supplemental doses of gallamine were administered when necessary. Three samples of c.s.f. were obtained by lumbar puncture, one before and two at different times after the injection of gallamine. At the same time blood samples were obtained in syringes containing 0·1 ml of heparin 5%.

Animal experiments

Dogs weighing 6–16 kg were used. They were anaesthetized with intravenous pentobarbitone sodium (30 mg/kg). The experimental procedures for recording arterial blood pressure and respiration were the same as those described by Devasankaraiah *et al.* (1973). The cerebral ventricles were perfused from lateral ventricle to cisterna magna according to the method described for cats by Bhattacharya & Feldberg (1958). The rate of perfusion was 0·1 ml/min, and the perfusion fluid was artificial c.s.f. of the following composition (g/litre): NaCl 8·1; KCl 0·25; $CaCl_2$ 0·14; $MgCl_2$ 0·11; $NaHCO_3$ 1·76; NaH_2PO_4 0·072; urea 0·13; glucose 0·61. Gallamine solutions were either injected intravenously or infused intravenously at a rate of 0·4 ml/min with a slow infusion pump.

Bioassay

The samples of c.s.f., effluent or plasma were assayed biologically for gallamine-like activity on acetylcholine-induced contractions of frog rectus muscle as described for curare by Burn (1952) and with the modification given by Devasankaraiah *et al.* (1973). The preparation was usually sensitive to 0·5 μg of gallamine. Control samples of c.s.f. and of plasma potentiated the acetylcholine-induced contractions of the frog rectus muscle. As the potentiating effect of plasma was strong, the values obtained for the gallamine concentrations of plasma are probably too low.

Drugs

In clinical administration Flaxedil brand of gallamine solutions in vials (40 mg/ml) was used. For the experiments on dogs, gallamine triethiodide (Flaxedil) supplied through the courtesy of May & Baker was used.

Results

Clinical studies

As shown in Table 1, samples of lumbar c.s.f. withdrawn from six patients during an operation 15 min after an intravenous injection of 2 to 3·8 mg/kg gallamine exerted gallamine-like activity on the frog rectus muscle equivalent to between 0·15 and 0·6 μg/ml. The activity of a second sample withdrawn at the end of the operation 70 to 110 min after the injection was about the same whether it had been necessary during this time to give additional injections of smaller amounts of gallamine or not. The Table also shows that the gallamine concentration in plasma collected 15 min after the injection varied widely from patient to patient (between 0·6 and 40 μg/ml) and decreased in plasma collected 70 to 110 min after the injection.

TABLE 1. *Gallamine-like effect (expressed in terms of gallamine μg/ml) in lumbar c.s.f. collected from six male patients after its intravenous injection*

Patient no.	Weight (kg)	Dose of gallamine given (mg/kg)	Gallamine conc. (μg/ml) 15 min	70–110 min
1	50·0	3·2	0·31 (0·6)	
2	36·3	3·3	0·6 (40·0)	0·75 (8·0)
3	33·1	3·8	0·15 (2·5)	0·2
4	40·0	3·0		0·5 (10·0)
5	42·7	2·8 + 0·9 at 25′ 0·9 at 75′	0·2 (20·0)	0·1 (3·3)
6	40·0	2·0 + 2·0 at 15′	0·3 (15·0)	0·35 (13·5)

The figures in brackets refer to plasma concentration of gallamine (μg/ml).

Experiments on dogs

Intravenous injection of gallamine

An intravenous injection of gallamine (1 mg/kg) produced immediate respiratory arrest and artificial ventilation was applied. Respiration began to recover within 10 min but artificial ventilation was continued for 40 to 50 min to ensure adequate oxygenation. The arterial blood pressure did not change during this time.

As seen from Tables 2 and 3, the gallamine concentration in plasma was maximal 15 min after the injection when it was between 0·7 and 6·7 μg/ml. It then declined. Table 2 gives the gallamine-like activity of samples of cisternal c.s.f. collected 15, 30 and 60 min after the injection. All samples showed gallamine-like activity corresponding to between 0·2 and 1 μg/ml. The peak concentration was obtained

TABLE 2. *Concentration of gallamine in consecutive samples of cisternal c.s.f. and plasma of anaesthetized dogs after intravenous injection of 1 mg/kg gallamine*

Expt. no.	Weight (kg)	Gallamine concentration (μg/ml) c.s.f. 15 min	c.s.f. 30 min	c.s.f. 60 min	plasma 15 min	plasma 30 min	plasma 60 min
1	6	0·33	0·4	0·2			1·67
2	12	0·4	0·33	1·0	3·0	0·5	nil
3	13	0·33	0·56	0·33	0·75	0·75	0·3

either in the 30 or in the 60 min sample. In Expt. 2 of the Table, a fourth sample of c.s.f. (not included in the Table) was collected 120 min after the injection. It no longer exerted gallamine-like activity although a plasma sample collected at this time showed gallamine activity corresponding to 1 μg/ml. Table 3 gives the gallamine-like activity in the cisternal effluent collected during perfusion of the cerebral ventricles. In all three experiments the output of gallamine was maximal in the sample collected during the first 15 min after the gallamine injection when it was between 130 and 175 ng/min and declined to between 27 and 68 ng/min in the second 15 min sample, but in the third 30 min sample a further decline occurred in only one of the three experiments.

TABLE 3. *Output of gallamine in ng/min in cisternal effluent on perfusion from lateral ventricle, and its plasma concentration in anaesthetized dogs after intravenous injection of* 1 *mg/kg gallamine*

Expt. no.	Weight (kg)	Gallamine output in effluent (ng/min) 0–15 min	16–30 min	31–60 min	Plasma gallamine concn. (μg/ml) 15 min	30 min	60 min
4	10	130	27	27	0·7	0·5	0·4
5	10	175	63	67	1·4	1·0	0·7
6	14	130	68	18	6·7	2·0	1·33

Intravenous infusion of gallamine

A continuous intravenous infusion of gallamine for 2 h at a rate of 10 (μg/kg)/min did not affect arterial blood pressure nor did it depress respiration ; there was in fact some slight increase in the respiratory amplitude as illustrated in Figure 1.

As seen from the results of Tables 4 and 5, the concentration of gallamine in samples of plasma collected during the 2 h infusion varied greatly from dog to dog. Larger dogs had higher plasma gallamine concentration than smaller dogs, proportional to the total dose infused per minute. In the same dog, the plasma

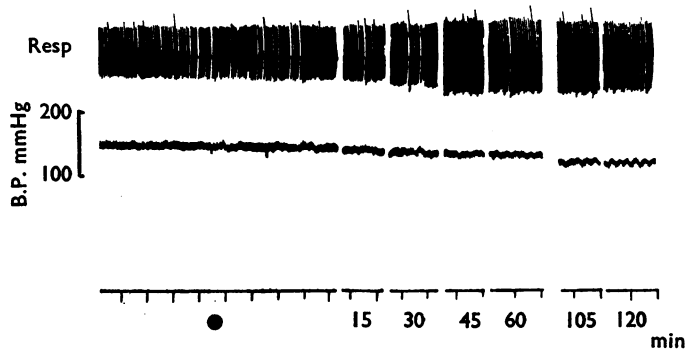

FIG. 1. Record of respiration and blood pressure from a dog (6 kg) under pentobarbitone anaesthesia. At the black dot gallamine i.v. infusion at 10 (μg/kg)/min was started. Records taken at the time noted under each panel after commencement of infusion. (Time 1 min.)

TABLE 4. *Concentration of gallamine in consecutive half hourly or hourly samples of cisternal c.s.f. and plasma obtained from anaesthetized dogs during continuous intravenous infusion of* 10 (μg/kg)/*min gallamine*

Expt. no.	Weight (kg)	Gallamine concentration (μg/ml) c.s.f. 30 min	60 min	120 min	plasma 30 min	60 min	120 min
7	12·0	0·5	0·63	0·4	0·5		0·4
8	12·7	0·5	0·5	0·6	0·8	0·75	0·25
9	16·0	0·5	0·5	0·67	1·8	1·5	1·25

concentration of gallamine showed some fluctuations in the samples collected at different times of the infusion being higher initially in three, and lower in two of the dogs than at the end of the infusion. During the infusion gallamine-like activity appeared in the cisternal c.s.f. As shown in Table 4, the activity was nearly the same in all three dogs and in the samples collected 30, 60 or 120 min after the beginning of the gallamine infusion. As seen from the results of Table 5, gallamine-like activity appeared also in the cisternal effluent when the cerebral ventricles were perfused during the infusion. The output of gallamine ranged from 20 to 90 ng/min and declined during the 2 h infusion.

TABLE 5. *Output of gallamine in ng/min in cisternal effluent on perfusion from lateral ventricle of anaesthetized dogs during intravenous infusion of gallamine,* 10 (μg/kg)/min

Expt.	Weight	Gallamine output in effluent (ng/min)				Plasma gallamine concn. (μg/ml)			
no.	(kg)	0–15 min	16–30 min	31–60 min	61–120 min	15 min	30 min	60 min	120 min
10	7·5	90	40	40	30	1·0	0·75	1·0	0·68
11	6·0	90	60	54	34	0·5	0·5	0·67	1·0
12	15·0	25	55	20	30	2·0	2·9	3·3	3·3

Discussion

The present experiments show that after the intravenous administration of gallamine the lumbar c.s.f. obtained from anaesthetized patients and the cisternal c.s.f. obtained from anaesthetized dogs or, on perfusion of their cerebral ventricles, the cisternal effluent exerted gallamine-like activity when tested on the acetylcholine-induced contraction of the frog rectus muscle. These findings agree with the results obtained by Devasankaraiah *et al.* (1973) in similar studies with tubocurarine and suggest that gallamine itself, or if not, a derivative of it which has retained its biological activity, passed from the blood into the liquor space. The appearance of gallamine-like activity in the c.s.f. of patients was obtained with doses of gallamine (2–3·8 mg/kg) which are of the order (3–5 mg/kg) used in clinical anaesthetic practice and are therefore of clinical interest.

It is not possible from the data available to give the reason why Dal Santo (1972) in his studies in anaesthetized dogs on the urinary excretion and distribution in the body of [^{14}C]-gallamine could not detect any radioactivity in the cisternal c.s.f. after an intravenous injection of a trace dose of 50 μCi gallamine equivalent to 50×10^6 counts/min, particularly since in a previous similar study (1964) with [^{14}C]-dimethyl-(+)-tubocurarine injected intravenously in a trace dose equivalent to 25×10^6 counts/min he could detect up to 20×10^{-5} of the injected amount in the cisternal c.s.f. In his experiments with labelled gallamine about 7 samples of c.s.f. were collected in 7 hours. In the present experiments gallamine-like activity was detected only in those samples of c.s.f. collected during the first hour after a single intravenous injection of gallamine, because a sample collected after the second hour no longer exerted such activity. It is possible that in the experiments of Dal Santo collection of the samples of c.s.f. started too late after the injection of the labelled gallamine, at a time when the gallamine that had passed into the c.s.f. had disappeared, or if a derivative, had passed into the c.s.f. that it was one which did not contain radio-active carbon.

In the past, the passage of quaternary ammonium compounds across the blood-c.s.f. barrier has been doubtful. The present findings with gallamine and the

earlier ones with tubocurarine by Mahfouz (1949) Dal Santo (1964) and Devasankaraiah *et al.* (1973) however suggest that this barrier is not absolute and that small amounts of these muscle relaxants pass into the c.s.f. Neither hypoxia nor a fall in blood pressure, nor histamine release accounts for this passage, because in the experiments on dogs with intravenous infusion of gallamine the appearance of gallamine-like activity in the c.s.f., or in the effluent on perfusion of the cerebral ventricles, occurred without changes in respiration or blood pressure and gallamine, unlike (+)-tubocurarine, does not release histamine.

The finding that 15 min after an intravenous injection of gallamine, gallamine-like activity was detected in the lumbar c.s.f. of patients and in the cisternal c.s.f. of dogs, suggests that the gallamine passes equally well into the spinal and cerebral c.s.f. space. On the other hand, the gallamine-like activity found in the cisternal c.s.f. may well have passed, partly at least, from the cerebral ventricles into the subarachnoid space. This conclusion is based on the finding that on perfusion of the cerebral ventricles the highest values for gallamine-like activity were found in the first 15 min samples after an intravenous injection of gallamine and decreased steeply in the second 15 min sample, whereas in the cisternal c.s.f. the highest values were found not in the first sample collected 15 min but in the second one collected 30 min after the injection, or there was a slight decrease only in the second sample.

The concentration of gallamine in c.s.f. was always less than in plasma, but a fixed ratio of the two concentrations cannot be given from the results obtained. This is due to the fact that on account of the strong potentiating effect which plasma exerts on the acetylcholine-induced contractions of the frog rectus muscle the values obtained for plasma concentration were too low and did not give the true concentrations of gallamine in plasma.

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