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Quantitative Aspects of the Chronotropic and Neuromuscular Effects of Gallamine in Anesthetized Man

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The chronotropic and neuromuscular properties of gallamine were studied in 48 patients anesthetized with halothane. In all cases gallamine produced tachycardia that was greatest at a dosage of 100 mg regardless of the method of administration. Heart rate increased further when atropine, 2 mg, was given after gallamine, indicating that gallamine does not produce complete vagolysis. The magnitude of the tachycardia with gallamine was much less than that following atropine, in either incremental doses of 0.2 mg or a single bolus of 2.0 mg, suggesting that gallamine may not act in the same manner as atropine. The degree of neuromuscular block of the hand muscles after gallamine paralleled the increase in heart rate in both onset and extent; however, the duration of tachycardia was longer. (Key words: Gallamine; Tachycardia; Atropine; Vagal block; Neuromuscular block.)

THAT GALLAMINE causes tachycardia is well known to anesthesiologists, and sometimes it may be a factor in the choice of a muscle relaxant. It is thought that gallamine affects only cardiac vagal efferent endings,[1] but it is not known to what degree these endings are blocked. The purpose of this study was to compare the chronotropic effect of gallamine in man with that of atropine, and in addition, to correlate heart rate changes with degree of neuromuscular block over a wide range of gallamine dosages.

Methods

Forty-eight surgical patients, 18 to 61 years of age and of ASA class I physical status, were studied following premedication with pentobarbital, 100 mg, only. Induction of anesthesia was accomplished with sodium thiopental, 150–250 mg, followed by succinylcholine and endotracheal intubation. Anesthesia was maintained with nitrous oxide, 2.5 l/min, oxygen, 2.5 l/min, and halothane, 1 to 1.5 per cent, delivered from a Fluotec vaporizer into a circle absorption system. Ventilation was controlled with a mechanical ventilator sufficient to maintain end-tidal CO_2 between 3 and 4 per cent as measured with a Godart capnograph. The study was begun 20 to 30 minutes after the start of anesthesia and was concluded prior to operation.

Stimulating needle electrodes (Burroughs-Wellcome Block-Aid Monitor) were placed in the forearm over the ulnar nerve and the contractions of the opponens pollicis muscle were measured with a Statham force transducer.[2] The signal was amplified and recorded, together with the electrocardiogram, on a Sanborn recorder.

Three groups of patients were studied. In Group A, 13 patients were given gallamine in incremental doses of 20 mg each, allowing 2 to 2.5 minutes between doses. These were continued until there was no further increase in heart rate and no twitch response of the hand muscles. At this point, atropine (2.0 mg) was administered to produce total vagal efferent block and thereby permit determination of the degree of vagal blockade achieved with gallamine. In Group B, 27 patients received gallamine as a single bolus of 100, 200, 300, or 400 mg, the change in heart rate was recorded, and then atropine (2.0 mg) was given to produce full atropinization. In Group C, eight patients received atropine in increments of 0.2 mg every 2 to 3 minutes until there was no further increase in heart rate, that is, until vagal blockade was complete.

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TABLE 1. Group A (n = 13); Results of Sequential Administration of Gallamine Followed by Atropine*

	Gallamine Cumulative Dose (mg)						Atropine, 2 mg
	0	20	40	60	80	100	
Per cent depression of twitch response	76.0 ± 12	41.6 ± 24	84.3 ± 17	97.0 ± 3.6	99.7 ± 0.6	100	
Heart rate (beats/min)		85.3 ± 13.7	90.2 ± 14.0	92.6 ± 14.8	93.6 ± 14.5	93.8 ± 14.5	106 ± 14
Per cent change		12 ± 8	19 ± 8	22 ± 10	24 ± 11	24 ± 11	41 ± 16
Per cent of maximal heart rate change		52 ± 27	80 ± 16	93 ± 8	99 ± 2	100	

* All values are means ± 1 SD.

Results

Group A patients (table 1) given gallamine in incremental doses showed progressive blocks of the twitch response and increases in heart rate until a total of 60 mg of gallamine had been given. The average decrease of neuromuscular twitch and increase in heart rate reached approximately 95 per cent of the change ultimately achieved with 100 mg gallamine. The heart rate attained with 100 mg was the maximum tachycardia produced by gallamine administered in 20-mg divided doses, since an additional 20 mg (120 mg total) did not increase heart rate further. The similarity of the two response curves (fig. 1) suggests that the neuromuscular and chronotropic effects of gallamine occur at the same rate and to the same extent. In those cases in which prolonged observation was possible, the heart rate effects always outlasted the neuromuscular blockade.

When gallamine was given as a single bolus (Group B patients, table 2), the increase in heart rate expressed as per cent change from control was not significantly different ($P > 0.05$) over the range of 100 to 400 mg. When these large doses of gallamine were followed by atropine (2 mg), the heart rates increased in all but three patients. Two of these patients had received 300 mg and one, 400 mg of gallamine. The increase in heart rate resulting from gallamine given as a bolus of 100 mg was almost the same as that seen after 100 mg given in divided doses.

Patients in Group C (table 3) who received incremental doses of atropine showed progressive increases in heart rate until 1.6 mg had been given. Thereafter, there were no further increases in heart rate with additional doses of 0.2 mg. Atropine had a much greater effect on heart rate than did gallamine at all dose levels studied (fig. 2).

Discussion

These data confirm the positive chronotropic effect of gallamine, which diminishes with repeated doses and reaches a maximum at about 100 mg. In this respect, the chronotropic effect is similar to the neuromuscular blocking effect, which conflicts with earlier observations that the cardiac vagus was more susceptible to gallamine than was the neuromuscular junction.[3] This change in heart rate may be clinically useful as a rough index for estimating the degree of muscular relaxation, that is, when the maximum increase in heart

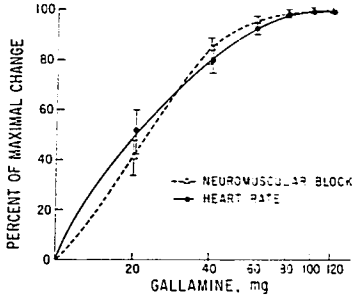

FIG. 1. Twitch depression and increases in heart rate following gallamine in incremental (20 mg) doses in 13 subjects (mean ± SE). Gallamine was administered in incremental doses at 2–3-minute intervals. Gallamine is plotted on a log scale against the per cent of maximal change from control on a linear scale.

TABLE 2. Group B: Increases in Heart Rate after a Single Dose of Gallamine Followed by Atropine

	Dose (mg)			
	100 (N = 6)	200 (N = 8)	300 (N = 6)	400 (N = 7)
Control heart rate	78 ± 9	72 ± 13	85 ± 15	78 ± 11
Heart rate after gallamine	98 ± 11	100 ± 13	106 ± 8	102 ± 13
Per cent change	25 ± 9	42 ± 18	28 ± 14	31 ± 6
P value compared with 100 mg		>0.05	>0.5	>0.05
Heart rate after atropine (2.0 mg)	115 ± 8	112 ± 11	112 ± 10	107 ± 14

rate is reached the twitch response in the hand muscles should be abolished. However, it should be noted that gallamine-induced tachycardia outlasts the neuromuscular block; therefore, the heart rate would not indicate subsequent recovery of neuromuscular transmission.

The heart rate changes with gallamine differ from those with atropine in that the tachycardia produced by gallamine is less than that with atropine regardless of dosage. In this study, incremental doses of gallamine (20 mg) produced continuous increases in heart rate which were less than the increases following atropine in increments of 0.2 mg (fig. 2). The doses chosen, though arbitrary, are clinically applicable. A possible explanation may be related to the findings of a recent study which showed that in rabbits, nondepolarizing muscle relaxants antagonized the cardiac effects of acetylcholine, suggesting that gallamine may bind acetylcholine receptor sites in the heart.[4] This proposed mechanism differs from the competitive antagonism of acetylcholine by atropine, which may be more effective than a possible receptor binding by gallamine.

When single large doses of gallamine are given, the tachycardia is not significantly greater than that seen with 100 mg. Two patients receiving 300 mg and one patient given 400 mg had heart rate values that were not further increased by atropine; however, the average heart rate change of all patients receiving these doses was less than that produced by 2 mg of atropine (see table 2). It is possible that gallamine produced total cardiac vagal blockade in three patients. However, it is also possible that sympathetic tone was minimal in these patients, and, therefore, atropine could not further increase the heart rate, regardless of gallamine.

Changes in heart rate can result from a variety of factors influencing the autonomic nervous system, including level of anesthesia, acid–base changes, and body temperature. These factors were kept constant so far as possible. In the presence of halothane or cyclopropane anesthesia, atropine produces a greater increase in heart rate compared with heart rate changes in unanesthetized subjects.[5] It is possible that in this study the increase in heart rate with gallamine might have been less had an anesthetic other than halothane been used.

These data suggest that gallamine does not produce total cardiac vagal efferent blockade. However, they do not explain how this area is affected, nor why no other muscarinic receptors apparently are affected.[1] Farman and Kennedy[6] earlier demonstrated that the tachy-

TABLE 3. Group C: Increases in Heart Rate Following Atropine, n = 8

	Dose (mg)								
	0	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6
Beats/min	70 ± 10	75 ± 11	96 ± 17	105 ± 21	112 ± 22	115 ± 21	118 ± 24	122 ± 27	125 ± 24
Per cent change	—	8.0 ± 7	37 ± 12	49 ± 17	60 ± 18	65 ± 21	78 ± 20	80 ± 22	83 ± 20

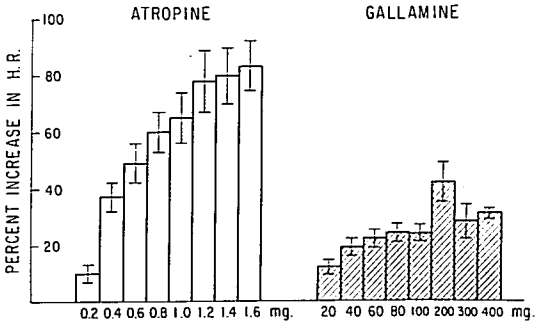

FIG. 2. Chronotropic effects of gallamine and atropine (mean ± SE) in five similar groups of patients under halothane anesthesia. Gallamine was given in single injections of 200, 300, and 400 mg to three separate groups, whereas gallamine 20 to 100 mg represents the fourth group of patients, which received incremental doses. Atropine in 0.2-mg doses was given to the fifth group.

cardia from gallamine was not maximal, since atropine produced increases in heart rate and cardiac output in patients anesthetized with nitrous oxide who were given gallamine (120 mg) prior to atropine.

Smith and Whitcher[7] found increases in cardiac output and left ventricular work following gallamine in five anesthetized patients who did not receive atropine. It is likely that any positive inotropic influence was secondary to the chronotropic effect of gallamine in their study. Brown and Crout[8] showed in guinea pigs and cats that gallamine increases cardiac rate and contractile force by releasing norepinephrine from adrenergic nerve endings in the heart by an unknown mechanism. There is considerable species variation regarding sympathetic cardiac tone: for example, rabbits do not develop tachycardia after gallamine.[9] In dogs, gallamine increases heart rate and blood pressure, but does not have any apparent cardiovascular effects after cervical vagotomy (J. H. E.: unpublished data). In preliminary studies in anesthetized man, we have not observed any changes in heart rate or blood pressure when gallamine was given after 2 mg of atropine. This suggests that inhibition of the cardiac vagus, although different from that caused by atropine, is the only cardiac effect of gallamine.

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