CARDIOVASCULAR EFFECTS OF GALLAMINE TRIETHIODIDE IN MAN

BY

B. R. KENNEDY AND J. V. FARMAN

SUMMARY

The effect of intravenously administered gallamine triethiodide (0.5–1.0 mg/kg) on cardiovascular function was estimated in patients anaesthetized with thiopentone, tubocurarine, nitrous oxide and trichloroethylene and artificially ventilated. A 40 per cent rise in heart rate and a 35 per cent rise in cardiac output were observed, with no significant change in stroke volume. A modest rise in mean arterial pressure and a similar fall in total peripheral resistance resulted. Stroke work was found to be increased slightly. The effects of the two different dose levels of gallamine did not differ significantly. The results do not support the idea of an inotropic action of gallamine and the changes produced in the peripheral circulation are thought to represent passive responses to the increase in cardiac output.

The synthetic muscle relaxant gallamine triethiodide (Flaxedil) was first described in 1947 (Bovet, Depierre and Lestrange) and introduced into anaesthetic practice in the following year (Huguenard and Boué, 1948). Although its primary action at the myoneural junction has been carefully evaluated (Wein, 1948; Unna et al., 1950; Unna and Pelikan, 1951), its other actions, notably on the cardiovascular system, have been less exhaustively examined.

The occurrence of circulatory changes following the use of gallamine triethiodide in anaesthesia was first reported in 1949 (Lamoureux and Bourgeois-Gavardin). These authors observed that tachycardia was an almost unvarying sequel to its administration, and this finding has been confirmed in many subsequent reports.

Less unanimity is apparent in accounts of blood pressure changes induced by gallamine triethiodide. In some instances, rises in blood pressure have been found (Unna and Pelikan, 1951; Foldes et al., 1952; Foldes, Machaj and Carberry, 1954), in others the level has remained unaltered (Mushin et al., 1949; Condon, 1951; Doughty and Wylie, 1951; Greenfield, Imig and Evonuk, 1961; Walts and Prescott, 1965) and in one investigation a fall was recorded (Fahmy, 1960). In general such investigations have paid scant attention to the production of standard conditions, but in a recent study in which different doses of gallamine triethiodide were given under clearly defined circumstances (Thomas, 1963) some degree of hypertension was found to occur in 75 per cent of cases.

The purpose of the present investigation was to establish the nature and degree of alterations in various circulatory functions following intravenous administration of gallamine triethiodide.

METHOD

The 14 subjects were all adult inpatients with no known cardiorespiratory disease. All were undergoing surgery for which endotracheal intubation, muscle relaxation and intermittent positive pressure ventilation would normally have been employed. The ages, weights and sex of the patients, together with the dosage of thiopentone used are shown in table I. In every instance the objects and nature of the investigation were explained to the patient beforehand and consent obtained.

Papaveretum and hyoscine were given intramuscularly for premedication (see table II) and the time of administration recorded. Anaesthesia was induced with intravenous thiopentone sodium in an amount approximately one and a half times that required to abolish eyelash reflex, and was immediately followed by tubocurarine in the doses shown in table I. The lungs were inflated with a mixture of nitrous oxide and oxygen, and the trachea intubated with a cuffed tube. Anaesthesia was maintained with nitrous oxide (60 per
Table I

Ages, weights and sex of the patients studied with dosage of thiopentone and gallamine triethiodide.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Thiopentone (mg/kg)</th>
<th>Gallamine (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>82</td>
<td>4.9</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>M</td>
<td>72</td>
<td>6.9</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>F</td>
<td>55</td>
<td>6.3</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>70</td>
<td>5.0</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>F</td>
<td>64</td>
<td>4.7</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>M</td>
<td>67</td>
<td>6.3</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>F</td>
<td>65</td>
<td>5.4</td>
<td>0.5</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>F</td>
<td>65</td>
<td>5.4</td>
<td>0.5</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>M</td>
<td>72</td>
<td>4.9</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>F</td>
<td>75</td>
<td>4.1</td>
<td>0.5</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>M</td>
<td>74</td>
<td>5.4</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>41</td>
<td>M</td>
<td>67</td>
<td>6.7</td>
<td>1.0</td>
</tr>
<tr>
<td>13</td>
<td>55</td>
<td>F</td>
<td>52</td>
<td>5.8</td>
<td>1.0</td>
</tr>
<tr>
<td>14</td>
<td>28</td>
<td>M</td>
<td>91</td>
<td>4.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Mean: 41.3, SD: 9.24

Table II

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose of tubocurarine (mg)</th>
<th>Premedication (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>40</td>
<td>Papaveretum, 20, hyoscine, 0.4</td>
</tr>
<tr>
<td>65–80</td>
<td>30</td>
<td>Papaveretum, 20, hyoscine, 0.4</td>
</tr>
<tr>
<td>50–65</td>
<td>25</td>
<td>Papaveretum, 15, hyoscine, 0.4</td>
</tr>
<tr>
<td>40–50</td>
<td>20</td>
<td>Papaveretum, 10, hyoscine, 0.4</td>
</tr>
</tbody>
</table>

RESULTS

Dye dilution curves were obtained and blood pressure and heart rate measured before injection of gallamine triethiodide and afterwards at the intervals specified. Mean arterial pressure and
relative changes from the control levels of cardiac output, stroke volume, peripheral resistance and left ventricular stroke work were calculated. Results were not included in the series where a discrepancy of 30 seconds or more existed between the intended and the actual time of the estimation, and in some instances the investigation had to be terminated before the 10-minute measurement to avoid further delaying the commencement of surgery.

The patients were grouped according to the dosage of gallamine triethiodide used: those in Group A were given 0.5 mg/kg while Group B received 1.0 mg/kg. A total of 14 patients was studied, 10 in Group A and 4 in Group B.

The results obtained for each parameter were considered separately and examined statistically in the following ways. In each group, significant differences were sought between the control values and the results at each of the four time intervals. The significance of the difference of the means of the two groups was tested at each of the specified time intervals. Finally the mean values of all the results following the injection of gallamine triethiodide were calculated for each of the two groups and the significance of the difference determined.

Cardiac output (CO).

Increase in cardiac output occurred in both groups. The average increase in Group A was 34.4 per cent and in Group B was 36.6 per cent. In both groups the increases were significant at all time intervals \((P<0.05)\). The average increases in output are shown in figure 1. No statistically significant difference was found between the mean values at any of the time intervals. Neither was there any significant difference between the overall means of the two groups.

Stroke volume (SV).

No significant changes from the control values of stroke volume were found in either group except at the 10-minute time of measurement in Group B. The average stroke volume in Group A was 96.9 per cent of the control volume and in Group B 97.2 per cent of the control volume. The average changes in stroke volume of the two groups are seen in figure 2. No statistically significant difference was found between the two groups at any of the time intervals, nor between the mean values of all the post-gallamine triethiodide results.

Heart rate.

After gallamine triethiodide, an increase in heart rate was found consistently. The average increase in heart rate after gallamine triethiodide was 39.6 per cent in Group A and 40.8 per cent in Group B. The difference from the control rate was significant for all time intervals except the 10-minute in Group A. Significance was not reached here and in the case of some other measurements at this time of estimation, as the number of observations was small, so that significance required a difference of more than 2 SE. Although the average increase was highest for this measurement the wider scatter of results and smaller number of cases prevented significance being achieved. The average control heart rate in both groups was 62. The average percentage increases in the rate at the times of measurement are shown in figure 3. The increases in heart rate were not significantly different in the two groups, either at any of the individual times of measurement, or in the means of all the post-gallamine results.

Mean arterial pressure (MAP).

MAP was derived from the formula:

\[ MAP = \text{Diastolic BP} + \frac{1}{4} \text{ Pulse pressure}. \]

Elevation of MAP was found in all patients on every occasion except one after injection of gallamine triethiodide. The average increase in MAP in Group A was 13.80 per cent and in Group B 10.43 per cent. Pressures which differed significantly from the control MAP were found at 1, 3, and 5 minutes in Group A, and at all times except the 1-minute estimation in Group B.

Figure 4 shows the percentage increases in MAP at the different times of measurement. No significant difference was found between the values for the two groups at any of the times of measurement, or in the mean values of all the post-gallamine triethiodide results.

Total peripheral resistance (TPR).

TPR was derived from the formula:

\[ TPR = \frac{\text{MAP}}{\text{CO}}. \]

Falls in resistance occurred in both groups at all the times of measurement. These represented statistically significant changes from the control.
The effect of gallamine triethiodide on cardiac output.

The effect of gallamine triethiodide on heart rate.

The effect of gallamine triethiodide on peripheral resistance.

The effect of gallamine triethiodide on mean arterial pressure.

The effect of gallamine triethiodide on left ventricular stroke work.

The control values are expressed as 100 per cent. The group which had 0.5 mg/kg of gallamine triethiodide are shown (●●●●●) and the group which had 1.0 mg/kg as (○○○○○).
value in all instances except the 1-minute estimation in Group B. The overall drop in resistance in the two groups was 14 and 18.73 per cent respectively. The average changes at the different intervals are shown in figure 5. The falls in TPR were not significantly different between the groups at any of the times of measurement, or for the overall means.

Left ventricular stroke work (LVSW).

LVSW was derived from the formula:

\[ \text{LVSW} = \text{SV} \times (\text{MAP} - 5 \text{ mm Hg}) \]

The average LVSW after gallamine triethiodide rose by 14.1 per cent in Group A and by 7.76 per cent in Group B. Although a modest increase in stroke work was common to both groups, increases were only significant at the 1, 3, and 5-minute measurements in Group A and at the 10-minute measurement in Group B. The average changes at the different time intervals are shown in figure 6. No significant differences were found in the results for LVSW between the groups at any time interval, or for the overall mean rises.

DISCUSSION

In the assessment of a drug, it is axiomatic that the administration of other drugs immediately preceding and during the period of study should be avoided. It is, however, difficult to approach this ideal state in a study of the physiological changes induced by a muscle relaxant in a dose which causes muscle paralysis. Use of such drugs in doses normally employed in clinical practice virtually necessitates the administration of general anaesthesia. The maintenance of physiological homeostasis throughout the period of investigation is also of importance, in order that changes may validly be compared with control observations. Although it was assumed that a steady state had developed by the time control measurements were made, which was not less than 15 minutes after induction of anaesthesia, it is accepted that these values might not be representative of the patients' normal. The circulatory effects of induction of anaesthesia are, however, usually transient (Graf, Ström and Wåhlin, 1963), and the return to normal is usually most pronounced during the first 10–15 minutes (Quilligan, Hendricks and Hingson, 1957). Had the initial measurements been made before induction, it is doubtful whether the results obtained would have been of greater value as apprehension in this case about the impending surgical operation is known to increase the cardiac output (Wade and Bishop, 1962). In the case of muscle relaxants, fallacious conclusions may be reached in the interpretation of alterations in cardiovascular function which follow their administration, either because of a variable degree of respiratory paralysis and carbon dioxide retention or because artificial ventilation is instituted immediately. Changes directly attributable to artificial ventilation (Prys-Roberts et al., 1967) and to hypocapnia (Theye, Milde and Michenfelder, 1966) or to hypercapnia (Prys-Roberts and Kelman, 1966) are already known to occur.

For these reasons it was decided to conduct this investigation on anaesthetized patients in whom full muscle paralysis had already been induced and artificial ventilation instituted. Some modification of the circulatory effects of gallamine triethiodide is possible but the anaesthetic agents were chosen and used in a dosage likely to have a minimum effect on either the central or peripheral components of the cardiovascular system.

The tachycardia which follows administration of gallamine triethiodide is marked both in degree and in rapidity of onset, and in the present series the average increase in rate was over 40 per cent. Tachycardia is said to occur however small the dosage of gallamine triethiodide (Doughty and Wylie, 1951) and has long been believed to result from blockade of the muscarinic effects of acetylcholine liberated from the post-ganglionic vagal nerve endings (Riker and Wescoe, 1951). In this action, the drug resembles atropine, although it is much weaker (Laity and Garg, 1962), but remarkably it exhibits this atropine-like effect at no other site (Paton, 1959). Neither is there any evidence of general sympathetic stimulation (Wein, 1951) and the effects on preganglionic sympathetic nerves are minimal (Millar and Biscoe, 1965). A direct stimulant effect on intracardiac \( \beta \) receptors has recently been demonstrated (Morgenstern and Splinth, 1965) but the extent to which the tachycardia results from this mechanism has not yet been decided.

Cardiac output is the product of stroke volume and heart rate, and changes in cardiac output are
the resultant of changes in these variables. In the present investigation the increase in cardiac output (overall mean 35.5 per cent) after gallamine triethiodide was entirely due to an increase in heart rate with no significant alteration in stroke volume. The effects of increase in heart rate on the cardiac output and stroke volume differ according to the aetiology of the tachycardia. It has been shown in innervated left ventricular preparations that the vagi exert a tonic depressant effect on the contractility of the ventricular myocardium (De Geest et al., 1965; Levy et al., 1966), but in the intact animal a reduction in vagal tone has been shown to cause a marked fall in stroke volume (Rushmer, 1966). Tachycardia caused by electrical stimulation of the sinoatrial node in the intact animal causes a very significant drop in diastolic, systolic and stroke changes in ventricular diameter in contrast to the increased heart rate and maintained stroke volume which is the normal response to exercise (Rushmer and Smith, 1959). During exercise, the heart is made a much stronger pump by sympametic stimulation which prevents a reduction in stroke volume. In this respect, the response to gallamine triethiodide resembles that which follows exercise, as the stroke volume is maintained in face of an increased pulse rate. The possibility that this could result from an increase in myocardial contractility following \( \beta \) receptor stimulation has been suggested by Brown and Crout (1966, 1968).

The effects of intravenous atropine on the cardiovascular system in anaesthetized patients are less consistent, but in an investigation (Farman and Kennedy, 1968) in which anaesthesia was induced and maintained in a manner similar to that employed here, the response to 0.6 mg of atropine given intravenously, closely resembled that of gallamine triethiodide. Atropine appears devoid of any sympathetic stimulating action, and the case for the possession of such an effect by gallamine triethiodide is not strengthened by these findings. It would appear that the heart is capable of maintaining its control level of stroke volume when the drug-induced increase in heart rate is of moderate proportions.

The difficulties of attempting to separate a primary change in cardiac output accompanied by a secondary effect on the peripheral circulation from primary peripheral effects with secondary central compensation have been discussed elsewhere (Gorten et al., 1961). Increases in mean arterial pressure were seen consistently, although they did not achieve significance at all the times at which measurements were made. The overall increase in mean arterial pressure was 12 per cent, accompanied by a mean fall in total peripheral resistance of 16 per cent. There is no evidence to suggest that gallamine triethiodide has any action on blood vessels either by a ganglionic effect (Riker and Wescoe, 1951) or by a direct action on the vessel wall. We therefore conclude that the increase in cardiac output which we observed represented the primary change, and that this additional flow was accommodated by a passive rise in arterial pressure combined with a passive fall in peripheral resistance caused by arteriolar distension.

Left ventricular stroke work was increased in both groups of patients although significant levels were not always reached. A rise in stroke work is expected in view of the maintained stroke volume in association with an elevation of mean arterial pressure.

The mean increase in LVSW in our patients was not marked, but the heart rate increased by 40 per cent, representing a considerable increase in the work done compared with the control period. Although doubts have been expressed regarding the validity of values for stroke work based on mean values (Rushmer, Vancitters and Franklin, 1963), this measurement undoubtedly gives some indication of the changing demands made on the myocardium.

There were no significant differences in the results obtained following the two different doses of gallamine triethiodide, but the changes in each parameter were found to be much more consistent with 1 mg/kg gallamine triethiodide than with 0.5 mg/kg. Changes similar in nature and degree to those we observed following intravenous gallamine triethiodide have been recently reported by Smith and Whitcher (1967) who investigated its effects during anaesthesia when muscle relaxation adequate to allow intermittent positive pressure ventilation was provided by halothane. This similarity exists despite the larger dose/weight ratio of gallamine triethiodide (1.5 mg/kg) and the different pharmacological background of the study.


**EFFETS CARDIO-VASCULAIRES DU TRIETHIODIDE DE GALLAMINE SUR L'HOMME**

**SOMMAIRE**

L'action du triéthiodide de gallamine, à raison de 0,5–1,0 mg/kg, administré par voie i.v. sur la fonction cardio-vasculaire fut évaluée sur des malades anesthésiés par le thiopentone, la tubocurarine, le protoxyde d'azote et le trichloréthylène et ventilés artificiellement. Un accroissement de 40 pour cent dans le rythme cardiaque et une augmentation de 35 pour cent dans le débit cardiaque sans changement notable du volume systolique furent constatés. Il en est résulté une augmentation modérée de la pression artérielle moyenne et une chute similaire de la résistance périphérique totale. Une hausse légère du travail systolique fut constatée. Les effets des deux seuils différents de la dose de gallamine ne différaient pas d'une manière significative. Les résultats ne permettent pas de soutenir l'hypothèse d'une action inotrope de la gallamine et les changements provoqués dans la circulation périphérique sont censés représenter des réponses passives à l'augmentation du débit cardiaque.

**ZUSAMMENFASSUNG**

Der Einfluß von intravenös verabreichtem Gallamin-triethiodid (0,5–1,0 mg/kg) auf die Funktion von Herz und Kreislauf wurde bei Patienten, die mit Thiopentan, Tubocurarin, Lachgas und Trichloräthylen narkotisiert und künstlich beatmet wurden, untersucht und beurteilt. Es wurden eine Zunahme der Herzfrequenz um 40 Prozent und ein Anstieg des Herzminutenvolumens um 35 Prozent beobachtet, wobei eine signifikante Änderung des Schlagvolumens ausblieb. Dabei ergaben sich eine mäßige Erhöhung des mittleren arteriellen Druckes und ein mäßiger Abfall des gesamten peripheren Widerstandes. Ferner wurde gefunden, daß die Schlagarbeit leicht erhöht war. Die Wirkung der zwei verschiedenen Mengen Gallamin unterschied sich nicht signifikant. Die Ergebnisse unterstützen die Vorstellung einer inotropen Wirkung von Gallamin nicht. Die Veränderungen, die im peripheren Kreislauf ausgelöst wurden, stellen nach Ansicht der Autoren eine passive Antwort auf den Anstieg des Herzminutenvolumens dar.

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**EDINBURGH AND EAST OF SCOTLAND SOCIETY OF ANAESTHETISTS**

**Syllabus 1968–69**

**1968**

**SATURDAY, OCTOBER 26**

Combined Meeting with Glasgow and West of Scotland Society of Anaesthetists will be held in the University of Edinburgh Staff Club, Chambers Street, Edinburgh, at 5.15 p.m.

**INSTRUMENTATION AND MONITORING**

Dr. J. M. M. Neilson, Department of Medical Physics, The Royal Infirmary, Edinburgh.

A Buffet Supper will follow the Meeting.

**TUESDAY, NOVEMBER 12**

**PRESIDENTIAL ADDRESS,** Dr. A. S. Brown.

**TUESDAY, DECEMBER 10**

**THEATRE DESIGN,** Professor D. M. Douglas, Department of Surgery, The University, Dundee.

The Meetings will be held in the Royal College of Surgeons of Edinburgh at 7.45 for 8 p.m. unless otherwise specified.

**1969**

**TUESDAY, JANUARY 14**

**The Sick Child Area,** Dr. G. Jackson Rees, Consultant Anaesthetist, Royal Infirmary, Royal Children's Hospital and Alder Hey Hospital, Liverpool.

**TUESDAY, FEBRUARY 11**

**Burns, Old and New,** Dr. C. M. Howie, Consultant Anaesthetist, Bangour General Hospital.

**FRIDAY, FEBRUARY 28**

**INFORMAL DINNER in University Staff Club.**

**TUESDAY, MARCH 11**

**Members' Short Papers.**

**TUESDAY, APRIL 29**

**Annual General Meeting.**