THE HÆMODYNAMIC EFFECTS OF SODIUM AMOBARBITAL IN HYPERTENSION

BY

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It has long been accepted that barbiturates tend to lower the systemic arterial pressure in patients with hypertension, and this effect has been used in various diagnostic sedation tests. However, because of the inadequate description of the drug’s effect on the cardiac output in hypertension, the hæmodynamic mechanism responsible for the hypotensive action is not clear. As barbiturates are often administered at the same time as powerful hypotensive agents either for sedation or anaesthesia, it is important to know the mode of action of the drug on the cardiovascular system.

The purpose of this paper is to describe the acute effects of sodium amobarbital on the cardiac output, stroke output, blood pressure, and peripheral resistance in a series of patients with hypertension.

SUBJECTS AND METHODS

The subjects of this study were 13 patients with hypertension admitted to the medical wards for diagnosis and treatment: 7 were women and 6 were men, and their average age was 52 years, varying between 29 and 71 years. The diagnoses at the time of discharge are listed in the Table. The average of the control mean arterial pressures was 157 mm. Hg; one of the patients (M. M.) had a normal blood pressure (145/90 mm. Hg) at the time of study although she had had hypertension at the time of admission. None of the patients was acutely ill, had fundoscopic evidence of malignant hypertension (Keith-Wagner grades III and IV), or had signs of peripheral or pulmonary oedema. With the exception of patient M. M., all had electrocardiographic and radiological evidence of minimal to moderate left ventricular hypertrophy. None, except patient E. M., had received drugs during the several weeks before study; E. M. was on daily maintenance digitalis and received three daily oral doses of 60 mg. of guanethidine and one 500 mg. dose of chlorothiazide during the three days preceding investigation.

Patients received no premedication and the investigations were begun two hours after a light lunch. Cardiac outputs were measured by the indicator dilution method from dye curves recorded with a photographic apparatus†, chopper amplifier‡, and direct writer§ recording system (Gabe, Tuckman, and Shillingford, 1962). A catheter was passed to the right atrium and then the earpiece fastened to an ear pinna previously treated with vasodilating ointment§. When the catheter and earpiece were in place the patient was allowed to rest quietly for about 30 minutes, after which at least three control measurements of cardiac outputs and right atrial pressures were made: measurements of arterial pressures (by auscultation) and heart rates were obtained more frequently. Sodium amobarbital, 2.5 per cent, was then given slowly into an antecubital vein. The total dosages varied between patients and were decided from observations of arterial pressure.

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‡ Evershed and Vignoles Limited, Chiswick, England.
§ Trafuril (5% tetrahydrofurfuryl nicotinate).
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Fig. 1.—The haemodynamic effects of intravenous sodium amobarbital in 13 patients with hypertension. It will be seen that there is a fall in systolic arterial pressure, with a relatively unchanged diastolic pressure, after the administration of the drug. This is associated with a fall in cardiac output but no significant change in peripheral resistance. The heart rate shows a variable response but the stroke output falls. (C = control; A = maximal effect caused by the drug.)
and subjective effects; 305 mg. was the average amount (75 to 500 mg.) given over an average of 13 minutes with a range of 6 to 21 minutes. Haemodynamic measurements were made during and after the period of barbiturate administration; the average period after discontinuing the drug during which these measurements were made was 23 minutes and ranged between 8 and 32 minutes.

The 2 per cent Coomassie Blue indicator was given from a calibrated syringe through the cardiac catheter into the right atrium and, depending on the internal volume of the catheter, 20 to 40 mg. per in-

<table>
<thead>
<tr>
<th>Patient, sex and age (yr.)</th>
<th>C* or A*</th>
<th>Arterial pressure (mm. Hg) Syst. Diast.</th>
<th>Cardiac output†</th>
<th>Peripheral resistance†</th>
<th>Heart rate</th>
<th>Stroke volume†</th>
<th>Atrial pressure† (mm. Hg)</th>
<th>Amytal dose and depth of anaesthesia</th>
<th>Diagnosis and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. D. F M</td>
<td>C A</td>
<td>240/125</td>
<td>88</td>
<td>84</td>
<td>1.00</td>
<td>1.00</td>
<td>+3.2 0.0</td>
<td>250 mg.</td>
<td>Post-irradiation nephritis</td>
</tr>
<tr>
<td>F. D. M</td>
<td>C A</td>
<td>190/130</td>
<td>66</td>
<td>1.00</td>
<td>0.78</td>
<td>0.99</td>
<td>+3.5 -2.0</td>
<td>500 mg.</td>
<td>Chronic pyelonephritis</td>
</tr>
<tr>
<td>L. D. M</td>
<td>C A</td>
<td>180/100</td>
<td>72</td>
<td>0.99</td>
<td>1.00</td>
<td>0.93</td>
<td>+4.5 -1.0</td>
<td>450 mg.</td>
<td>Coarctation of aorta</td>
</tr>
<tr>
<td>F. F. M</td>
<td>C A</td>
<td>155/115</td>
<td>77</td>
<td>0.93</td>
<td>1.00</td>
<td>0.93</td>
<td>+6.5 -1.5</td>
<td>450 mg.</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>T. M. M</td>
<td>C A</td>
<td>165/120</td>
<td>74</td>
<td>0.92</td>
<td>1.00</td>
<td>0.92</td>
<td>+4.0 -1.5</td>
<td>75 mg.</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>E. S. F</td>
<td>C A</td>
<td>230/120</td>
<td>78</td>
<td>0.98</td>
<td>1.00</td>
<td>0.93</td>
<td>+5.0 0.0</td>
<td>175 mg.</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>W. H. M</td>
<td>C A</td>
<td>220/130</td>
<td>78</td>
<td>0.90</td>
<td>1.00</td>
<td>0.92</td>
<td>+5.5 -3.0</td>
<td>300 mg.</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>M. R. F</td>
<td>C A</td>
<td>225/115</td>
<td>56</td>
<td>0.89</td>
<td>1.00</td>
<td>0.95</td>
<td>+8.0 -3.0</td>
<td>500 mg.</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>W. O. M</td>
<td>C A</td>
<td>260/150</td>
<td>78</td>
<td>0.94</td>
<td>1.00</td>
<td>0.86</td>
<td>+5.5 -3.0</td>
<td>300 mg.</td>
<td>Unilateral renal disease</td>
</tr>
</tbody>
</table>

and subjective effects; 305 mg. was the average amount (75 to 500 mg.) given over an average of 13 minutes with a range of 6 to 21 minutes. Haemodynamic measurements were made during and after the period of barbiturate administration; the average period after discontinuing the drug during which these measurements were made was 23 minutes and ranged between 8 and 32 minutes.

The 2 per cent Coomassie Blue indicator was given from a calibrated syringe through the cardiac catheter into the right atrium and, depending on the internal volume of the catheter, 20 to 40 mg. per in-
**Hæmodynamic Effects of Sodium Amybarbital**

**Table (continued)**

<table>
<thead>
<tr>
<th>Patient, sex and age (yr.)</th>
<th>Arterial pressure (mm. Hg)</th>
<th>Cardiac output†</th>
<th>Peripheral resistance†</th>
<th>Heart rate</th>
<th>Stroke volume†</th>
<th>Atrial pressure‡ (mm. Hg)</th>
<th>Amytal dose and depth of anaesthesia</th>
<th>Diagnosis and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. S. M</td>
<td>C</td>
<td>205/115</td>
<td>1-00</td>
<td>66</td>
<td>1-00</td>
<td>+6-5</td>
<td>250 mg. Light sleep</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>170/110</td>
<td></td>
<td>60</td>
<td></td>
<td>0-0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. E. F</td>
<td>C</td>
<td>185/90</td>
<td>1-00</td>
<td>60</td>
<td>1-00</td>
<td>+6-5</td>
<td>200 mg. Light sleep</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>160/90</td>
<td>0-84</td>
<td>56</td>
<td>0-90</td>
<td>0-0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. M. F</td>
<td>C</td>
<td>145/90</td>
<td>0-84</td>
<td>58</td>
<td>+4-5</td>
<td>0-0</td>
<td>250 mg. Light sleep</td>
<td>Labile essential hypertension; 'normotensive' at time of study</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>145/95</td>
<td></td>
<td>66</td>
<td></td>
<td>0-0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. M. F</td>
<td>C</td>
<td>205/105</td>
<td>1-00</td>
<td>55</td>
<td>+10-5</td>
<td>0-0</td>
<td>240 mg. Light sleep</td>
<td>Chronic pyelonephritis; receiving guanethidine chlorothiazide, and digitalis</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>135/85</td>
<td></td>
<td>57</td>
<td>+7-5</td>
<td>0-0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>C</td>
<td>214/119</td>
<td>1-00</td>
<td>72</td>
<td>1-00</td>
<td>+5-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>170/110§</td>
<td>0-84§</td>
<td>70</td>
<td>0-84§</td>
<td>+3-1§</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* C = average of control values; A = maximal effect caused by drug.
† To make the changes of cardiac output, peripheral resistance, and stroke volume readily apparent, the values in each series are expressed relative to the average of the control determinations in that series, this being expressed as unity.
‡ Maximal and minimal pressures during expiration and inspiration respectively; reference point is 5 cm. below sternal angle.
§ Percentage change of systolic pressure = \(-21\) Percentage change of mean pressure (diastolic +40% pulse pressure) = \(-15\) per cent.

|| Averages do not include patients M. M. and E. M.

| *Statistically significant at the p = 0.02 level or less. |

Injection were delivered to the patient. However, in any one procedure all injections were of equal quantity. The total dosage to any patient did not exceed 5 mg. per kg. body weight.

Changes of cardiac output were calculated from the non-calibrated earpiece dye dilution curves (Gabe et al., 1962). The curves were plotted on semilogarithmic paper and the areas measured by the usual method of numerical summation at one-second intervals until the downslope exponentials, and from there were calculated to infinity by standard methods of integration (Lilienfield and Kovach, 1956). Since the recording system used was linear over the range of blood dye concentrations expected here, and since in any one procedure all injections of dye were of equal quantity, the relative cardiac outputs represented by a series of earpiece curves are related as the reciprocals of the areas under the curves. Peripheral resistance as commonly defined is the ratio of mean arterial pressure to cardiac output; \( PR = \frac{\text{mean blood pressure}}{\text{cardiac output}} \).

Necessarily then, relative changes in peripheral resistance during a procedure can be calculated from the relative changes in mean arterial pressure and cardiac output.
RESULTS

Results from the 13 procedures are presented in the Table. Fig. 1 gives these data in graphic form. It will be seen from the Table that the depth of anaesthesia was light in all procedures. One patient did not experience subjective effects, 4 became drowsy, and 8 went into a light sleep; the patients in this last group were easily awakened by being spoken to. The barbiturate was administered slowly over 13 minutes; when the administration was stopped the arterial pressure decreased to its lowest level for approximately (average) 15 minutes (range 8 to 32 minutes), after which it began to rise slowly. In most of the tests the arterial pressure was still substantially reduced 30 minutes after the sodium amobarbital administration was stopped.

In all cases there was a fall in the systolic arterial pressure varying from 25 to 70 mm. Hg. On the other hand the diastolic pressure showed little change. The fall in the systolic pressure was associated with a drop in the cardiac output varying from 8 to 22 per cent. The average peripheral resistance was not significantly altered and the effect of the drug on the heart was variable.

Eleven of the investigations were in non-treated patients with hypertension, one in a patient treated for hypertension (E. M.) (digitalis, guanethidine, and chlorothiazide), and one in a patient with normal blood pressure (M. M.). When considering the effects of barbiturates in hypertension in the discussion, only the results from the 11 patients with hypertension, who were not treated, are analysed. The results from the procedures with E. M. and M. M. are included because it is of interest that on the one hand the only patient (M. M.) who did not exhibit a decrease in arterial pressure had a normal pressure at the time of study and on the other hand the patient (E. M.) who showed the greatest arterial pressure decrease was the only one on antihypertensive treatment. In several of the procedures technical difficulties prevented the recording of successful series of dye curves and atrial pressures.

DISCUSSION

It is well known that barbiturates will lower systemic arterial pressure in both patients with normal, and patients with high, blood pressure. Since systemic arterial pressure is dependent on cardiac output and impedance to flow, the simplest analysis of the drug’s hypotensive action requires simultaneous measurements of arterial pressure and cardiac output with calculation of peripheral resistance from their ratio.

Previous works on the hemodynamic effects of barbiturates in man are frequently difficult to interpret as they include different barbiturate preparations, different routes and rates of administration, and in some reports the drugs have been combined with other agents such as nitrous oxide, morphine, scopolamine, or atropine. The present discussion will be limited to situations in which the barbiturates are given slowly either intravenously or by mouth, and adjuvant drugs are limited to morphine and scopolamine (or atropine) in the usual premedication dosages.

Several studies allow reasonable quantitative analysis of the hemodynamic effects of barbiturates in patients with normal blood pressure (McClure et al., 1939; Johnson, 1951; Winchell, Taylor, and Chapman, 1951; Price et al., 1952; Etsten and Li, 1955). These showed that mean arterial pressure remained unchanged during hypnosis, usually decreased in surgical anaesthesia (4 to 13%), and that the fall was due mostly to a change in systolic pressure. Heart rate was unaltered in hypnosis but during surgical anaesthesia it increased by 14 to 16 beats a minute. This increase occurred even in the absence of any hypotensive effect. Two of the reports (Johnson, 1951; Etsten and Li, 1955) used direct Fick and indicator dilution methods to measure cardiac output. Their results showed that cardiac output and peripheral resistance did not change significantly during hypnosis but in surgical anaesthesia the former fell by 25 to 29 per cent and the latter increased by 18 to 32 per cent. It follows from these results that there was no change in stroke volume during hypnosis but a very significant decrease during surgical anesthesia.

In considering the hemodynamic effects of barbiturates in hypertension, many authors have written with reference to the sedation tests introduced by Allen in 1936 (Allen, Lundy, and Adson,
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1936) to choose suitable patients for sympathectomy. In patients with hypertension most workers agree that during hypnosis there are decreases of both mean arterial pressure (due mostly to alteration of systolic pressure) and of heart rate. The average decreases in mean arterial pressure and heart rate vary respectively between 9 and 22 per cent and 5 and 10 beats a minute (Winchell et al., 1951; Allen et al., 1936; Grob and Langford, 1953; Kory and Mabe, 1954; Nelson et al., 1955; Dal Palü and Crepaldi, 1958).

Sedation tests in patients with raised blood pressure assume that barbiturates lower arterial pressure by decreasing peripheral resistance. However, knowledge of the drug’s action on cardiac output in such patients is incomplete. Three groups of workers (Winchell et al., 1951; Dal Palü and Crepaldi, 1958; Kory and Mabe, 1954) have investigated this question, two using ballistocardiography and pulse pressure contour analysis, and the third using direct Fick method, reported only in abstract form. During sodium amobarbital hypnosis the first two studies reported a decrease in cardiac output and an increase in peripheral resistance, but the third reported inconsistent changes in cardiac output and an average decrease in peripheral resistance of 15 per cent. We have not been able to find data on the haemodynamic effects of barbiturates in patients with hypertension during surgical anaesthesia. In the patients with hypertension in the present investigation arterial pressure was consistently lowered by sodium amobarbital during light hypnosis and indeed even during lighter sedation. This decrease was due to reduction of cardiac output and not of peripheral resistance. The pulse rate did not change significantly and the decrease in stroke volume paralleled the decrease in cardiac output. These results suggest that the haemodynamic basis of hypotension caused by barbiturates in the patients with high blood pressure during light sedation and hypnosis is similar to that in patients with normal blood pressure at the stage of surgical anaesthesia. The reduction of arterial pressure is an expression of the decreased cardiac output and not of peripheral resistance which remains unchanged or increases. On the other hand the hypotension experienced by subjects with normal pressure during surgical anaesthesia is accompanied by tachycardia, but in patients with hypertension during light hypnosis the hypotension is associated with bradycardia or no change in heart rate.

It seems clear that the basis of the blood pressure fall caused by barbiturates in both normal tension and hypertension is due to a decrease in cardiac output. This change in cardiac output could be due to a reduction of venous return to the heart, or depression of the myocardial contractility, or both. In the patients with hypertension investigated in the present study (light sedation and hypnosis), right atrial pressure consistently decreased: similarly, in patients with normal blood pressure* Price et al. (1952) found that barbiturates reduced “central venous pressure” (surgical anaesthesia). Both sets of results are consistent with a hypothesis that barbiturates decrease cardiac output primarily by reducing venous return to the heart; it can be speculated that this is secondary to peripheral venous pooling (Johnson, 1951; Etsten and Li, 1955; Marshall and Shepherd, 1961).

**SUMMARY**

The haemodynamic mechanism by which barbiturates lower the blood pressure in patients with hypertension has been studied by measuring the systemic arterial pressure, heart rate, cardiac output and right atrial pressure during periods of light sedation or sleep. The results show that the fall in arterial pressure caused by the drug is due to a decrease in cardiac output, while the peripheral resistance remains unchanged. Right atrial pressure also decreases and is consistent with the hypothesis that barbiturates decrease the cardiac output by reducing the venous return to the heart. The relation of these findings to the “sedation test” and the haemodynamic action of barbiturates in subjects with a normal blood pressure is discussed.

* Etsten and Li (1955) reported that in patients with normal pressure right atrial pressure did not change during thiopental anesthesia, but they did not publish their results.
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REFERENCES


