CLINICAL EXPERIENCES WITH METARAMINOL AS
A VASOPRESSOR AGENT IN SPINAL ANESTHESIA

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Many vasoressor drugs have been introduced to minimize the hypotension associated with spinal anesthesia. Each has its own advantages and disadvantages. Based on mechanisms of action, these drugs can be classified into two groups.

Drugs increasing cardiac output:
(a) by direct stimulation of myocardium, and
(b) by constricting veins and venules to increase venous return.

Drugs increasing peripheral resistance:
(a) by peripheral vasoconstriction, and
(b) by stimulating vasomotor center.

The desirable actions of an ideal pressor drug, as listed by Hellerstein,1 include: elevation of blood pressure; increase in peripheral resistance; increase in coronary blood flow; significant cardiotonic action; prompt pressor effect; easy controllability; absence of secondary vasodilatation; and absence of tachyphylaxis and administration by all routes without tissue damage. It is unlikely that any agent will have all these actions, but metaraminol* (aramine bitartrate) appears to possess most of them.2-3

The purpose of this investigation is to evaluate the vasoressor effects of metaraminol in spinal anesthesia, and to compare them with ephedrine sulfate, a widely used reference vasoressor.2,3,12

Chemical Considerations. In 1910, Barger and Dale3 set forth the basic principles governing relationship of molecular structure to pharmacologic activity. Minor modifications of structure permit production of a wide variety of agents with varying attributes. Metaraminol is levo-1-(m-hydroxyphenyl-2 amino-propanol-hydroxy-D-tartrate). It is a phenylethylamine derivative, structurally related to the catechol amines.2 There is a methyl group on the alpha carbon but the hydroxyl group in the para position is missing. It thus resembles ephedrine and R-amphetamine (fig. 1). Metaraminol is a soluble white crystalline substance and is stable as a dry powder.

Essential Pharmacology.2 Metaraminol is a potent vasoressor agent with prolonged duration of action.4 Although the primary site of action appeared originally to be peripheral, evidence now indicates a significant myocardial action.4-7 Samoff has demonstrated that the amine increases cardiac contractility, cardiac output, aortic blood pressure, and coronary blood flow by a direct effect on the myocardium.4,8 Injected in the presence of hypotension, it increases coronary blood flow and lowers atrial pressure with an increase in ventricular stroke work. Cardiac arrhythmias have not been observed. With use of the time-dissociation technique, Samoff also demonstrated an increase in peripheral resistance,
resulting in increase in systemic pressure, an effect independent of the direct myocardial action.

Renal blood flow is only slightly decreased in normotensive dogs. This can be contrasted to a marked decrease caused by norepinephrine.\textsuperscript{4,9} In hypotensive states, renal blood flow and glomerular filtration rate increase when metaraminol is administered. This contrasts with the renal vasoconstriction attendant to the administration of norepinephrine and of most other vasopressors.

The drug is effective both by oral and parenteral routes. When given subcutaneously or intramuscularly, local ischemic effects are not noted in contrast to norepinephrine. Following subcutaneous injection the duration of action averages one and one-half hours. The prolonged action is probably due to lack of susceptibility of the drug to the effect of phenol and amine oxidases.\textsuperscript{10}

Central nervous system stimulation does not occur and intestinal motility is inhibited. The toxic dose for man has not been established but is beyond the usual therapeutic range. Tachyphylaxis has not been observed.

**METHOD**

Eight hundred and fifty unselected patients undergoing major or minor surgical procedures were studied. Single injection spinal anesthesia using tetracaine was given to each patient. The anesthetic technique was standardized in the following manner:

Premedication consisted of sodium amytal, 100 mg., and atropine or scopolamine, 0.4 mg. Control blood pressure readings were obtained by auscultation at the right brachial artery, with the patient on the operating table in the supine position. Lumbar puncture was performed and the prophylactic vasopressor was then injected into the erector spinae muscle three to ten minutes prior to the injection of the spinal anesthetic agent. A hyperbaric spinal anesthetic solution of tetracaine 1 per cent and dextrose 10 per cent, in equal parts, was used in all cases. The anesthetic level as indicated by dermatomes (according to Keegan) was determined at least four times during the first half-hour and then rechecked closely during the ensuing hour.

Patients were divided into three groups: a control group consisting of 200 patients in whom no prophylactic vasopressor agent was used, a second group of 250 patients treated with ephedrine, and a third group of 400 patients treated with metaraminol. Each group was separated into two categories according to the level of spinal anesthesia. The low spinal anesthesia category consisted of those patients whose level of anesthesia was at eighth thoracic segment or below, and the high spinal anesthesia category was composed of patients whose level of anesthesia was above eighth thoracic segment. The distribution of patients in these categories are given in Table 1. In all cases, the dose of vasopressor agent was kept constant. Thus, the dose of ephedrine sulfate was 50 mg. and that of metaraminol was 5 mg.

After administration of the spinal anesthetic solution, blood pressure determinations were made every three minutes for one hour. Only four blood pressure values were selected from each chart: the highest systolic blood pressure, the lowest systolic blood pressure, and their corresponding highest and lowest diastolic blood pressures. These values were expressed as a percentage deviation of the control value. In each of the three groups of patients the percentage deviation of each of these four values was averaged. Hypotension was considered to be present when the systolic blood pressure declined 25 per cent or more from control values.\textsuperscript{11,12}

**RESULTS**

*Incidence of Hypotension. Control Series.* All patients in the control group exhibited some reduction in systolic blood pressure. The data show that the percentage decline in systolic pressure was proportional to the height of the spinal anesthesia on a segmental basis.

**TABLE 1**

<table>
<thead>
<tr>
<th>Patient Distribution According to Sensory Levels of Anesthesia</th>
<th>Number of Patients with Level below 76</th>
<th>Number of Patients with Level above 76</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>72</td>
<td>178</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>224</td>
<td>176</td>
</tr>
</tbody>
</table>
TABLE 2
INCIDENCE OF HYPOTENSION (BLOOD PRESSURE
DECREASE OF 25 PER CENT OR MORE)
OCcurring During Spinal
Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>High Spinal</th>
<th>Low Spinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls—no vasopressor</td>
<td>65</td>
<td>95</td>
<td>22</td>
</tr>
<tr>
<td>Ephedrine treated</td>
<td>16</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Metaraminol treated</td>
<td>15</td>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>

Comparison of effect of metaraminol with ephedrine as related to untreated subjects.

Thus, with each additional segment anesthetized, one could observe an average decrease in systolic pressure of about two percent, from the pre-anesthetic value. The over all incidence of hypotension was 65 per cent. Nearly all (95 per cent) high spinal anesthetics were accompanied by lowering in blood pressure sufficient to be designated as hypotension, while only 22 per cent of low spinal anesthetics exhibited hypotension (table 2). These results correspond closely to the data of Dripps and King.13

Ephedrine-Treated Series. Two hundred and fifty patients were given ephedrine intramuscularly. The over all incidence of hypotension was 16 per cent. Approximately 25 per cent of the patients having a high spinal anesthetic developed such a reduction in systolic pressure.

Metaraminol-Treated Series. Four hundred patients were treated with metaraminol. In these patients, the over all incidence of hypotension was 15 per cent, a value identical with the figure for ephedrine. Thus, as a prophylactic agent for the prevention of hypotension metaraminol was of equal merit with ephedrine.

Extent of Pressure Changes. Metaraminol sharply limited the severity in decline of systolic pressure (table 3). For all levels of spinal anesthesia the systolic pressure decreased an average of 10 per cent in contrast to an average reduction of 28 per cent in systolic pressure in the patients used as controls. When the cases were subdivided from the standpoint of whether the sensory anesthesia was high or low the protective action was more pronounced. Thus, in patients with sensory levels of eighth thoracic segment and above, the systolic pressure declined 14 per cent in contrast to controls who exhibited a 35 per cent reduction in pressure. With sensory levels below eighth thoracic segment, the systolic pressure decreased only 8 per cent in contrast to the control group where the systolic pressure decline was 20 per cent.

Comparison of the extent of pressure change after metaraminol was made with ephedrine (table 4). The average change in systolic pressure after either of these agents was nearly the same. Although the average diastolic pressures were well above those in the control group, the values for diastolic pressure were lower in the metaraminol treated patients compared to ephedrine treated patients; that is, ephedrine raised diastolic pressure to a greater extent than aramine.

When hypotension occurred, metaraminol caused a rise in both systolic and diastolic pressure. This was rapid following the intravenous administration of 1 to 2 mg. and occurred in two to four minutes. After intramuscular injection, the onset of action was noted in five to eight minutes while the full response was achieved in 12 to 15 minutes.

In about 20 per cent of all patients given

TABLE 3
AVERAGE SYSTOLIC DECREASE IN BLOOD PRESSURE OCCURRING DURING SPINAL ANESTHESIA.
DIVIDED INTO TWO SENSORY ANESTHESIA LEVEL GROUPS ABOVE AND BELOW T8

<table>
<thead>
<tr>
<th></th>
<th>Per Cent T8 and above</th>
<th>Number</th>
<th>Per Cent below T8</th>
<th>Number</th>
<th>Average Per Cent for All Cases</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>15.13</td>
<td>178</td>
<td>7.10</td>
<td>72</td>
<td>9.73</td>
<td>250</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>14.00</td>
<td>176</td>
<td>8.00</td>
<td>224</td>
<td>10.02</td>
<td>400</td>
</tr>
<tr>
<td>Controls</td>
<td>35.0</td>
<td>100</td>
<td>20.00</td>
<td>100</td>
<td>28</td>
<td>200</td>
</tr>
</tbody>
</table>
The systolic pressure actually increased over the preanesthetic baseline value and was stabilized at an elevated level for the duration of action of the vasopressor drug. This type of action was more marked after metaraminol, the systolic increase averaging 19 per cent while with ephedrine it was 14 per cent. Also, in about 20 per cent of all patients, diastolic pressure did not decrease. Actually these patients exhibited a 12 per cent increase above baseline diastolic pressure. These patients were chiefly in the low spinal group.

**Duration of Action.** To determine the duration of action of a single intramuscular dose of metaraminol, 20 patients were observed after a continuous spinal anesthesia was given. This group of patients usually required repeated administration of a vasopressor to maintain the blood pressure. One single intramuscular injection of the drug was used prophylactically; thereafter, it was found necessary to administer metaraminol about every 45 to 60 minutes. In a similar group treated with ephedrine the doses had to be repeated every 30 to 45 minutes. In general, the duration of metaraminol action was longer than that of ephedrine.

Occasionally, single intramuscular injections of metaraminol produced an excessive pressor response. Under these circumstances hypotension often followed a variable but briefer period of pressor action and vasopressor therapy had to be repeated in about 20 to 30 minutes. Overshooting appears to diminish the duration of effective action. Attaining hypertensive levels apparently evokes counter-regulatory mechanisms which inhibit pressor action.

**Continuous Intravenous-Drip Administration.** Metaraminol was administered in dilute solution for the maintenance of the systolic pressure in 100 patients given spinal anesthesia. These patients were not pretreated with a prophylactic vasopressor prior to the induction of spinal anesthesia. An intravenous infusion of 5 per cent dextrose in water containing 10 or 20 mg. of metaraminol per 100 ml. was started as soon as spinal anesthesia was instituted and the patient placed in position for the operation.

By titrating the dose against a pressure response, a fine adjustment of doses was permitted and a most satisfactory and controllable method provided. For the management of hypotensive states which develop during anesthesia, it was considered the most efficient method to stabilize the blood pressure and has become the method of choice. Blood pressure could be stabilized over a period of three hours with a total dose of 5 to 8 mg.

When using metaraminol by the continuous-drip technique, it was necessary to administer the solution in two steps: First, in the initial phase, the intravenous drip rate had to be rapid (about 60 to 100 drops per minute) to achieve the desired plasma level and pressure response. Second, in the maintenance phase, the drip rate was slowed to 10 to 20 drops per minute and finely adjusted to stabilize the pressure. It was found that if the initial drip rate was slow and less than 1 to 2 mg. were administered in five minutes, a good pressure response was not obtained. This appeared to be a form of acute tolerance. This might have been a true drug resistance, but more likely it represented the stimulation of counter-regulatory mechanisms.

**Discussion**

Metaraminol causes an increase in both systolic and diastolic pressure. This pressor effect is more pronounced on the systolic pressure than the diastolic pressure. Ephedrine also raises both systolic and diastolic pressure, but the diastolic rise is greater than that observed with metaraminol (table 4). Widening of the pulse pressure with metaraminol indicates a prevailing direct myocardial effect of this drug, an observation which supports...
The laboratory findings of Sarnoff. In a few cases the hypertensive response to metaraminol was of such degree that a ganglionic blocking agent or sympatholytic agent had to be used. Similar responses to ephedrine were not observed in this series.

Under the conditions maintained in this investigation metaraminol 5 mg. and ephedrine 50 mg. do not differ significantly as prophylactic drugs in preventing spinal hypotension. However, the clinical observations indicate that some differences between the two drugs exist. Metaraminol has a longer duration of action, an absence of tachyphylaxis to single injections and a greater direct myocardial stimulating activity. Subjective reactions such as central nervous system stimulation to metaraminol were not observed.

**Conclusions and Summary**

The vasopressor action of metaraminol was studied in 400 patients receiving spinal anesthesia and compared to a similar patient group of 250 patients treated with ephedrine and an untreated control group of 200 patients.

Metaraminol was found to be a potent vasopressor drug effective in lowering the incidence and decreasing the extent of the hypotension of spinal anesthesia.

Metaraminol was effective in raising systolic pressure to higher levels than was ephedrine and appeared to have a prevailing central cardiac action. The duration of action was longer than that of ephedrine.

Continuous intravenous drip metaraminol solution was the most efficient and controllable method of administration.

**References**


