Observations on the Hemodynamic Properties of a Thiophanium Derivative, Ro 2-2222 (Arfonad), in Human Subjects

By N. S. Assali, M.D., Roy A. Douglass, Jr., M.D., and Roy Suyemoto

Observations on the hemodynamic properties of a thiophanium derivative (Arfonad) have been made on normotensive nonpregnant and pregnant subjects and on patients with hypertensive complications of pregnancy. The drug was given by single intravenous injections and by intravenous drip infusion. The hypotensive effects of single injections were compared with those of a standard tetraethylammonium chloride (TEAC) test. The authors observed that the hemodynamic effects of Arfonad were similar in some respects to those of tetraethylammonium chloride or spinal anesthesia. A fall in the cardiac output occurred when the blood pressure fell following Arfonad administration. The authors discuss these hemodynamic effects in terms of differences in response to ganglionic blocking agents of the various groups of subjects studied.

Animal experiments carried out by Randall and his associates have shown that the pharmacologic activities of certain thiophanium derivatives are similar in many respects to those of tetraethylammonium ion. The vasodepressor action of one of these compounds, d-3,4 (1',3'-dibenzyl-2'-keto-imidazolido)-1,2-trimethylene thiophanium d-camphor sulfonate, known by its code number as Ro 2-2222 or commercially as Arfonad, was found to be 30 times more potent than tetraethylammonium. Sarnoff and his associates administered Arfonad to animals as well as to normotensive and hypertensive men and obtained a graded vasodepressor effect which was similar but preferable to spinal anesthesia. These authors also observed a blockade of the pressor response to cold and a rise in the skin temperature of the lower extremities. They concluded that the action of this drug is similar in some respect to that of ganglionic blocking agents. Green gave the drug to normotensive subjects and also observed a marked rise in the skin temperature of the lower extremities, without much change in that of the upper extremities. McCubbin and Page, on the other hand, believe that Arfonad in dogs acts directly on the vessel walls, the ganglionic blocking effects playing a minor role.

The present study was undertaken in order to investigate some of the hemodynamic effects of Arfonad in pregnant subjects. In previous studies we have shown that normotensive pregnant subjects respond with a marked fall in blood pressure to autonomic blocking agents in contrast to patients with toxemia of pregnancy in whom the response is negligible. It was thought that these contrasting results observed in these two groups of patients together with determination of responses to Arfonad in similar groups of subjects might throw light on the hemodynamic activities of Arfonad.

Material and Methods

The material consisted of 56 subjects comprising the following groups: (a) 10 normotensive nonpregnant subjects, (b) 20 normotensive pregnant subjects in the last trimester of gestation, (c) 10 patients with acute toxemia of pregnancy, and (d) 16 patients with essential hypertension associated with pregnancy.

The diagnosis of acute toxemia and of essential hypertension was made according to the criteria...
Three normotensive pregnant subjects were given single injections of 0.03 mg. per kilogram; three others were given 0.05 mg. per kilogram; two received 0.07 mg. per kilogram and two received 0.09 mg. per kilogram. None of these patients showed any significant vasodepressor effect. Moderate tachycardia was present in the patients who received 0.07 and 0.09 mg. per kilogram.

The remaining normotensive pregnant and essential hypertensive pregnant patients received intravenous injections of Arfonad in doses varying from 0.1 to 0.2 mg. per kilogram. In this dosage, the drug evoked a significant fall in blood pressure which paralleled that produced by the injection of 400 mg. of tetraethylammonium chloride (fig. 1). The vasodepressor action of the single dose lasted for 3 to 10 minutes although in two normotensive pregnant subjects who received 0.15 mg. per kilogram the blood pressure remained low for approximately 30 minutes. At the height of hypotension, the pulse rate increased by an average of 30 beats per minute.

The toxemic and normotensive nonpregnant subjects were similarly given single doses of 0.1 to 0.2 mg. per kilogram. The fall in blood pressure in these two groups was less significant than in the previous groups. The pulse rate increased slightly in some cases and remained unchanged in others. No significant side effects such as dryness of the mouth and blurring of the vision were observed in any of the patients who received Arfonad in single injections.

Fig. 1. Effects of single doses of Ro 2-2222 on the blood pressure and pulse rate in normal pregnancy as compared with a standard test with 400 mg. of tetraethylammonium chloride (TEAC). Note that there was insignificant difference between the effects of 0.1, 0.13, 0.15 mg. per kilogram and the TEAC test.
2. Effects of Intravenous Infusion

This method of administration was used in 10 normotensive pregnant, 5 normotensive nonpregnant, 10 toxemic, and 12 essential hypertensive pregnant subjects. Arfonad was given in a solution containing 2 mg. per cubic centimeter, and the rate of infusion was regulated as to secure a significant fall in blood pressure. The response to the drug in these patients was taken as the average of the three lowest blood pressure readings observed during the infusion.

A. Blood Pressure and Pulse Rate. Normal pregnant and essential hypertensive pregnant subjects responded in the same manner to infusion of Arfonad. In the normotensive group, there was an average fall of 37 per cent in the systolic and 46 per cent in the diastolic blood pressure, the rate of infusion varying from 3 to 8 mg. per minute; in the hypertensive group, the fall averaged 32 per cent systolic and 49 per cent diastolic blood pressure, the rate of infusion varying from 6 to 18 mg. per minute (fig. 2). In all but three normotensive pregnant subjects, the vasodepressor action could be maintained for as long as the infusion was continued. In these three instances the vasodepressor action persisted for half an hour after the interruption of the infusion and then began to recede gradually. The majority of patients showed insignificant changes in pulse rate during the infusion. In four normotensive subjects the pulse rate increased about 20 beats per minute but returned to control levels while the blood pressure was still low.

Three normotensive pregnant subjects were given intravenous injections of 25 mg. ephedrine during Arfonad infusion. In each instance the blood pressure returned immediately to or became higher than the control levels (fig. 3).

Intravenous infusion of the drug to normotensive nonpregnant subjects in doses varying from 8 to 60 mg. per minute resulted in a fall in blood pressure to approximately 10 per cent of the control level (fig. 2). Tachycardia was present in two cases, but in the others the pulse rate did not change.

In the toxemic group, the intravenous infusion of Arfonad in doses varying from 8 to 30 mg. per minute produced an average fall of 22 per cent in systolic and of 17 per cent in diastolic blood pressure (fig. 2). Again, the pulse rate remained unchanged in the majority of cases.

B. Cardiac Output and Peripheral Resistance. Estimations of cardiac output and peripheral resistance were carried out on five normotensive pregnant, three essential hypertensive pregnant, and two normotensive nonpregnant subjects (table 1). Two to three determinations were made during the control period and 7 to 12 determinations during and after the infusion.

The normotensive pregnant and essential hypertensive pregnant patients who showed a significant fall in the blood pressure, also showed a decrease in the cardiac output varying from 0.5 to 2.2 liters per minute (table 1). The fall in the cardiac output was closely related to the fall in blood pressure and was mainly due to a decrease in the stroke volume (fig. 4).
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Fig. 3. The effect of Ro 2-2222 infusion in normotensive pregnancy. The initial rate of the infusion was 16 mg. per minute. This produced a severe drop in blood pressure with signs of circulatory collapse. These were improved and the blood pressure was kept around 90/50 by frequently readjusting the rate of infusion. The variations in blood pressure readings were probably due to variations in the rate of infusion. Note that the pulse rate showed insignificant changes. At 48 minutes, 25 mg. ephedrine were given intravenously. This produced a marked rise in the blood pressure.

Table 1.—Cardiac Output and Total Peripheral Resistance Before and After Arfonad in Two Normal Nonpregnant Women, Five Normal Pregnant Women and Three Hypertensive Pregnant Women

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Control</th>
<th>After Arfonad</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean Arterial</td>
<td>Pulse</td>
</tr>
<tr>
<td>A. N.</td>
<td>Normal pregnant</td>
<td>88</td>
<td>82</td>
</tr>
<tr>
<td>L. S.</td>
<td>Normal pregnant</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>N. J. R.</td>
<td>Normal pregnant</td>
<td>86</td>
<td>84</td>
</tr>
<tr>
<td>M. K.</td>
<td>Normal pregnant</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>F. B. L.</td>
<td>Normal pregnant</td>
<td>83</td>
<td>115</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>J. T.</td>
<td>Essential Hypert. (preg.)</td>
<td>140</td>
<td>96</td>
</tr>
<tr>
<td>E. R.</td>
<td>Essential Hypert. (preg.)</td>
<td>130</td>
<td>102</td>
</tr>
<tr>
<td>E. F.</td>
<td>Essential Hypert. (preg.)</td>
<td>143</td>
<td>84</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>138</td>
<td>94</td>
</tr>
<tr>
<td>T. W.</td>
<td>Normal nonpregnant</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>L. B.</td>
<td>Normal nonpregnant</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>89</td>
<td>89</td>
</tr>
</tbody>
</table>
significantly, the cardiac output remained relatively unchanged.

![Cardiac output determinations during Ro 2-2222 infusion](image)

**Fig. 4.** Cardiac output determinations during Ro 2-2222 infusion. In this patient the cardiac output was reduced by about 2 liters at the height of blood pressure fall. Note the close relationship between blood pressure and cardiac output changes.

![Skin temperature changes during Ro 2-2222 infusion](image)

**Fig. 5.** Skin temperature changes during Ro 2-2222 infusion. This patient had a marked fall in blood pressure during the infusion. Note the marked rise in the temperature of the lower extremities and the negligible changes in that of the upper extremities. Similar changes were observed in all the subjects studied. The changes in the skin temperature did not show any relationship to the blood pressure response.

Total peripheral resistance was calculated from the formula: \( R = \frac{P_m}{CO} \), where \( R \) represents total peripheral resistance, \( P_m \) average estimations of mean arterial pressure and \( CO \) average values for cardiac output. The values for total peripheral resistance in the normal nonpregnant and normal pregnant subjects were approximately the same but they were slightly higher than normal values reported by Goldring and Chassis.\(^{10} \) The values for the essential hypertensive pregnant group were similar to those reported by these authors. Arfonad produced an average fall of 24.8 per cent in the peripheral resistance of the normotensive pregnant group and 18.8 per cent in the essential hypertensive group. In the normotensive nonpregnant subjects the change was slight.

**C. Skin Temperature.** Three normotensive pregnant, two toxemic and two normotensive nonpregnant subjects were studied. The patients were maintained recumbent in a constant temperature room with the larger portion of the body uncovered for at least half an hour. Readings were then taken from different areas but additional attention was given to changes in the temperature of the extremities. In all patients, infusion of Arfonad was followed by a rise of 4 to 8 degrees in the skin temperature of the lower extremities, the temperature of the upper extremities remaining practically unchanged (fig. 5). The changes in skin temperature showed no relationship to the magnitude of blood pressure fall.

**D. Vasopressor Reflexes.** Five normotensive pregnant, two toxemic nonpregnant and four essential hypertensive pregnant patients were subjected to cold pressor tests by immersing the hand to the wrist in ice water for one minute. Some of these patients were studied with both single injections and intravenous infusion of Arfonad. All patients showed in the control period, a pressor reaction to cold of varying magnitude. After the administration of the drug the pressor reaction was partially or totally abolished (fig. 6).

The pressor response to the Valsalva maneuver was also studied in some of these patients. In all but one case, there was a partial or total blockade of the Valsalva "overshoot."

Postural hypotension was present in nearly all patients studied with intravenous infusion, but could not be detected after single injec-
tions, probably because of the short duration of the action of the drug.

E. Side Effects. Yawning and a sensation of warmth were the only complaints of the patients who did not have a significant fall in blood pressure, even when Arfonad was given at a rate of 30 to 60 mg. per minute. When severe hypotension occurred, nausea, vomiting, pallor, dizziness and other signs of circulatory collapse were present. These symptoms subsided rapidly when the blood pressure was elevated to control levels either by raising the lower extremities to an angle of 90 degrees or by injection of 25 mg. of ephedrine intravenously.

Fig. 6. This patient was one of the two who had prolonged response to a single injection of 0.15 mg. per kilogram. Note the marked pressor reaction to cold in the control period and the elimination of this reaction after Ro 2-2222.

**Discussion**

Randall and his co-workers demonstrated in animals that the blocking effects of Arfonad were exerted mostly at the ganglionic level of sympathetic and parasympathetic pathways. These authors were able to produce a blockade of transmission through the superior cervical ganglion and through the carotid sinus reflex and blockade of the vagus action on the heart. They were unable to show any neuromuscular blocking action. The ganglionic blocking and vasodepressor effects of Arfonad could be counteracted by neostigmine and ephedrine.

Sarnoff and associates administered Arfonad to hypertensive patients with heart failure by intravenous drip infusion and obtained a graded reduction of arterial pressure concomitant with a fall in pulmonary venous pressure.

The present data on the vasodepression produced by Arfonad in pregnant human subjects are in close agreement with those presented by Sarnoff and his associates. In our patients who showed a fall in the blood pressure, the hypotension could be regulated to a desired level by merely changing the rate of infusion. Although in three patients there was some indication of presence of cumulative effect, in the majority, the blood pressure returned to control levels shortly after the interruption of infusion.

Sarnoff observed increased cardiac output at the height of hypotension after Arfonad. In our cases, there was a decrease in the cardiac output whenever the blood pressure fell significantly. Similar reduction in cardiac output has been reported following induction of high selective spinal anesthesia in pregnant women. The discrepancy between our results and those reported by Sarnoff and his co-workers may be due to a difference in the type of patients studied. While their patients were in heart failure, presumably with a low output, ours were healthy young subjects with normal output. Further studies are in progress in order to elucidate this question.

Concomitant with the decrease in cardiac output, Arfonad evoked a significant reduction in the total peripheral resistance. This was to be expected since most of the normotensive pregnant and essential hypertensive subjects showed signs of peripheral circulatory collapse at the height of blood pressure fall. The simultaneous reduction in peripheral resistance and cardiac output suggests that in pregnant subjects Arfonad acts like spinal anesthesia by blocking neurogenic impulses to both arteriolar and venous system. This blockade probably results in pooling of blood in the venous side of the circulation, interfering with the venous return to the right heart and with right auricular filling. As in the case of spinal anesthesia, raising the legs to an angle of 90 degrees at the height of Arfonad induced hypotension was sufficient to restore the pooled blood to the systemic circulation, thus improving the cardiac
output and raising the blood pressure to control levels. The similarity between the actions of Arfonad and selective spinal anesthesia is also evidenced by their identical effects on renal hemodynamics. The hypotensive effect of spinal anesthesia is accompanied by significant reduction in the renal plasma flow with a simultaneous increase in the renal resistance.\textsuperscript{11} The data on renal hemodynamics obtained with Arfonad\textsuperscript{9} closely paralleled that of spinal anesthesia and showed that during the hypotensive phase the total peripheral resistance decreased while the renal resistance increased. This divergence in response of the kidneys and other segments of the vascular bed indicates that there is a difference in the mechanisms which control the circulation of blood to various areas of the body. Freis and his associates\textsuperscript{2} have observed similar differences in their studies on the hemodynamic effects of hexamethonium.

A rise in the skin temperature of the lower extremities without a significant change in that of the upper extremities after Arfonad was observed by Green\textsuperscript{2} and by Sarnoff and associates,\textsuperscript{5} and is confirmed in the present study. This phenomenon, unexplained at present, would seem to indicate that in the lower extremities there is increased vasomotor tone which makes this part of the vascular bed more responsive to the effects of ganglionic blocking agents.

The present data with single injections of Arfonad show that within the range of dosage given, the hypotensive effects of this drug are not much different from those of tetraethylammonium chloride. Whether larger doses could evoke different responses cannot be stated from these observations. The vaso depressor response observed in normotensive pregnant and essential hypertensive subjects and the negligible response of normotensive nonpregnant and toxemic subjects resemble closely the results obtained with both tetraethylammonium chloride and spinal anesthesia. However, unlike tetraethylammonium chloride, Arfonad was very effective in reducing the blood pressure and blocking the vaso depressor reflexes when given by intravenous drip infusion. The observations of Ulrich and coworkers\textsuperscript{33} and of Brust and Ferris\textsuperscript{34} have indicated that intravenous drip infusion of tetraethylammonium chloride even when given at a rate which should result in severe toxic side effects, does not produce any vasodepressor action in normotensive and hypertensive subjects. Also, the side effects peculiar to tetraethylammonium chloride are not observed after Arfonad. Thus, while the effects of Arfonad and tetraethylammonium chloride when given by rapid injection are similar, Arfonad, unlike tetraethylammonium chloride, possesses peculiar pharmacologic properties which also make it effective when given by slow intravenous infusion.

**Summary and Conclusions**

1. Studies on the hemodynamic effects of Arfonad were carried out on 10 normotensive nonpregnant, 20 normotensive pregnant, 10 toxemic and 16 essential hypertensive pregnant subjects.

2. Arfonad given by single intravenous injection in doses of 0.1 to 0.2 mg. per kilogram produced a significant blood pressure fall in the normotensive pregnant and essential hypertensive subjects which was parallel to the fall observed with 400 mg. of tetraethylammonium chloride. The same dosage produced a negligible blood pressure change in the toxemic and normotensive nonpregnant groups.

3. Intravenous infusion of Arfonad also resulted in a marked fall in the blood pressure of the normotensive pregnant and essential hypertensive groups. In the majority of patients, the hypotensive effect lasted for as long as the infusion continued. Toxemic and normotensive nonpregnant subjects showed much less blood pressure fall even when the rate of infusion was much higher.

4. At the height of hypotension, the cardiac output and peripheral resistance were significantly reduced, the pressor responses to cold and to Valsalva maneuver were abolished, and the skin temperature of the lower extremities rose more markedly than that of the upper extremities.

5. It is concluded that in human pregnant subjects, some of the hemodynamic effects of Arfonad resemble those of tetraethylammonium chloride or selective spinal anesthesia.
ACKNOWLEDGMENTS

The authors are indebted to Dr. John Braunstein and to Miss Mary Jane Tompkins for the cardiac output determinations.

Sumario Español

Observaciones de las propiedades hemodinámicas de un derivado de thiophanium (Arfonad) han sido hechas en sujetas normotensas embarazadas con complicaciones hipertensas del embarazo. La droga se administró mediante inyecciones intravenosas sencillas y mediante infusiones a gota intravenosas. Los efectos hipotensos de inyecciones sencillas fueron comparados a aquellos de una prueba standard de cloruro de tetraetilamonio (TEAC). Los autores observaron que los efectos hemodinámicos de Arfonad fueron similares en algunos aspectos a aquellos del cloruro de tetraetilamonio o anestesia espinal. Una reducción en la producción cardíaca ocurrió cuando la presión arterial disminuyó luego de la administración del Arfonad. Los autores discuten estos efectos hemodinámicos en términos de diferencias en reacción a los agentes bloqueadores gangliónicos de los varios grupos de sujetos estudiados.

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