HYPOTENSIVE EFFECTS OF IPRONIAZID AND CARBOXAZID

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The authors have investigated the hemodynamic changes accompanying the hypotension that occasionally follows administration of amine oxidase inhibitors, particularly iproniazid phosphate. Iproniazid was given intravenously and orally, in varying doses, to hospitalized patients with toxemia of pregnancy or with essential hypertension associated with pregnancy. Similar observations were made with carboxazid, an analogue of iproniazid. Data on blood pressure in supine and upright positions and on renal hemodynamics and cardiac output indicated that the hypotension was probably caused by venous pooling and by a decrease in the cardiac output rather than by a true vasodilator action.

Several investigators have observed a certain degree of hypotension after the administration of amine oxidase inhibitors, particularly iproniazid (Marsilid) phosphate.[1] Others attempting to evaluate this action in ambulatory hypertensive patients have found that daily doses of 100 to 600 mg. of this drug produced orthostatic hypotension which varied in degree from patient to patient.[2]

The present study was aimed at investigating the hemodynamic and renal effects of acute and chronic administration of iproniazid in patients with (1) toxemia of pregnancy and (2) essential hypertension associated with pregnancy. Similar observations on the effects of carboxazid (Marplan), a newly developed analogue of iproniazid, have also been included.

Material and Methods

The study was divided into four parts, and the methods and the materials used for each part are described.

Part 1.—Iproniazid was administered intravenously to 15 hospitalized patients (10 with toxemia of pregnancy and 5 with essential hypertension associated with pregnancy). The criteria for the diagnosis of toxemia of pregnancy have been outlined elsewhere.[3] The patients were given bed rest for 10 to 24 hours prior to the test. Control blood pressure recordings (by Sphygmomanometer) were taken every 1 to 2 minutes for 30 to 40 minutes prior to injection of the drug. Thereafter, iproniazid was given in rapid intravenous injections in doses varying from 0.7 to 2 mg. per kilogram of body weight. Blood pressure and pulse rate continued to be recorded every minute for about 30 minutes, with the patient in the supine position, and for another 20 to 30 minutes, with the patient in the standing position. Further recordings were taken when the patient resumed the recumbent position.

Part 2.—Iproniazid was administered orally to 12 untreated, hospitalized patients (5 patients with toxemia of pregnancy and 7 with essential hypertension). In each patient, control blood pressure readings were recorded four times daily for two to four days. Thereafter, iproniazid was given orally in progressively increasing doses from 50 mg. to 150 mg. per day. During the treatment, four to six blood pressure recordings were taken daily, with the patient in the recumbent position. Ten to 12 blood pressure recordings were taken daily, with the patient in a standing position.

Part 3.—The effect of iproniazid-induced hypotension on renal hemodynamics and cardiac output was investigated in four patients with essential hypertension associated with pregnancy. Renal blood flow and glomerular filtration rate were measured by the para-aminohippurate and inulin clearances according to techniques described elsewhere.[3] Renal vascular resistance was estimated from the arterial blood pressure and renal blood flow. Cardiac output was determined by the conventional dye technique. Control values were obtained when the patients were given iproniazid therapy, but they had shown no hypotensive effect. The same studies were repeated during the hypotensive phase and when the drug was either withdrawn or the dose reduced and blood pressure had returned to control values (normal).

Part 4.—The effects of orally administered carboxazid on blood pressure and renal hemodynamics were studied in patients with essential hypertension associated with pregnancy. The procedure was similar to that described in Part 3 except that carboxazid (instead of iproniazid) was given, in doses of 10 to 20 mgs. per day.

Results

The results of the four parts of the study are presented in corresponding sequence.

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Effects of Intravenous Administration.—Figure 1 shows a typical response to iproniazid in a patient with severe preeclampsia, whereas Figure 2 illustrates a typical response of a patient with essential hypertension. The other patients responded in a similar manner. It is evident that iproniazid in the doses given had no significant effect on the patient's blood pressure with the patient in either the supine or the upright position. The patient's pulse rate, likewise, did not change. When ipronoazid was given at high doses, bizarre side-effects such as flushing, dizziness, and mental stimulation were observed.

Effects of Oral Administration of Iproniazid.—The results of orally administered iproniazid varied according to the dose and varied with the same dose in different patients. Figure 3 illustrates the response of a patient with essential hypertension, whereas table 1 summarizes all the data. No postural hypotension was observed during the administration of 50 mg. of iproniazid per day. However, when the dose reached 100 to 150 mg. per day, a moderate to severe orthostatic hypotension occurred and became evident approximately 30 to 40 minutes after ingestion of the drug. The patient felt a sensation of fainting and imminent collapse which was accompanied by a blood pressure fall that varied from 30 to 40 mm. Hg systolic and 10 to 30 mm. Hg diastolic. The patient's blood pressure and general condition improved when she reassumed a supine position. It is of interest that some patients with the same degree of hypertension, who received the same dose of iproniazid, did not have a postural effect. Again, at high doses, the drug induced some bizarre mental side-effects, which, in many instances, could not be accurately described.

Effects of Iproniazid on Renal Hemodynamics and Cardiac Output.—Table 2 lists the values for renal hemodynamics and cardiac output during the periods of control, iproniazid-induced hypotension and recovery. A marked decrease in urine flow, renal plasma flow, glomerular filtration rate, and cardiac output occurred when the blood pressure fell, and vascular resistance increased. When hypo-

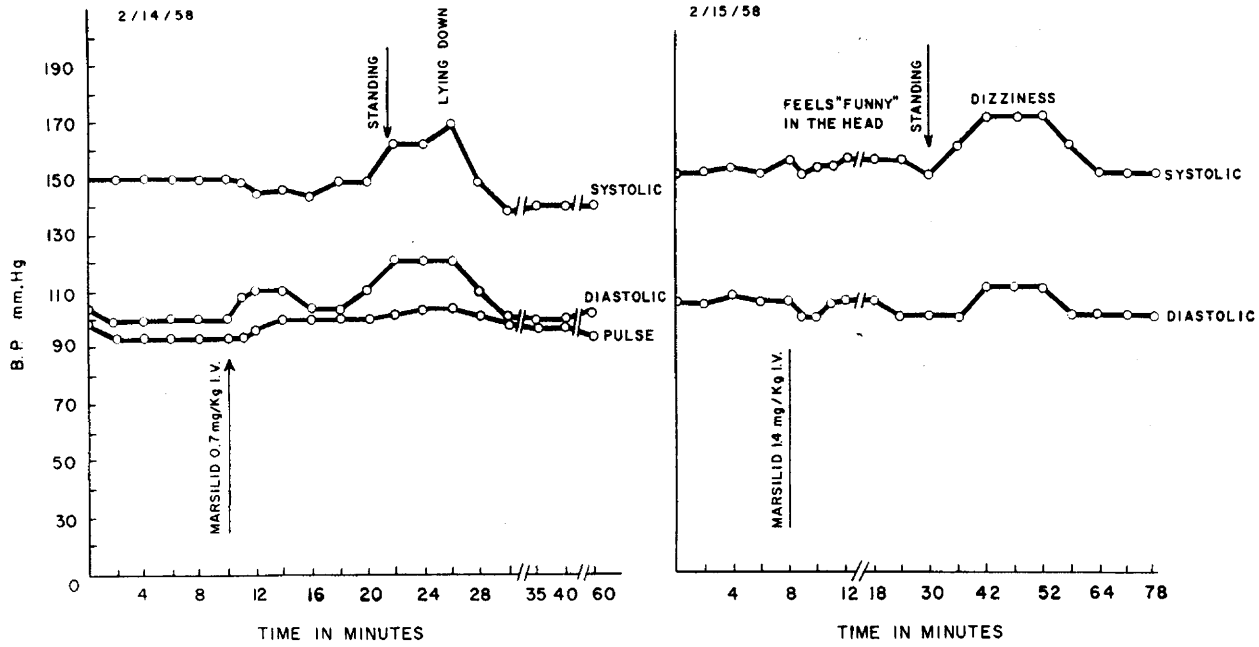

Fig. 1.—Effects of intravenous administration of iproniazid (Marsilid) phosphate on blood pressure and pulse rate of a pregnant patient with preeclampsia. In the first test, 0.7 mg. per kilogram of body weight was given, with lack of postural hypotensive effect. Twenty-four hours later, 1.4 mg./kg. was given without hypotensive action.

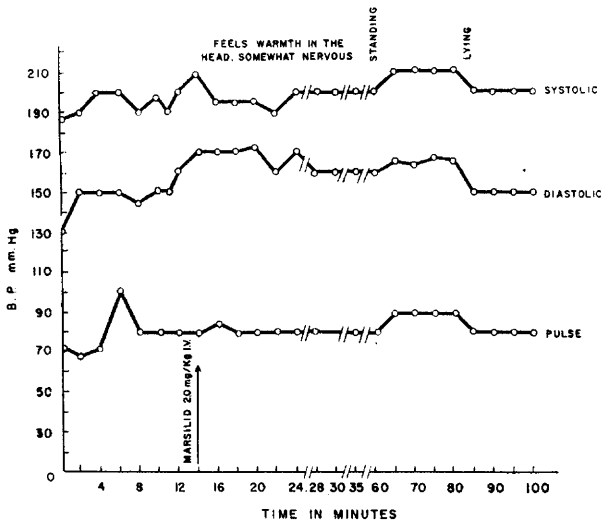

Fig. 2.—Effects of intravenous administration of 2.0 mg./kg. of iproniazid (Marsilid) phosphate to patient with essential hypertension. Despite appearance of side-effects, no hypotensive action was observed.

tension subsided with the patient's resumption of the recumbent position, the values for renal hemodynamics and cardiac output returned to control levels.

Effects of Carboxazid.—In the doses given, carboxazid had no significant action on the supine blood pressure and on the renal plasma flow and glomerular filtration rate. Control blood pressure ranged from 160/95 mm. Hg to 210/120 mm. Hg. It remained practically the same after administration of carboxazid. Postural hypotension occurred in three cases, but in only one case was it severe enough to warrant discontinuance of therapy.

Comment

It is evident from the present data that the fall in blood pressure which follows the administration of iproniazid and its analogue, carboxazid, is inconsistent and requires continuous oral administration of 100 to 150 mg. per day of iproniazid or 20 mg. or more of carboxazid for a few days to become

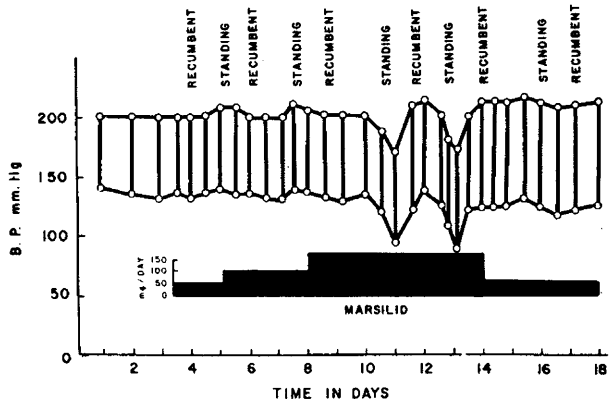

Fig. 3.—Effects of oral administration of iproniazid (Marsilid) phosphate to hospitalized patient with essential hypertension in whom orthostatic hypotension occurred. When dosage reached 150 mg./day for 3 to 4 days, postural hypotension of varying magnitude began to occur one-half hour after ingestion of drug. Patient's hypotension was relieved rapidly by reassuming recumbent position. When dose was decreased, orthostatic effect subsided.

evident. Given intravenously in doses up to 2 mg. per kilogram of body weight, iproniazid failed to produce any hypotensive action. Thus, the occurrence of hypotension seems to depend upon the establishment of a critical blood level through cumulation. However, since not all patients exhibit the same vascular response, it seems also that the hypotensive action of iproniazid and its analogue is peculiar to certain subjects.

As to the hemodynamic mechanisms of this hypotension, the present data seem to indicate that it is orthostatic in nature, probably caused by venous pooling. This hypothesis receives support from the clinical observations [4] which indicate that the fall in blood pressure is more evident when the patient assumes the upright position. This fact together with the striking decrease in cardiac output, renal plasma flow, and glomerular filtration rate, as well as the increase in renal vascular resistance, simulate the hemodynamic action of ganglionic blocking agents.[5] Whether iproniazid in large doses produces, by some unknown mechanism, a blockade of the venomotor tone and a sequestration of blood into the venous side of the circulation cannot be stated from the present study.

TABLE 1.—*Effects of Oral Administration of Iproniazid on Patients' Blood Pressure as Compared with Control Blood Pressure*

		Test Results				
		Daily Dose mg.	Length of Treatment, Days	Supine Blood Pressure C*	Supine Blood Pressure A†	Postural Hypotension
Diagnosis	Patient					
Toxemia	1.....	50	3	160/110	150/105	0
		100	3	150/104	150/100	0
	2.....	50	4	170/112	172/114	0
		150	2	170/110	162/110	moderate
	3.....	50	3	150/90	148/88	0
		150	3	150/88	142/88	0
	4.....	100	3	165/108	160/110	moderate
		150	3	160/110	155/100	severe
	5.....	50	4	180/108	175/104	0
		150	2	175/105	170/100	moderate
	6.....	50	6	190/110	180/100	0
		150	5	180/100	180/104	severe
	7.....	100	8	180/110	175/100	severe
	8.....	50	2	200/140	200/140	0
Essential Hypertension		100	3	210/145	200/140	0
		150	6	204/150	210/160	severe
	9.....	150	6	170/110	170/112	0
	10.....	50	5	190/105	200/110	0
		150	3	200/110	180/105	moderate
	11.....	100	12	160/95	170/110	0
	12.....	50	4	185/105	190/110	0
		100	3	190/110	175/105	0
		150	3	175/105	180/110	severe

* C, control blood pressure, represents average of all the readings recorded prior to drug administration.
† A, response to drug, as tabulated for each patient according to the dose given and refers to the lowest readings recorded during therapy.

From the clinical point of view, it seems unlikely that the hypotension induced by use of iproniazid is of any benefit to the hypertensive patient. Its inconsistency together with the unfavorable hemodynamic and renal effects indicate that the fall in blood pressure is a side-effect rather than a true vasodilator action.

TABLE 2.—*Effects of Iproniazid Therapy During Control, Hypotension, and Recovery Periods*

		Test Results*				
Patient	Period	UF ml./min.	RPF ml./min.	GFR ml./min.	RV mm.Hg/ ml./min.	CO Liter/ min.
1	Control	4.8	550	115	7	5.6
	Hypotension	1.1	380	85	14	4.1
	Recovery	2.8	485	98	8	5.2
2	Control	3.7	615	125	10	...
	Hypotension	0.8	425	75	22	...
	Recovery	4.1	535	110	12	...
3	Control	2.9	515	108	6	7.2
	Hypotension	0.7	465	70	12	4.8
	Recovery	3.1	550	110	7	6.9
4	Control	5.5	680	128	5	...
	Hypotension	1.0	495	101	13	...
	Recovery	4.2	610	135	6	...

* UF, urine flow; RPF, renal plasma flow; GFR, glomerular filtration rate; RV, renal vascular resistance; CO, cardiac output.

Summary and Conclusions

The hemodynamic and renal effects of acute and chronic administration of Marsilid and its analogue, Marplan, were investigated in patients with toxemia

of pregnancy and in patients with essential hypertension associated with pregnancy. Acute intravenous injections of iproniazid in doses varying between 0.7 mg. and 2.0 mg. per kilogram of body weight did not produce any hypotensive effect with the patient in either a supine or a standing position. Oral administration of iproniazid in doses of 100 to 150 mg. per day elicited orthostatic hypotension in about 50 per cent of the cases. This hypotension was accompanied by a decrease in cardiac output, urine flow, renal plasma flow, and glomerular filtration rate. Renal vascular resistance increased. Oral administration of carboxazid in doses of 10 to 20 mg. produced inconsistent orthostatic hypotension.

On the basis of the present data, it is concluded that the hypotension associated with the use of iproniazid or with the use of its analogue, carboxazid, represents a side-effect rather than a true vasodilator action. It is probably caused by venous pooling and a decrease in the cardiac output.

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The iproniazid and carboxazid used in this study were provided as Marsilid and Marplan, respectively, by Hoffmann-La Roche, Inc., Nutley, N. J.

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HYDRAMNIOS AND CONGENITAL ANOMALIES

STUDY OF SERIES OF SEVENTY-FOUR PATIENTS

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A series of 74 patients with hydramnios was studied; 80% were multiparas and there were five sets of twins. There was a high rate of cesarean section (21.6%), breech deliveries (6.8%), diabetes (18.9%) and preeclampsia (14.9%). Among the 79 neonates delivered, there were 23 deaths and the perinatal mortality was 29.1%. There is a remarkable association of hydramnios and congenital anomalies; 21 infants (26.6%) had congenital anomalies and 14 (17.7%) had pathological conditions. Anencephaly and hydrocephaly were the most common lesions; 6 infants had gastrointestinal defects and 10 had anomalous lesions which would have obstructed swallowing or prevented the passage of fluid through the gastrointestinal tract while in utero. Special emphasis should be placed on lesions in which there is urgent need for correction of respiratory obstruction, early surgery, or both. Routine gastric catheterization and aspiration are therefore valuable diagnostic procedures.

Hydramnios has been associated with a high incidence of congenital anomalies and mortality in infants for many years (table 1). Recently this relationship has been suggested as a diagnostic sign in early recognition and guidance to the therapy of obstruction in the alimentary tract of the newborn infant.[1]

The purpose of this report is to present our experience with this disorder from 1953 to 1958 at the Sloane Hospital for Women and to emphasize a method of diagnosis which is used at this hospital to facilitate the discovery of gastrointestinal obstruction in all infants. In addition, the physiological processes involved in the normal and pathological formation of amniotic fluid are reviewed.

In data compilation, both mother and infant clinical records were used. Only those cases were accepted in which there was convincing clinical evidence of excessive accumulation of amniotic fluid. Two liters were taken as the upper limit of normal.[2] The cases of acute and chronic hydramnios were analyzed together.

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