Successful Therapy of Prolonged Hypotension with an Adrenergic Beta-Receptor Blocking Agent

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PROLONGED hypotension may be a consequence of (1) decreased vasoconstrictor tone in the peripheral vasculature, (2) decreased cardiac output, (3) diminished circulating blood volume, (4) excessive vasodilator influences in the periphery, or (5) combinations of these factors. In this report two patients with persistent hypotension requiring continuous vasopressor therapy are presented. It was hypothesized, based on Ahlquist's concept of adrenotropic receptors, that an imbalance in function of alpha and beta receptors in the peripheral sympathetic nervous system might be an explanation for their prolonged hypotension. The availability of nethalide, [2-isopropylamino-1-(2-naphyl) ethanol hydrochloride], an adrenergic beta-receptor blocking agent, made it feasible to test this hypothesis.

Patient 1

A 56-year-old Caucasian housewife was hospitalized because of rectal bleeding that occurred 2 days before admission. She complained of a mild burning pain in the lower left abdomen.

At age 19 years the patient had spent 9 months in a tuberculosis sanitarium following two episodes of hemoptysis. Recent chest films had revealed stable fibrocalfic densities in the right lung apex. At age 52 years the patient was admitted to the Michael Reese Hospital because of a thyroid nodule, and a left hemithyroidectomy was done. Histologic sections revealed the nodule to be a small-cell carcinoma, and postoperative X-ray treatment was given. Subsequently she received 3 grains of thyroid extract daily. No evidence of metastasis was ever found. Two years later the patient was admitted to the hospital because of vaginal spotting, for which dilatation and curettage were performed. A sulfobromophthalein test was done at this time without adverse effects. For several years prior to the present hospital admission the patient had been under medical care for peptic esophagitis. There was no past history of allergic phenomena.

Physical examination on admission revealed a well-developed white woman in no acute discomfort. Her blood pressure was 150/100 mm. Hg sitting and 130/90 mm. Hg standing. The pulse rate was 72 beats per minute, and her temperature was 98.8°F. Examination of the head, ears, eyes, nose, and throat was not remarkable. The thyroid gland was not palpable, and there was no adenopathy. The lung fields were clear. The heart rhythm was regular, and no murmurs were heard. No masses or organs were palpated in the abdomen. There was mild right lower quadrant abdominal tenderness. Small external hemorrhoids were present, without evidence of bleeding. No stool was obtained on the initial rectal examination.

The hemoglobin was 14.7 Gm. per cent; the hematocrit value was 46 per cent. The white blood-cell and differential counts were normal. A urinalysis was negative except for a trace of albumin. The blood urea nitrogen, fasting blood sugar, serum calcium and phosphorus, alkaline phosphatase, and serum bilirubin determinations were normal.

One day after admission the patient was given 5 mg. per Kg. of body weight of sulfobromophthalein intravenously. One hour later she suffered a sudden syncopal episode. The blood pressure became unobtainable. A mottled erythematous rash was noted over the neck and chest. Intramuscular metaraminol raised the arterial blood pressure to 150/90 mm. Hg. At this time the patient complained of substernal pain that lasted for several seconds.

An emergency hemoglobin determination was 17.8 Gm. per cent; the hematocrit level was 55...
per cent. A serum transaminase test was normal, but on the next day a transaminase was 70. All subsequent transaminase values were normal. Serial electrocardiograms showed no evidence of myocardial ischemia or infarction. Repeated portable chest films showed no changes from previous x-rays.

After the initial fall in blood pressure and the response to metaraminol, the blood pressure fell again and faintness recurred. Metaraminol (100 mg. in 1,000 ml. of 5-per cent glucose in water) was started intravenously. For the next 3 weeks a continuous intravenous infusion of metaraminol solution had to be maintained. Many attempts were made to stop the vasopressor, but each time the blood pressure fell to unobtainable levels and syncope developed. Stool guaiac tests remained negative. The hemoglobin concentration ranged between 15 and 16 Gm. per cent. No polychromatophilia or eosinophilia was seen in peripheral blood smears. I-131 serum albumin plasma volumes were 28.4 ml. and 31.0 ml. per Kg. of body weight on two separate occasions. Twenty-five days after the onset of hypotension, prednisone, 5 mg. every 6 hours, was started. There was no discernible change in her clinical status.

On the twenty-seventh day after the onset of the hypotension the patient was given 10 mg. of guanethidine* intramuscularly. It was considered that the action of metaraminol might be potentiated by guanethidine. Six and one-half hours later the blood pressure could be maintained by one half of the previously required dosage of metaraminol solution. In 24 hours, however, the patient again required the previous dosage of vasopressor to maintain the blood pressure. Twenty milligrams of guanethidine given intramuscularly at this time had no further discernible effect.

The patient’s clinical status continued without significant change. Nethalide, 150 mg. orally every 6 hours, was begun 32 days after the onset of hypotension. The rate of metaraminol infusion was kept constant at 16 drops per minute. Thirteen hours later it became possible to halve the metaraminol concentration—from 100 mg. to 50 mg. in 1,000 ml. of 5-per cent glucose in water. Twelve hours later the concentration was again halved, and 24 hours later (2 days after nethalide was begun) the metaraminol solution could be stopped. There was no evidence of postural hypotension. Six days after the nethalide was started it was discontinued abruptly without adverse effects. The prednisone dosage was then tapered down and stopped.

Just before the nethalide was started the patient’s hemoglobin concentration was 14.7 Gm. per cent and no polychromatophilia was noted. On the day the nethalide was stopped the hemoglobin level was 11.2 Gm. per cent. The plasma volume had increased from 31 to 41.3 ml. per Kg. of body weight. A reticulocytosis of 148,900 was present, and polychromatophilia was seen. The reticulocyte count rose to 324,400, and then returned to normal in 1 month. Stool guaiac tests and a Coombs antiglobulin test were negative. Proctoscopy and x-rays of the colon, esophagus, stomach, and small bowel were all negative. The patient was discharged from the hospital with a hemoglobin level of 10.9 Gm. per cent.

One year later the patient was readmitted to the Michael Reese Hospital with hemoptysis, most likely due to apical bronchiectasis secondary to inactive pulmonary tuberculosis. The findings on physical examination were not remarkable. The hemoglobin concentration was 14.7 Gm. per cent and a reticulocyte count was 39,600. Tests for glucose-6-phosphate dehydrogenase, with and without nethalide added to the patient’s blood, showed normal activity. No precipitins against sulfbromophthalein could be demonstrated with an Ouchterlony plate. Passive transfer skin testing was not performed because of a questionable past history of hepatitis.

**Patient 2**

A 53-year-old Caucasian housewife was admitted to the hospital after the acute onset of anterior chest pain and shortness of breath. There was a history of anticoagulant therapy subsequent to previous hospitalization for an impending myocardial infarction.

Physical examination revealed a well-developed white woman whose sensorium was dulled because of the earlier administration of morphine sulfate. Her blood pressure was 130/90 mm. Hg. The pulse rate was 75 beats per minute. The respiratory rate was 30 per minute, and her temperature was 98.4F. Her pupils were pinpoint in size. There was no adenopathy. The chest was clear. The heart rhythm was regular, and no murmurs were audible. The abdomen was soft; no organs were palpated. The rest of the general physical examination was negative.

The initial hemoglobin concentration was 15.5 Gm. per cent; the hematocrit value was 46 per cent. A white blood-cell count was 6,366, with a normal differential count. A urinalysis was negative. Fasting blood sugar and blood urea nitrogen determinations were normal. The initial serum transaminase was 22. The prothrombin time was 11.6 seconds. On the second to fourth hospital days the transaminase levels were 27, 49, and 42, respectively. The initial electrocardiogram showed

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* Kindly provided by the Ciba Pharmaceutical Company.
slight nonspecific changes and 2 days later had returned to within normal limits.

The patient's hospital course was uneventful until 9 days after admission, when she again developed anterior chest pain unrelieved by sublingual nitroglycerin. The serum transaminase was 55. On the tenth hospital day hypotension ensued. The blood pressure was maintained with an intravenous drip of metaraminol solution (100 mg. in 1,000 ml. of 5-per cent glucose in water). Repeated attempts to stop the metaraminol were made, but each time the blood pressure fell precipitously and the patient became faint and cyanotic. On the thirteenth hospital day an electrocardiogram showed evidences of anterior wall ischemia.

Marked bradycardia with many premature ventricular systoles became manifest subsequent to the occurrence of the hypotension. Procaine amide and atropine sulfate were started. One day after the onset of the hypotension, cortisone (50 mg. orally every 6 hours) was begun. The dosage was decreased to 25 mg. every 6 hours 4 days later. Occasional episodes of anterior chest pain radiating to the left arm continued to occur.

Eight days after the development of hypotension, nethalide, 100 mg. orally every 4 hours, was started. Eight hours later the blood pressure could be maintained after the metaraminol solution concentration was halved. It was possible to reduce further the metaraminol concentration 16 hours later, and 48 hours after nethalide was begun the metaraminol therapy could be stopped. Postural hypotension was not present. The dosage of nethalide was gradually reduced, and the drug was stopped 9 days after it had been started. The cortisone dosage was gradually decreased, and then stopped before the patient left the hospital.

The patient's electrocardiograms remained normal from the second day of nethalide treatment until she was discharged from the hospital. Chest x-rays were negative. At the time of the onset of hypotension the hemoglobin concentration was 17.8 Gm. per cent and the white blood-cell count was 9,146. A peripheral blood smear was not done. On the last day of treatment with nethalide the hemoglobin level was 12.8 Gm. per cent, and a reticulocyte count was 200,000. Polychromatophilia was present in the peripheral blood smear. The reticulocytosis continued for the next 4 weeks. Stool guaiac tests were negative. Tests for Coombs antiglobulin and glucose-6-phosphate dehydrogenase activity were normal. A search for Heinz bodies by mixing the patient's blood with nethalide was negative. The hemoglobin concentration fell to 11.5 Gm. per cent, and then stabilized. A Cr$^{51}$ red cell survival study revealed a T-half life of 18 days (normal, 26 to 32 days). The curve could not be considered reliable, however, inasmuch as only three points were obtained. Ten weeks later the hemoglobin level was 13.2 Gm. per cent and a reticulocyte count was 70,000.

**Discussion**

It has recently been emphasized that prolonged hypotension, especially after myocardial infarction, is critically related to the effective circulating blood volume. Others have noted that the efficacy of norepinephrine and metaraminol in the treatment of cardiogenic shock and hypotension may be in part related to their venoconstrictor action. The rise in hemoglobin concentration after the onset of hypotension seen in both patients here presented probably was due to a decrease in circulating blood volume. The fall in plasma volume was confirmed in the first patient. No attempt was made to correct this deficit. Instead, a specific pharmacologic attempt was made to study the sympathetic nervous system in both patients.

The first patient, the fifteenth reported case of severe systemic anaphylactoid reaction to sulfobromophthalein, illustrates once more that this compound is potentially hazardous. The failure to demonstrate circulating precipitins by the Ouchterlony technic is not surprising in view of the low molecular weight of sulfobromophthalein. The cause of the hypotension in the second patient is less evident. Because of the character and location of the chest pain and the enzyme changes, a myocardial etiology was initially suspected. In view of the continued hypotension, the clinical picture, and the good pressor response to small doses of metaraminol, a peripheral origin for the hypotension was then considered more likely.

Studies in animals and man indicate that the pressor activity of norepinephrine is potentiated by guanethidine. Corcoran et al. reported the potentiation of the pressor response to norepinephrine by a small dose of guanethidine in a patient in severe shock with staphylococcal enteritis. Although the delayed potentiating response to intramuscular guanethidine in our first patient may have been due to the release of bound endogenous catecholamines, the persistence of the poten-
ADRENERGIC BLOCKING AGENT

A direct action of guanethidiné on receptor substance that increases sensitivity to various amines merits consideration.

The most tenable theory for adrenergic cellular receptor mechanisms is Ahlquist's.1 Two types of receptors are distinguished: (1) alpha receptors associated with sympathetic excitatory functions such as vasoconstriction, and stimulation of the uterus, nictitating membrane and dilator pupillae, and (2) beta receptors associated with sympathetic inhibitory functions such as vasodilatation and inhibition of uterine and bronchial musculature. Moreover, cardiac inotropic and chronotropic sympathetic receptors are excitatory beta receptors.

A beta-receptor blocking agent first became available with the introduction of a dichloro analog of isoproterenol.11 Because of de novo tachycardia produced by this drug, a less troublesome compound was needed for use in man. Nethalide has been shown to be an effective antagonist of adrenergic beta receptors.

In the application of Ahlquist's theory to the problem of protracted hypotension as exemplified by the two patients presented, it was considered that the hypotension might be a consequence of a disturbance of balance in the peripheral sympathetic nervous system. The shifts in plasma volume were considered as a possible additional consequence of such a disturbance. Left ventricular failure as the cause of the late-occurring and protracted hypotension seemed unlikely in view of the complete absence of any supporting clinical evidence.

It was reasoned that the imbalance in the peripheral sympathetic nervous system could be due to peripheral beta-receptor hypersensitivity or to alpha-receptor fatigue. It was our hypothesis that blocking the adrenergic beta receptors with nethalide would cause exogenous and endogenous catecholamines normally reacting with vasodilating receptors to be shifted to excitatory (vasoconstrictor) receptors. The results in the two patients serve to fortify this hypothesis. Sympathetic nervous system homeostasis was quickly obtained, and exogenous vasopressors were no longer needed. For reasons presently unknown, this homeostasis was subsequently unaltered when nethalide was discontinued. Though the proposed negative inotropism of any beta-receptor blocking agent might be expected to have a detrimental effect in patients with prolonged hypotension, the results in our two patients indicate otherwise. Preliminary hemodynamic observations in three patients (two of whom were hyperthyroid) have not revealed a significant fall in cardiac output following intravenous nethalide.13 It remains possible that the response in both our treated patients was unrelated to the known properties of nethalide.

A further consideration is that these patients may have been partly depleted of norepinephrine as a consequence of the metaraminol therapy. This would not be inconsistent with the hypothesis of relative peripheral adrenergic beta-receptor dominance and may have served to contribute to that state.

The reticulocytosis is of interest. Four other patients, not in clinical shock, also received nethalide for an average period of 6 days. No polychromatophilia or change in hemoglobin concentration was observed. A drug-induced hemolytic anemia in the present two patients, however, remains a possibility. It is also possible that in the presence of prolonged hypoxia, a consequence of the hypotension, erythropoiesis was stimulated by erythropoietin. Also, it is conceivable that diminished arterial perfusion of the bone marrow in prolonged hypotension is itself a bone marrow stimulus.

Summary

Two patients with prolonged hypotension requiring continuous vasopressor therapy are described.

In both patients treatment with nethalide, a beta-receptor blocking agent, appeared clinically effective in allowing the withdrawal of metaraminol therapy and the maintenance of normotension. The results in these patients

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tend to fortify a hypothesis of peripheral adrenergic beta-receptor dominance in patients with prolonged hypotension.

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**References**


**Motivation**

There is, however, in every well regulated mind, an elasticity bounding against oppression, a sense of accomplished duty, a proud consciousness of having conferred unrequited benefits, which sustain it amidst all the degradations of external forms, and individual or national ingratitude, and which incite it, in spite of every obstacle, to persevere in one undeviating course to the end of its mortal career.—Preface. *Collections from the Unpublished Medical Writings of the Late Caleb Hillier Parry, M.D.F.R.S.* Vol. I., London, Underwoods, Fleet-Street, 1825, p. 5.
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