Clinical Evaluation of Sodium Nitroprusside as a Hypotensive Agent

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INDUCED hypotension following its introduction in 1946 enjoyed a brief period of popularity which reached its peak in 1952. Since then, the indications for and use of this procedure have greatly decreased, but it still finds useful application. It has been used in the Cleveland Clinic chiefly for renal angiography of hypertensive patients and in some neurosurgical and cardiovascular procedures. The means of producing hypotension are various: *arteriotomy, conduction anesthesia,* and *ganglioplegia;* none has proved ideal.[1]

In the present study, a promising hypotensive agent, sodium nitroprusside, which is potent, inexpensive, quick in action, short in duration, and nontoxic in clinical dosage, was investigated. Its chemical and pharmacologic properties and performance in hypertensive and normotensive patients are described. It is not within the realm of this paper to discuss the indications or contraindications to controlled hypotension.

Chemical Properties and Preparation

Sodium nitroprusside ($Na_2Fe^{++}(CN)_5 \cdot H_2O$), a ferrous, hydrated, pentacyano-compound, was first described in 1849 by Playfair.[2] It is produced by the action of 30 per cent nitric acid on a ferrocyanide or ferricyanide. The nitroprussides are relatively stable substances and resist oxidation in a neutral or acid solution.[2] Sodium nitroprusside has a molecular weight of 297.91 and occurs in the form of rhomboid red crystals. It is inexpensive ($6.25 a pound). The specific gravity is 1.72 and the solubility is 40 Gm. in 100 ml. of water at 16° C.[3] It is commonly known in the clinical laboratory for its color reactions with acetone, aldehydes, alkali sulfides, and sulfur dioxide.

A stock solution of 10 mg./ml., prepared by the hospital pharmacist, contains 2 Gm. of sodium nitroprusside crystals dissolved in 200 ml. of sterile distilled water. As the solution does not tolerate sterilization by heat, it is passed through a sterile Seitz filter and is stored, under refrigeration, in a sterile, rubber-stoppered brown bottle. If the solution's color changes from brown to blue, the drug has been reduced and should not be used.

The concentration of the infusion for clinical use was 50 or 100 μg./ml. The weaker concentration was used in hypertensive patients receiving antihypertensive therapy. Twenty-five milligrams (2.5 ml. of stock solution) was diluted with 250 ml. of 5 per cent glucose in water to form a 0.01 per cent solution and administered through a Microdrip * venoclysis set. This set was connected to the tubing of another venoclysis set near the needle so there was no large reserve in the tubing when the administration was stopped. The diluted preparation was refrigerated for periods as long as two weeks with no apparent loss of vasodepressor activity.

Toxicity

Prolonged parenteral administration of sodium nitroprusside results in the accumulation of thiocyanate in the blood. Thiocyanate (SCN) is oxidized to cyanide (HCN) by a thiocyanate oxidase contained in erythrocytes.[4, 5] Pines and Crymble [4] reported that two patients who received thiocyanate by mouth for from 3 to 5 days had cyanide concentrations of 0.05 to 0.10 mg. per 100 ml. of whole blood. Gettler and Baine [6] stated that the minimal cyanide blood level observed

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* Venopak Microdrip List No. 4540, Abbott Laboratories, North Chicago, Illinois.

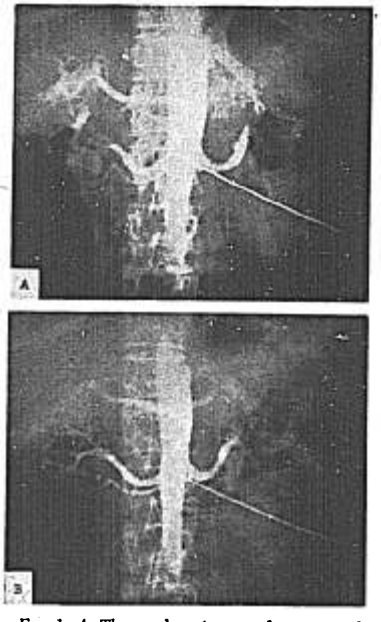

FIG. 1. *A*, The renal angiogram of patient with a systolic blood pressure of 220 mg. of mercury. There is poor visualization of the main branches of the right renal artery. *B*, The renal angiogram of the same patient after sodium nitroprusside with systolic blood pressure of 80 mm. of mercury. The branches of the right renal artery are well delineated.

to cause fatal poisoning was 0.34 mg. per 100 ml. Goldstein and Rieders [5] showed that the change from thiocyanate to cyanide in the presence of erythrocytes is most efficient at a *p*H of 7.4 and a temperature of 40° C.

Goldstein and Rieders [7] made cyanide determinations at from 4 to 7 hours after the intravenous injection of 700 mg. sodium thiocyanate in seven patients. The levels ranged from 0.010 to 0.050 mg. cyanide per 100 ml. whole blood. Cyanide causes histotoxic anoxia, and occasionally causes sodium diuresis and inhibits carbonic anhydrase.

During prolonged administration of nitroprusside in this study, serial determinations of the thiocyanate concentrations in whole blood were performed to aid in maintaining the level below 15 mg. per 100 ml. of whole blood.

Pharmacologic Properties

Page and others [8] reported on the cardiovascular actions of sodium nitroprusside in animals and hypertensive patients. Their observations point to the Fe-NO grouping in nitroprusside as the active depressor. It seems to act primarily on the vascular musculature independently of the nervous system. Its depressor action is augmented in both dogs and humans by autonomic ganglion-blocking agents. These studies suggested also that hypertensive patients are more sensitive to nitroprusside infusions than are normotensive subjects.

Clinical Evaluation

In this study we used infusions of sodium nitroprusside in patients during local or general anesthesia to lower arterial blood pressure.

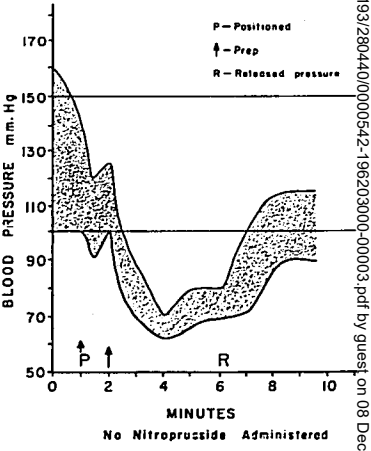

FIG. 2. Blood pressure recording of a patient who was positioned for renal angiography. Following the application of compression to the lower abdomen (*P*), the venous return was impaired and the systemic blood pressure decreased. This was corrected by releasing the compression at *R*; an increase in blood pressure resulted.

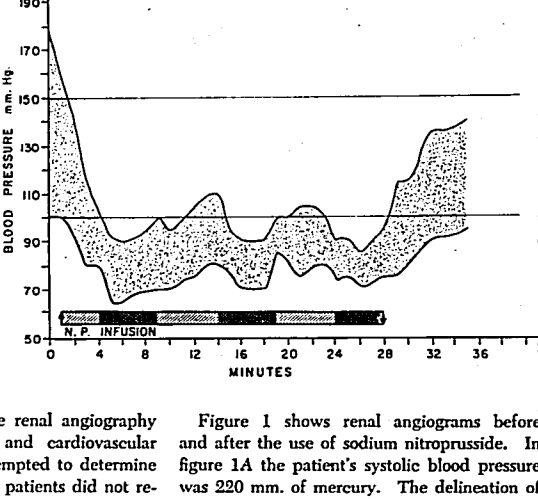

FIG. 3. Blood pressure recording of a patient in whom controlled hypotension was produced by infusion of sodium nitroprusside for renal angiography. Patient had been receiving antihypertensive drugs for the treatment of hypertension. The darker shades indicated an increased rate in the infusion of the sodium nitroprusside.

sure and thereby facilitate renal angiography or certain neurosurgical and cardiovascular procedures. Also, we attempted to determine whether any normotensive patients did not respond to nitroprusside infusion. These data will be presented under separate categories.

INFUSION OF SODIUM NITROPRUSSIDE FOR RENAL ANGIOGRAPHY

In our experience renal angiography is a valuable technique in the diagnosis of renal hypertension. It was observed that high intra-aortic pressures tended to carry injected contrast medium past the orifices of the renal arteries in the central aortic stream, resulting in inadequate filling and visualization of the renal vessels. It was reported in 1955[9] that temporary reduction of blood pressure with vasodilator drugs permitted better lateral dispersion of the contrast medium and facilitated compression of the iliac artery, so that adequate renal angiograms could be obtained with small volumes of injected medium. The lowered intra-aortic pressure allowed a faster injection of the small quantities of dye and thereby provided a greater concentration in the renal vessels. It was also observed that after withdrawal of the needle there was far less leakage of blood from the needle hole in the aorta.

Figure 1 shows renal angiograms before and after the use of sodium nitroprusside. In figure 1*A* the patient's systolic blood pressure was 220 mm. of mercury. The delineation of the smaller branches of the right renal artery is unsatisfactory. In figure 1*B* the systolic blood pressure had been reduced to 80 mm. of mercury by the infusion of sodium nitroprusside solution. The terminal arteries of the right kidney are well visualized and are seen to be normal.

At the Cleveland Clinic renal angiography is performed by translumbar aortography under local anesthesia. The patient is placed in a prone position; an inflatable pad is placed under the lower abdomen for compression of the iliac arteries and the fabric strap of the roentgenographic table is drawn snugly over the lumbosacral area. The blood pressure is determined after the patient is positioned and before the injection of the hypotensive agent, as the prone position and the compression of the abdomen may cause a fall in blood pressure. For example (fig. 2), in one patient the fall in blood pressure was secondary to impeded venous return resulting from compression applied to the lower abdomen; upon release of the compression, the cardiac output increased and blood pressure returned to its previous norm.

TABLE 1. Response to Administration of Sodium Nitroprusside in 44 Hypertensive Patients Undergoing Renal Angiography

Preoperative Systolic Blood Pressure (mm. Hg)	No. of Cases	Average Decrease in Preop. B. P. during Nitroprusside Administration		Average Decrease in Preop. B. P. at End of Procedure	
		mm. Hg	%	mm. Hg	%
154–199	32	78.5	53.5	30.2	82.3
200–249	9	102.2	49.7	36.6	81.9
250–300	3	160.0	39.3	70.0	74.3

If the patient tolerates the compression with no significant hypotensive response, the administration of sodium nitroprusside is begun very slowly (20 'microdrops' per minute) and the patient's response is noted. The systolic blood pressure is read every 5 or 10 seconds. At the first drop in blood pressure, which usually appears in from 1 to 2½ minutes, the flow of nitroprusside solution is adjusted to provide the desired level of hypotension. The usual total dose varies from 25 to 100 μg. The return of normal blood pressure usually requires from 1 to 5 minutes after the discontinuation of the administration. Hypertensive patients on antihypertensive therapy appear to be more sensitive than patients with no previous therapy. Figure 3 shows the blood pressure recording at one-minute intervals during the infusion of sodium nitroprusside in a patient who had had antihypertensive therapy. The blood pressure was lowered just prior to each aortic injection of contrast medium and was allowed to return to previous levels afterward.

Sodium nitroprusside was used for renal angiography in 44 hypertensive patients ranging in age from 2½ to 63 years (table 1). All patients had a prompt response to the vasodilator drug. The blood presure recovered upon cessation of administration of nitroprusside in all patients but two who required the use of a vasopressor drug to restore their blood pressure to the preoperative level.

The infusion of sodium nitroprusside is not harmful to the patient as long as he remains completely horizontal; he should not be allowed to sit up during the infusion or for 2 to 3 hours afterward.

In these 44 hypertensive patients, the preoperative blood pressure was the first blood pressure recording taken in the operating suite. The decrease in blood pressure was calculated from the lowest one recorded during nitroprusside administration. The blood pressure

TABLE 2. Response of Four Neurosurgical Patients to Sodium Nitroprusside Administered During Operation

Case No.	Age (year)	Position	Anesthesia Technique	Blood Pressure (mm. Hg)		Duration of Blood Pressure Control*		Pulse Rate (beats per minute)	
				Preop.	During Infusion	During Operation	Postop.	Preop.	During Infusion
1	48	Supine	Thiopental-N_2O-curare, Controlled hypothermia	120/90	80/60	30 min.		60	64
2	60	Supine	Thiopental-N_2O-curare, Controlled hypothermia	130/80	90/60	40 min.		64	60
3	64	Sitting*	Thiopental-N_2O-curare	250/160	160/110	45 min.	2 days	80	84
4	59	Sitting*	Thiopental-N_2O-curare	240/140	180/110	90 min.		80	70
			Second operation: Exploratory craniotomy	230/120	180/100	45 min.	1 day	120	116

* Modified sitting position with an anti-gravity suit as described by Gardner and Dohn.[10]

TABLE 3. Response of Four Cardiovascular Patients (Coaretation of Aorta) to Sodium Nitroprusside Administered During Operation

Case No.	Age (year)	Position	Anesthesia Technique	Blood Pressure (mm. Hg)		Duration of Blood Pressure Control (minutes)	Pulse Rate (beats per minute)	
				Preop.	During Infusion		Preop.	During Infusion
1	17	Right lateral decubitus	Thiopental-N_2O-curare	200/120	150/90	55	80	88
2	28	Right lateral decubitus	Thiopental-N_2O-curare	190/130	130/90	40	110	140
3	27	Right lateral decubitus	Thiopental-Fluothane-curare	200/110	140/100	20	100	130
4	37	Right lateral decubitus	Thiopental-N_2O-curare	220/140	150/110	90	80	110

taken at the end of the procedure was reported as the recovery blood pressure.

It was observed that there was relatively little downward drift of blood pressure after cessation of nitroprusside infusion. The return of the blood pressure to its preoperative level was prompt, usually within one to two minutes in most patients, with a few taking as long as five to ten minutes. There were no serious complications in any of these patients following controlled hypotension for renal angiography, either from the nitroprusside or from the procedure of translumbar aortography.

INFUSION OF SODIUM NITROPRUSSIDE DURING SURGICAL PROCEDURES

Sodium nitroprusside was used to produce controlled hypotension in ten patients during operation. Four were undergoing neurosurgical procedures (table 2), four had operations for coarctation of the aorta (table 3), and two had severe pressor response to vasopressor drugs administered during the course of a surgical procedure (table 4).

Of the neurosurgical patients, all of whom were hypertensive, two required controlled hypotension in the postoperative period as well

TABLE 4. Findings in Two Patients Given Sodium Nitroprusside to Control Hypertensive Crisis Induced by Vasopressor Drug

Case No.	Age (year)	Position	Anesthesia Technique	Vasopressor Drug	Blood Pressure (mm. Hg)			Duration of Blood Pressure Control (minutes)
					Preop.	After Vasopressor Drug	During Infusion of Sodium Nitroprusside	
1	46	Prone	Hypobaric spinal	Mephentermine (Wyamine), 7.5 mg. intraverous	80/60	220/160	110/70	60
2	61	Supine	One hour postthoracotomy	Metaraminol (Aramine), 10 mg. intramuscularly	Systolic, 90	Systolic, 250	Systolic, 140	90

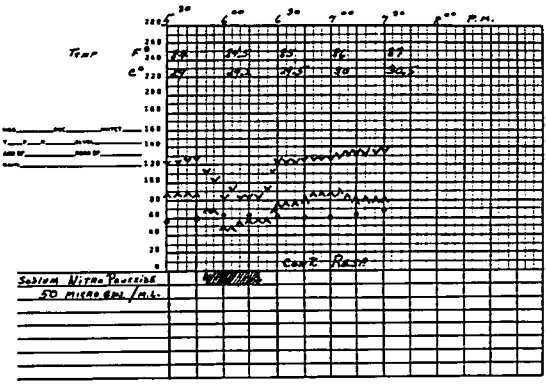

FIG. 4. Second page of anesthetic record of a patient during controlled hypothermia with thiopental-nitrous oxide and curare anesthesia. The controlled hypotension was adequately produced with intravenous infusion of sodium nitroprusside. The blood pressure returned to prehypotensive levels within ten minutes after cessation of administration of hypotensive agent.

as during operation (table 2). The other 2 patients with cerebral aneurysms required controlled hypotension during hypothermia. Figure 4 illustrates the compatability of sodium nitroprusside with controlled hypothermia. A 48 year old white man with cerebral aneurysm had a preinduction blood pressure of 170/70 mm. of mercury. Under hypothermia (84° F. or 29° C.), the blood pressure fell to 120/90 mm. of mercury. The blood pressure was reduced to 80/60 mm. mercury for 20 minutes by the intravenous infusion of 0.01 per cent sodium nitroprusside, and returned to 120/80 mm. of mercury within 10 minutes after the infusion of hypotensive agent was discontinued.

Infusion of Sodium Nitroprusside in Normotensive Patients

Twenty normotensive patients ranging in age from 12 to 73 years were given sodium nitroprusside during or after minor surgical procedures to evaluate their resistance to sodium nitroprusside. Eight patients were operated upon under sodium thiopental and nitrous oxide anesthesia and showed a good hypotensive response to a slow infusion of 0.01 per cent sodium nitroprusside. Twelve patients who were awake after anesthesia were given a single dose of nitroprusside, ranging from 2 to 3 μg./kg., and their blood pressure response was recorded. In 7 of these patients, a sudden drop in systolic blood pressure of 20 mm. of mercury or more occurred. This was considered a good response. The other 5 patients did not respond as dramatically and were considered to have a high tolerance to the hypotensive agent. These 5 patients were then given a 0.01 per cent sodium nitroprusside infusion until the systolic blood pressure was reduced by at least 20 mm. of mercury.

Peripheral vasodilatation was noted in 5 awake patients by flushing of face. The average onset of hypotension after administration of sodium nitroprusside was one to two and one-half minutes. The pulse rate tended to increase on the average of 16.7 per minute. The average decrease in systolic blood pressure was 35.4 mm. of mercury less than the normal blood pressure, or a reduction to 72.2 per cent of normal blood pressure. The recovery of the blood pressure averaged to 7.9 mm. of mercury less than the preoperative blood pressure or to 94.3 per cent of the preoperative blood pressure.

In general, it appeared that older patients were more susceptible to the hypotensive effect of nitroprusside than younger patients. However, there were no patients in whom hypotension could not be induced. Vasopressor agents were not needed in any of the normotensive patients to restore the blood pressure following infusion of sodium nitroprusside. The recovery period was very short in most cases (from 1 to 5 minutes).

Summary and Conclusions

Sodium nitroprusside was given for its hypotensive effect to 74 patients: in 44 as a definite aid in renal arteriography; in 10 during surgical procedures (4 neurosurgical, 4 operations for coarctation of the aorta, and 2 severe pressor responses to vasopressor drugs); and in 20 to evaluate the response of normotensive individuals. The administration of the drug is easily controlled; it is highly potent, and its effect on the blood pressure is of short duration. The agent appeared to have no paralyzing effect on the parasympathetic or sympathetic ganglia. The only side action noted was an occasional rise in pulse rate, which was probably secondary to fall in systemic blood pressure.

The chief advantages of this drug over others used for producing hypotension are the promptness of the appearance and disappearance of the effect, and the infallibility of its action. No patient in the series here reported failed to respond satisfactorily to this agent.

Sodium nitroprusside was prepared by the Pharmacy Department under the direction of Mr. Henry Szymczyk and Mr. James L. Lewis.

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HYPOTHERMIA Pathophysiologic effects of extracorporeal cooling at 10° C., circulatory occlusion and rewarming were studied in dogs with the following parameters being monitored: arterial and venous blood pressure, electrocardiogram, electroencephalogram, ventricular contractile force, peripheral and core temperatures, arteriovenous oxygen saturations, acid-base metabolism and histological changes. Ventricular contractile force increased 185 per cent on cooling. No metabolic acidosis resulted, and only a few minor histologic changes occurred in the heart, kidney and brain of the survivors. (*Trede, M., Foote, A. V., and Maloney, J. V.: Pathophysiologic Aspects of Profound Hypothermia with Extracorporeal Circulation, Ann. Surg. 154: 210 (Aug.) 1961.*)