Some Metabolic Effects of Sodium Nitroprusside in Man

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Summary

The infusion of sodium nitroprusside during surgical operations produced plasma levels of cyanide of up to four times the control value. Plasma thiocyanate showed little change except during prolonged infusion of the drug, but total plasma B₁₂ tended to fall, as did methylcobalamin. Other cobalamins showed little change after nitroprusside infusion for short periods. During longer infusions the ratio of methylcobalamin to adenosyl + hydroxocobalamin fell and cyanocobalamin concentrations were high.

Introduction

The use of sodium nitroprusside as a hypotensive agent was introduced to British anaesthetic practice in 1968 (Jones and Cole, 1968). Since that time there have been further reports on its use both during anaesthesia and in the treatment of hypertensive emergencies (Taylor *et al.*, 1970; Mani, 1971; Siegel *et al.*, 1971). Doubts have been expressed, however, about the safety of sodium nitroprusside since its immediate metabolic products are most probably cyanide and thiocyanate (Wilson *et al.*, 1971). In addition to their direct toxic effects it has been suggested that these substances interfere both with

iodine uptake by the thyroid (Nourok *et al.*, 1964) and with the metabolism of vitamin B₁₂ (Wilson and Matthews, 1966). The present study, which was designed to obtain further information about certain of these effects, was carried out during a recent clinical trial of sodium nitroprusside as a hypotensive agent (to be reported).

Patients and Methods

A saline solution of sodium nitroprusside (100 µg/ml) was administered by intravenous infusion to induce hypotension during anaesthesia in patients undergoing major orthopaedic surgery. The drip rate was controlled to maintain a systolic arterial pressure of 60 mm Hg in an effort to limit blood loss. A venous blood sample (30 ml) was taken before and immediately after the administration of sodium nitroprusside. The samples were taken into heparinized syringes, with precautions against exposure to white light, and the plasma was separated under red light within one hour. Aliquots were stored at -20°C in foil-wrapped tubes for the estimation of total B₁₂ and plasma cobalamins. Cyanide was isolated without delay from a 5-ml or preferably 10-ml aliquot of the separated plasma by the method of Boxer and Rickards (1950) and estimated by the Aldridge technique (Aldridge, 1945). Plasma thiocyanate was determined by the latter method using 1 ml of plasma deproteinized with 10% trichloroacetic acid. Erythrocyte cyanide was estimated as described elsewhere (Vesey and Wilson, 1974). Total B₁₂ was estimated by radioisotopic assay (Matthews *et al.*, 1967) and plasma cobalamins by a chromatobioautographic method (Linnell *et al.*, 1969 a; Linnell *et al.*, 1971). Two further patients with malignant hypertension resistant to more conventional drugs received prolonged treatment by intravenous infusion of sodium nitroprusside. One patient (case 18) was a girl of 12 years suffering from cerebral haemorrhage and malignant hypertension secondary to unilateral renal disease. She received 424 mg of the drug over a six-day period before nephrectomy. Two years later this girl was well. The second patient (case 19), aged 46 years and suffering from a dissecting aneurysm with malignant hypertension, received 2,277 mg over a five-day period.

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TABLE 1—Plasma Cyanide and Thiocyanate in 17 Patients before and after Nitroprusside Therapy

Case No.	Nitroprusside Infusion			Cyanide (nmol/100ml)		Thiocyanate (µmol/100ml)	
	Time (min)	Rate (µg/min/Kg)	Dose (µg/Kg)	Before	After	Before	After
1	20	4.3	86		30		9.3
2	85	4.9	417	0	50	4.3	5.2
3	75	7.2	540	5	139	9.5	10.1
4	45	5.2	234	24	237	19.7	21.3
5	90	4.2	378				6.5
6	50	7.2	360			11.3	12.7
7				25		1.4	
8	85	1.1	94	13	78	11.0	13.2
9	40	8.6	344			12.9	12.7
10	40	7.2	288	13	36	3.4	3.7
11	50	10.6	530			15.6	18.1
12	45	3.8	171		90		8.8
13	75	3.5	263	20	49	16.9	16.5
14	60	2.4	144	0	0	3.8	3.9
15	55	4.2	231	80	56	5.3	6.2
16	60	3.3	198	2	5	5.1	4.8
17	50	3.9	195	6	23	11.4	9.6
Mean ± S.E. of Mean No. of Patients t P				15.5 ± 6.3 11	66 ± 17.3 12	9.4 ± 1.51 14	10.16 ± 1.32 16
				8.032 <0.0005		0.5023 >0.10	

TABLE II—Data on Two Patients receiving Nitroprusside for an Extended Period

	Case 18		Case 19			
	Before Nitroprusside	After Infusion for 3 Days with 250mg	After 200mg	After 700mg	Before 5mg OHB ₁₂ (I.V.)	½ hr After OHB ₁₂ *
Plasma cyanide nmol/100ml	10	211	31	138	145	152
Plasma thiocyanate µmol/100ml	4.3	30	14.5	32.2	50.4	51.9
Red blood cell cyanide µmol/100ml			1.83	13.0	32	15.7
Total B ₁₂ pg/100ml		630	460	570	670	>2000
Me B ₁₂ pg/100ml		201	345	312	249	>220
CNB ₁₂ pg/100ml		252	0	0	200	>760
Ado B ₁₂ + OHB ₁₂ pg/100ml		177	115	258	221	>1020
% CNB ₁₂		42	0	0	30	38
Me B ₁₂ : Ado B ₁₂ + OHB ₁₂		1.1	3.0	1.2	1.1	0.2

Me B₁₂ = Methylcobalamin.CNB₁₂ = Cyanocobalamin.Ado B₁₂ = Adenosylcobalamin.OHB₁₂ = Hydroxocobalamin.

*The patient was still being infused with nitroprusside.

TABLE III—Plasma Cobalamins before and after Nitroprusside Therapy in 11 Patients

Case No.	Total B ₁₂ (pg/ml)		Me B ₁₂ (pg/ml)		CNB ₁₂ (pg/ml)		Ado B ₁₂ + OHB ₁₂ (pg/ml)		Me B ₁₂ : Ado B ₁₂ + OHB ₁₂ (pg/ml)	
	Before	After	Before	After	Before	After	Before	After	Before	After
2	355	215	213	129	0	0	142	86	1.5	1.5
3	355	310								
4	275	250								
8	645	680	368	306	0	129	277	245	1.3	1.2
9	1,030	785	412	377	154	180	464	220	0.9	1.7
10	275	280	69	98	22	22	184	160	0.4	0.6
11	275	260	205	170	0	0	70	90	2.9	1.9
13	425	345	173	124	136	90	111	124	1.6	1.0
15	535	370	305	226	27	11	203	133	1.5	1.7
16	460	460	329	276	0	51	131	133	2.5	2.0
17	350	275	214	129	10	30	126	116	1.7	1.1
Mean difference ± S.E. of mean	-59 ± 24.6		-50.3 ± 11.8		± 18.2 ± 16.5		-44.6 ± 26.9		-0.18 ± 0.18	
t test on paired data	2.4		4.2		1.1		1.7		1.0	
P	0.05		0.005		0.1		0.1		0.1	

Me B₁₂ = Methylcobalamin.CNB₁₂ = Cyanocobalamin.Ado B₁₂ = Adenosyl cobalamin.OHB₁₂ = Hydroxocobalamin.

Results

The results of plasma thiocyanate and cyanide determinations before and after nitroprusside infusion for a short period are shown in table I. In most patients there was a slight rise in plasma thiocyanate after nitroprusside infusion but the mean plasma cyanide level rose to more than four times the pre-treatment level—a highly significant increase. When infusion was continued over a longer period in two patients (cases 18 and 19) there was a considerable rise in both plasma thiocyanate and plasma cyanide (table II). In case 19 estimation of erythrocyte cyanide showed that a high proportion of cyanide was taken up by the red cells. After an injection of hydroxocobalamin (5 mg intravenously) the erythrocyte cyanide concentrations fell sharply despite continued infusion of nitroprusside.

The results of plasma total B₁₂ and cobalamin estimations are shown in table III. Plasma total B₁₂ was significantly lowered by nitroprusside infusion though in no case did the post-infusion value fall below the lower limit of normal (180 pg/ml). The mean methylcobalamin concentration was also reduced significantly after treatment with nitroprusside and in four cases the post-treatment plasma methylcobalamin was below the lower normal limit (130 pg/ml) (Linnell *et al.*, 1971). Changes in the levels of the other cobalamins were slight. In one of the patients who received a prolonged infusion of nitroprusside (case 19) there was a progressive rise in plasma B₁₂ and a fall in both methylcobalamin and the ratio methylcobalamin : adenosylcobalamin + hydroxocobalamin. In both patients cyanocobalamin levels were high after several days' continuous infusion; surprisingly in case 19 the level rose most markedly after parenteral hydroxocobalamin.

Discussion

Nitroprusside has been shown to liberate cyanide when incubated with liver (Hill, 1942), blood, washed erythrocytes, plasma, and urine (Page *et al.*, 1955; Vesey and Wilson, 1974) in vitro. Hydrogen cyanide has also been detected in cases of nitroprusside poisoning (*Pharmaceutical Journal*, 1936, 1948; Lazarus-Barlow and Norman, 1941; Hill, 1942). Our study, using more sensitive techniques for cyanide determination than hitherto employed, showed that cyanide was liberated in vivo from therapeutic doses of nitroprusside. The onset of hypotension is very quick and is not thought to be related to the liberation of cyanide (Johnson, 1929; Page *et al.*, 1955), which occurs slowly in vitro (Vesey and Wilson, 1974). Nevertheless, the plasma cyanide may reach relatively high levels in patients receiving the drug for only an hour. These levels in a number of cases exceed the levels reported for patients with tropical neuropathy due to chronic exposure to ingested cyanide from cassava (Osuntokun, *et al.*, 1970). The preliminary study in one patient (case 19) showed that a large amount of the liberated cyanide was in the separated and washed erythrocytes. Indeed, it can be shown that all the cyanide added to a sample of blood in vitro will pass rapidly into the erythrocytes (Vesey and Wilson, 1974). This may well affect oxygen transport because of the inhibitory action of cyanide on carbonic anhydrase (Horejsi and Komarkova, 1960) in addition to the known effect of cyanide (Schubert and Brill, 1968), and hence nitroprusside (Sekul *et al.* 1954), on cellular respiration.

Cyanide is converted to thiocyanate by the enzyme rhodanese (Lang, 1933). Thiosulphate, which acts as the sulphur donor for this enzyme, is derived from cysteine by way of β-mercaptopyruvate. The liver and kidneys contain large

amounts of the enzyme rhodanese and it was surprising that during nitroprusside infusion plasma thiocyanate levels rose so slowly. A further enzyme, β -mercaptopyruvate sulphur transferase, is also active in converting cyanide to thiocyanate (Fiedler and Wood, 1956). This enzyme occurs in the erythrocytes but in man the red cell activity is low and the availability of β -mercaptopyruvate is probably a further factor (Sorbo, 1957; Kun and Fanshier, 1959). This fact together with the accumulation of cyanide in the erythrocytes may explain the slow rise in plasma thiocyanate. In both animals (Mushett *et al.*, 1952; Friedberg *et al.*, 1965) and man (Lutier *et al.*, 1971) hydroxocobalamin has been shown to be a potent antidote to cyanide. Probably much of the cyanocobalamin so formed is excreted (Smith, 1968) but evidently a proportion of the cyano radical is incorporated into the 1-C metabolic pool (Boxer and Richards, 1952). In practice, therefore, it may be wise to give large doses of hydroxocobalamin intravenously before and during the infusion of sodium nitroprusside. The fall in total plasma cobalamins after nitroprusside therapy is noteworthy since it has been shown that there is an inverse relationship between plasma B_{12} and plasma cyanide levels (Wilson and Matthews, 1966). This fall may be a temporary event, however, since in one patient (case 19) a steady rise in total plasma B_{12} was apparent and could have been due to mobilization of stored B_{12} . The fall in plasma methylcobalamin after nitroprusside therapy indicated a possible effect on B_{12} distribution and metabolism. A reduction in plasma methylcobalamin levels also occurs in patients with vitamin B_{12} deficiency. In these cases the ratio methylcobalamin:adenosylcobalamin + hydroxocobalamin is also reduced (Linnell *et al.*, 1969 a; Linnell *et al.*, 1971) but in patients receiving nitroprusside therapy for a short period there was no significant decrease in the value. In one patient receiving prolonged infusion (case 19), however, there was a fall in this ratio.

Though in the present study plasma cyanocobalamin did not invariably rise after a short period of nitroprusside infusion it did rise to a high level in patients receiving the drug for longer periods. Individuals exposed to excess dietary cyanide or having a fault in cyanide metabolism have been found to have raised levels of cyanocobalamin (Linnell *et al.*, 1969 b; Osuntokun *et al.*, 1974). In two patients (cases 9 and 13; table III) there was an initially high level of plasma cyanocobalamin with raised plasma thiocyanate levels which suggested that they were smokers.

While nitroprusside is a valuable hypotensive agent without obvious toxic effects when used for a limited period cyanide is liberated in vivo and may have adverse biochemical effects, particularly on B_{12} metabolism. For this reason it may prove dangerous when given to patients who have low plasma B_{12} levels, who have impaired liver function, or who suffer from Leber's optic atrophy. We therefore recommend that hydroxocobalamin should be given to patients undergoing nitroprusside therapy. Further work is planned to try to assess the degree of risk to the patient to determine the mechanism of

nitroprusside breakdown and hypotensive action, and to develop a simple means of monitoring cyanide levels in patients receiving nitroprusside.

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References

- Aldridge, W. N. (1945). *The Analyst*, **70**, 474.
 Boxer, G. E., and Rickards, J. C. (1950). *Archives of Biochemistry*, **30**, 372.
 Boxer, G. E., and Rickards, J. C. (1952). *Archives of Biochemistry*, **39**, 7.
 Fiedler, H., and Wood, J. L. (1956). *Journal of Biological Chemistry*, **222**, 387.
 Friedberg, K. D., Grutzmacher, J., and Leudle, L. (1965). *Archives Internationales de Pharmacodynamie et de Thérapie*, **154**, 327.
 Hill, H. E. (1942). *Australian Chemical Institute Journal and Proceedings*, **9**, 89.
 Horejsi, J., and Komarkova, A. (1960). *Clinica Chimica Acta*, **5**, 392.
 Johnson, C. C. (1929). *Archives Internationales de Pharmacodynamie et de Thérapie*, **35**, 480.
 Jones, G. O. M., and Cole, P. (1968). *British Journal of Anaesthesia*, **40**, 804.
 Kun, E., and Fanshier, D. W. (1959). *Biochimica Biophysica Acta*, **32**, 338.
 Lang, K. (1933). *Biochemische Zeitschrift*, **259**, 243.
 Lazarus-Barlow, P., and Norman, G. M. (1941). *British Medical Journal*, **11**, 407.
 Linnell, J. C., Mackenzie, H. M., Wilson, J., and Matthews, D. M. (1969 a). *Journal of Clinical Pathology*, **22**, 545.
 Linnell, J. C., Wilson, J., and Matthews, D. M. (1969 b). *Clinical Science*, **37**, 878.
 Linnell, J. C., Hoffbrand, A. V., Peters, T. J., and Matthews, D. M. (1971). *Clinical Science*, **40**, 1.
 Lutier, F., Dusoleil, P., and de Montgros, J. (1971). *Archives des Maladies Professionnelles, de Médecine du Travail et de Sécurité Sociale*, **32**, 683.
 Mani, M. K. (1971). *British Medical Journal*, **3**, 407.
 Matthews, D. M., Gunasegaram, R., and Linnell, J. C. (1967). *Journal of Clinical Pathology*, **20**, 683.
 Mushett, C. W., Kelly, K. L., Boxer, G. E., and Rickards, J. C. (1952). *Experimental Biology and Medicine*, **81**, 234.
 Nourok, D. S., Glasscock, R. J., Solomon, D. H., and Maxwell, M. H. (1964). *American Journal of Medical Science*, **248**, 129.
 Osuntokun, B. O., Adeyua, A. O. G., and Aladetoyinbo, A. (1970). *Lancet*, **2**, 372.
 Osuntokun, B. O. (1972). *Plant Foods for Human Nutrition*, **2**, 215.
 Osuntokun, B. O., Matthews, D. M., Hussein, H. A. A., Wise, I. J., and Linnell, J. C. (1974). *Clinical Science*. In press.
 Page, I. H., Corcoran, A. C., Dustan, H. P., and Koppanyi, T. (1955). *Circulation*, **11**, 188.
Pharmaceutical Journal, (1936) **82**, 125.
Pharmaceutical Journal, (1948) **160**, 287.
 Schubert, J., and Brill, W. A. (1968). *Journal of Pharmacology and Experimental Therapeutics*, **162**, 352.
 Sekul, A. A., Booth, W. H., and Rice, J. C. (1954). *Federation Proceedings*, **13**, 403.
 Siegel, P., Moraca, P. P., and Green, J. R. (1971). *British Journal of Anaesthesia*, **43**, 790.
 Smith, E. L. (1968). *Plant Foods for Human Nutrition*, **1**, 7.
 Sorbo, B. (1957). *Biochimica Biophysica Acta*, **24**, 324.
 Taylor, T. H., Styles, M., and Lamming, A. J. (1970). *British Journal of Anaesthesia*, **42**, 859.
 Vesey, C. J., and Wilson, J. (1974). In preparation.
 Wilson, J., and Matthews, D. M. (1966). *Clinical Science*, **31**, 1.
 Wilson, J., Vesey, C. J., and Cole, P. V. (1971). *British Medical Journal*, **4**, 116.