BLOOD CYANIDE AND THIOCYANATE CONCENTRATIONS PRODUCED BY LONG-TERM THERAPY WITH SODIUM NITROPRUSSIDE

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Sodium nitroprusside (SNP) is used widely in the long-term management of a variety of cardiovascular emergencies (Zietsche and Franciosa, 1977; Cohn and Burke, 1979). Its evanescent action, attributable in part to rapid breakdown in the blood stream (Kreye, 1980), is a major advantage, allowing a fine control of its therapeutic action. As a result, however, there are two potential problems during long-term infusion. First, the patient is exposed, for a prolonged period, to increased, but non-lethal concentrations of cyanide (HCN). Second, thiocyanate (SCN), a product of HCN detoxication, accumulates in the extracellular fluid and can itself produce toxic effects in high concentration (Wald, Lindberg and Barker, 1939; Russell and Stahl, 1942).

During deliberate hypotension, blood HCN concentrations are the major concern. These have been shown to be related to the total dose of SNP and various figures for safe limits have been published (Davies et al., 1975; Editorial, 1975; Vesey, Cole and Simpson, 1976; Aitken et al., 1977; Michenfelder, 1977). However, different criteria will apply to the long-term administration of SNP, because of both the inevitably prolonged exposure to HCN, and the potential for SCN toxicity. To date, few dose limits have been recommended (Mitenfelder and Tinker, 1977; Schulz, Dohring and Rathsack, 1978). We have measured plasma and RBC HCN or plasma SCN concentrations or both, in 30 patients who were receiving prolonged therapy with SNP for various cardiovascular problems, so as to make tentative suggestions for safe maxima for rate of administration and total dose of the drug.

PATIENTS AND METHODS

Blood samples were obtained during or near the end of infusion, or at both times, from a series of 30 patients (aged 11 months–72 yr) undergoing long-term therapy with SNP for periods of 12–314 h. The blood was taken into heparinized syringes and transported in ice and water to the laboratory for immediate separation, and determination of HCN concentration. Plasma for SCN measurement was stored at −20 °C and analysed later. In three of the patients, more detailed studies were undertaken by taking multiple samples. Cyanide data from six
patients were rejected subsequently: four, because the dose rate either was not recorded at the time of sampling, or had been altered shortly before the blood was taken, and in the other two because hydroxycobalamin and isosorbide dinitrate had been administered, and it was considered that these could have altered HCN disposition in the blood. In addition, SCN values from two patients were rejected because of acute renal failure, and a third patient’s plasma sample was lost.

As previously described (Vesey, Cole and Simpson, 1976; Vesey and Wilson, 1978), HCN was isolated from 5-10 ml of both plasma and saline-washed, packed red cells, by acidifying with three volumes of 10% trichloroacetic acid (TCA) and transferring the HCN into a small volume of sodium hydroxide 0.2 mol litre$^{-1}$ by means of a stream of scrubbed nitrogen (Boxer and Rickards, 1951). SCN was determined in protein-free extracts of plasma (0.5 ml + 4.5 ml of 5% TCA in duplicate and centrifuged for 20 min at 2500 rev min$^{-1}$. Measurement of the isolated HCN and of the extracted SCN was made by means of an autoanalytical technique (Vesey and Kirk, 1985).

RESULTS

The results for the three individual patients studied in detail are shown in figures 1, 2 and 3. In the first patient both plasma HCN (ranging from 0.08 to 0.26 µmol litre$^{-1}$) and red cell HCN (2.10-6.14 µmol litre$^{-1}$) concentrations varied with the rate of infusion (0.49-1.99; mean SNP 0.94 µg kg$^{-1}$ min$^{-1}$). Plasma HCN concentration showed a significant correlation with dose rate at the 5% level. In contrast, plasma SCN increased continuously from a value of 48 µmol litre$^{-1}$, at the beginning of infusion, to 500 µmol litre$^{-1}$ after a total dose of SNP 1010 mg (17.7 mg kg$^{-1}$) had been infused over 13 days, and was significantly correlated with the cumulative

![Fig. 1. Variations in plasma and red cell cyanide (HCN) concentration with dose rate of nitroprusside (SNP), and increases in plasma thiocyanate (SCN) concentration with increasing SNP dose in a 50-year-old female patient with myocardial infarction and ischaemic VSD. To place these HCN and SCN values in perspective, mean values ± SD (Wilson and Matthews, 1966; Vesey and Wilson, 1978) for healthy smokers and non-smokers are shown on the right of the figure. (The apparent anomaly that smokers have a lower RBC HCN concentration than non-smokers may result from the fact that only a small sample of subjects have so far been studied (Vesey and Wilson, 1978) and that blood samples were not taken immediately after smoking, so that induced cyanide metabolism has produced lower values.) Correlations: Plasma HCN v. SNP dose rate: $r = 0.58, n = 11, P = 0.05; y = 0.084x + 0.0739$. RBC HCN v. SNP dose rate: $r = 0.48, n = 10, P = 0.05; y = 1.72x + 2.73$. SCN v. total SNP dose: $r = 0.96, n = 11, P < 0.001; y = 23.7x + 81.2.$

![Fig. 2. Changes in dose rate, RBC and plasma cyanide (HCN) concentrations, and plasma thiocyanate (SCN) concentration in a 51-year-old male patient with a dissecting aortic aneurysm. Correlations: Plasma HCN v. SNP dose rate: $r = 0.85, n = 10, P < 0.01; y = 0.266x - 0.188$. RBC HCN v. dose rate: $r = 0.92, n = 10, P < 0.01; y = 16.9x - 16.6$. Plasma SCN v. SNP dose: (a) first period of infusion $r = 0.97, n = 4, P < 0.05; y = 14.4x + 295$. (b) second period of infusion $r = 0.998, n = 6, P < 0.001; y = 25.4x + 384$. This patient was a smoker (20 cigarettes per day) and, therefore, would have started with an increased plasma SCN concentration (Vesey, 1981)—as shown by the regression equation. ▲ = Calculated SCN value.
dose of SNP (fig. 1). A further blood sample, taken 18 h after the end of the infusion, demonstrated the absence of HCN in the plasma. The red cell concentration (HCN 0.64 μmol litre\(^{-1}\)) had decreased to well within the normal range (Vesey and Wilson, 1978), and plasma SCN concentration had decreased to 416 μmol litre\(^{-1}\).

A similar pattern was seen in the second patient (fig. 2), whose clinical management has been reported previously (Hillman and Krapez, 1978). Again, HCN concentrations varied with the rate of SNP infusion, but because of the higher dose rates (SNP 1.14–3.79, mean 2.31; and 0.62–2.61, mean 1.79 μg kg\(^{-1}\) min\(^{-1}\), in the two periods of infusion) the maximum concentrations of HCN were higher than in the previous patient (0.76 and 0.88 μmol litre\(^{-1}\) in plasma; 57.3 and 22.9 μmol litre\(^{-1}\) in RBC). Plasma and red cell HCN concentrations correlated significantly with dose rate. Apart from the 48-h period when oral hypotensive agents were used, plasma SCN concentration increased uniformly with the increasing dose of SNP and correlated significantly with the dose of SNP. Apart from the 48-h period when oral hypotensive agents were used, plasma SCN concentration increased uniformly with the increasing dose of SNP and correlated significantly with the dose of SNP. This patient was a smoker (20 cigarettes a day) and had, initially, an increased plasma SCN concentration (Vesey, 1981). This increased to SCN 510 μmol litre\(^{-1}\) at the end of the first infusion (after a total of SNP 15.4 mg kg\(^{-1}\)) and, following the second infusion (SNP 19.98 mg kg\(^{-1}\)), increased to a final value of SCN 880 μmol litre\(^{-1}\).

The third patient (fig. 3) received SNP 28.2 mg kg\(^{-1}\). Plasma SCN concentration increased from a pre-infusion value of 79 μmol litre\(^{-1}\) to a final measured value of 850 μmol litre\(^{-1}\) towards the end of the infusion, and showed a significant correlation with the dose of SNP. Since both the rate of infusion and the increase in plasma SCN were uniform it can be calculated that the concentration had increased to about SCN 910 μmol litre\(^{-1}\) when the infusion was finally stopped at a total dose of SNP 30.5 mg kg\(^{-1}\). Fourteen days later it had decreased to SCN 90 μmol litre\(^{-1}\) plasma. Although the infusion rate was maintained constant at SNP 4.3 μg kg\(^{-1}\) min\(^{-1}\), RBC and plasma HCN concentrations in the second blood sample (12.5 and 0.21 μmol litre\(^{-1}\), respectively) were considerably lower than in the first or last samples taken during infusion (HCN 80.3 and 0.56 μmol litre\(^{-1}\), respectively). This could be a result of the fact that the second blood sample was taken during the administration of plasma protein fraction (PPF), a volume of PPF 250 ml having been infused up to this point. This is receiving further study.

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**Fig. 3.** Plasma and red cell cyanide (HCN) and plasma thiocyanate (SCN) concentrations, and dose rate in a 51-year-old female patient treated for ergotamine poisoning. Correlation: Plasma SCN vs. SNP dose: \(r = 0.99, n = 4, P = 0.01; y = 26.6x + 65\). Also shown are HCN concentrations 6 days after the end of infusion and plasma SCN concentrations before the start of the infusion, and 6 and 14 days after the infusion ended. ▲ = Calculated plasma SCN value.

**Fig. 4.** Plasma cyanide (HCN) concentrations obtained from 24 of the patients, plotted against the nitroprusside (SNP) infusion rates. Correlation: \(r = 0.64, n = 51, P < 0.001; y = 0.267x - 0.0733\). The diagram also indicates that a critical value of HCN 1 μmol litre\(^{-1}\) in plasma corresponds to an infusion rate of SNP 4 μg kg\(^{-1}\) min\(^{-1}\).
FIG. 5. Red cell cyanide (HCN) concentrations recorded in the same patients as in figure 4, plotted against infusion rate of sodium nitroprusside (SNP). 
Correlation: \( r = 0.71, \, n = 50, \, P < 0.001; \, y = 20.6x - 17.9 \). Red cell HCN v. plasma HCN: 
\( r = 0.92, \, n = 50, \, P < 0.001. \)

FIG. 6. Plasma thiocyanate (SCN) concentrations, recorded in 27 patients, plotted against sodium nitroprusside (SNP) dose. 
Correlation: \( r = 0.95, \, n = 51, \, P < 0.001; \, y = 24.6x + 74.9 \). Assuming the linear relationship between plasma thiocyanate and nitroprusside dose holds at higher values, extrapolation suggests that a critical value of SCN 1725 μmol litre\(^{-1}\) in plasma corresponds to an infused dose of SNP 70 mg kg\(^{-1}\).

DISCUSSION

Blood cyanide concentration and dose rate of nitroprusside

Changes in HCN concentrations in two of the individual patients studied in detail (figs 1, 2) show an obvious relation to the variations in SNP infusion rates. This is confirmed by the significant correlations between both plasma and RBC HCN concentrations and SNP dose rate for all patients (figs 4 and 5). The results further show (figs 1 and 4) that plasma HCN concentration may increase above normal values when infusion rates are greater than SNP 1 μg kg\(^{-1}\) min\(^{-1}\). Since the supply of thiosulphate is the limiting factor determining the rate of HCN detoxication (Sorbo, 1975), differences in HCN concentrations between patients with similar SNP doses rates may be the result of individual differences in this supply. Indeed, physiologically increased concentrations of thiosulphate lead to an increased rate of HCN detoxication (Tinker and Michenfelder, 1980; Braverman, Ivanovich and Shah, 1982). When SNP is infused rapidly, HCN may be liberated faster than it can be detoxicated by the tissues because of the limited availability of thiosulphate. As a result, blood concentrations of HCN will increase above normal, and will tend to lag behind any subsequent reduction in infusion rate. These two factors, individual differences in thiosulphate supply and the effect of prior infusion rates, may explain the wide scatter in plasma and RBC concentrations from 27 patients are related to the cumulative doses of SNP in figure 6. Plasma HCN concentrations (fig. 4) showed a significant correlation with the rates of infusion (\( r = 0.64, \, n = 51, \, P < 0.001 \)). RBC concentrations of HCN (fig. 5) showed a similar correlation with dose rate (\( r = 0.71, \, n = 50, \, P < 0.001 \)), and a close correlation with the plasma HCN concentrations (\( r = 0.92, \, n = 50, \, P < 0.001 \)). The distribution of the few HCN concentrations at high infusion rates suggests that there could be an exponential relationship to dose rate, but logarithmic transformation did not improve the correlation for plasma HCN concentration (\( r = 0.61 \)) although it did for RBC HCN concentration (\( r = 0.82 \)). Neither RBC HCN or plasma HCN concentrations showed any relation to total dose of SNP; there was, however, a highly significant correlation between plasma SCN concentration and the total amount of SNP infused (fig. 6) (\( r = 0.95, \, n = 51, \, P < 0.001 \)).
HCN concentrations, and the relatively low correlations with recorded SNP infusion rates in this study.

In order to limit the increase in plasma HCN concentrations to less than 3 μmol litre\(^{-1}\) (that is, one-third of the calculated minimum lethal plasma concentration) a maximum dose of SNP 1.5 mg kg\(^{-1}\) was recommended for hypotensive anaesthesia (a dose rate of 8.3–25 μg kg\(^{-1}\) min\(^{-1}\)) for infusions of between 1 and 3 h (Vesey, Cole and Simpson, 1976). Whilst this has gained support from the findings of other workers (Michenfelder, 1977); some have suggested higher (SNP 3–3.5 mg kg\(^{-1}\) (Davies et al., 1975; Editorial, 1975)) and some lower (0.5 mg kg\(^{-1}\) (Aitken et al., 1977)) maximum doses. However, it is certain that a lower safe maximum dose rate is necessary for long-term infusions. Chronic exposure to HCN is likely to exhaust detoxication mechanisms, particularly in sick patients, and cyanide concentrations which may be tolerated in the short-term, may prove toxic over longer periods. In fact Lawrence (1947) showed that, in anaesthetized dogs, the longer the time of sodium cyanide infusion, the lower was the lethal dose rate.

There is very little published information to guide us in deciding what is a safe plasma HCN concentration when maintained for several days or weeks. For example, smokers continuously expose themselves to relatively large amounts of HCN, but their plasma concentrations are only slightly greater than those of non-smokers (Wilson and Matthews, 1966) (fig. 1). One cigarette yields up to 0.5 mg of HCN and 1.0 mg of nitriles (which release HCN in vivo) (Vesey, 1981). Thus, an inhaling smoker consuming 50 cigarettes a day would absorb at least HCN 25 mg. As a bolus, HCN 25 mg would be lethal. Over a 12-h period this would be equivalent to an average HCN intake of 34.7 μg min\(^{-1}\), or 0.50 μg kg\(^{-1}\) min\(^{-1}\) in a 70-kg man. Since SNP contains 45% HCN by weight, this would be equal to an infusion of SNP about 1.0 μg kg\(^{-1}\) min\(^{-1}\) (also see Addendum). It would appear, therefore, that the body is able to tolerate this level of HCN exposure (except in some acquired or inherited toxic ambiolyrias (Wilson, 1965; Foulds, Bronte-Stewart and Chisholm, 1968)). Indeed, figure 4 shows that at infusion rates of SNP up to 1 μg kg\(^{-1}\) min\(^{-1}\) there was only one recorded plasma HCN concentration above the normal range (Wilson and Matthews, 1966).

In contrast to the near normal HCN concentrations in smokers, Osuntokun (1973) reported significantly increased mean plasma HCN concentra-

**Thiocyanate accumulation related to SNP dose**

Since SCN is excreted by the kidneys at a relatively slow rate, because some 90% of that filtered by the glomeruli is reabsorbed (Pullman and McClure,
plasma concentrations of the anion increase linearly throughout SNP administration, as illustrated by the measurements made in patients 1–3 (figs 1–3). Both in these three patients, and with the data obtained from the 27 patients, there was a close correlation between plasma SCN concentration and the cumulative dose of SNP. The slow rate of SCN excretion is further illustrated by the fact that the increase in plasma SCN concentration in patient 3 did not return to the pre-infusion value for 14 days. If there is a break in infusion, therefore, it cannot be assumed that plasma SCN will have decreased to a normal value. This was demonstrated in patient 2, in whom, after a gap of 48 h, the second period of infusion commenced with a calculated increase in plasma SCN concentration of 350 μmol litre⁻¹. Similarly, as this patient also demonstrates, smokers may already have a high plasma SCN concentration before infusion, and this should be taken into account.

Although SCN is generally considered to be non-toxic, it was shown early to have a weak hypotensive action (Pauli, 1903; Barker, 1936) and, until the late 1950s, patients with refractory hypertension were prescribed large doses of sodium or potassium thiocyanate to be taken by mouth over long periods, sometimes for many years. Toxic effects, such as anaemia, psychosis, coma and death, occurred at plasma SCN concentrations greater than 20 mg dl⁻¹ or 3450 μmol litre⁻¹ (Garvin, 1939; Barker, Lindberg and Wald, 1941; Barnett, Jackson and Spaulding, 1951; Frohman and Klocke, 1963). Barker (1936), therefore, introduced the monitoring of plasma SCN concentrations during thiocyanate therapy and suggested that concentrations between 6 and 10 mg dl⁻¹ (1035–1725 μmol litre⁻¹) decrease arterial pressure, while significant toxicity arose in such patients infused at rates of up to SNP 1000 mg day⁻¹. The much longer half-life of plasma SCN in patients with renal failure receiving SNP (9 days compared with 3 days in healthy subjects given SCN (Schulz, Bonn and Kindler, 1979)) makes monitoring of SCN concentrations mandatory in such patients. However, if these patients undergo dialysis then plasma SCN concentration will be decreased rapidly (Danzig and Kringle, 1955; Christensen and Williams, 1962).

In conclusion, therefore, it is suggested that the maximum safe sustained dose rate for long-term SNP infusions is less than 8 μg kg⁻¹ min⁻¹ (11.5 mg kg⁻¹ day⁻¹), and near to 4 μg kg⁻¹ min⁻¹ (5.8 mg kg⁻¹ day⁻¹). In addition we suggest that the maximum total dose of SNP is in the region of 70 mg kg⁻¹ for periods of less than 14 days in patients with adequate renal function. In the presence of renal insufficiency the concentration of SCN should be monitored. The administration of hydroxycoberalin will aid in HCN detoxication and counteract any effect of SCN on haematopoiesis (Frohman and Klocke, 1963), but the continuous infusion of thiosulphate is not a suitable HCN antagonist during long-term SNP infusions, since it will increase the rate of SCN accumulation and produce hypovolaemia (Michenfelder and Tinker, 1977).

ADDENDUM

The calculation can be made in another way. The HCN concentration in cigarette smoke is variously quoted as 37.7–44.6 μg per 35-ml puff (Brummemann, Yu and Hoffmann, 1977), 28–39 μg per 35-ml puff (Collins, Sarji and Williams, 1970), and 400 p.p.m. or 0.48 μg ml⁻¹ (Darby and Wilson, 1967; Rickert, Robinson and Young, 1980). The total volume of smoke inhaled per cigarette is approximately 570 ml (Russell et al., 1982) and, therefore, for a smoker of 50 cigarettes per day (yielding say, HCN 0.88 μg ml⁻¹; that is, the mean of the highest and lowest yields of HCN quoted), the total HCN inhaled and—since HCN readily passes into the tissues—the amount absorbed = HCN 358 μg kg⁻¹ in a 70-kg smoker. Over 12 h this would be equivalent to a dose of HCN 0.50 μg kg⁻¹ min⁻¹. Since SNP
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REFERENCES


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