SOME PHYSIOLOGICAL AND METABOLIC EFFECTS OF SODIUM NITROPRUSSIDE AND CYANIDE IN THE DOG

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SUMMARY

The cardiovascular and acid-base changes following equivalent i.v. bolus doses of sodium nitroprusside (SNP) and potassium cyanide (KCN) have been studied in two groups of anaesthetized dogs. In a third group, the metabolic changes produced by i.v. infusion of SNP 1.5 mg kg$^{-1}$ at a constant rate over 1 h have been studied. In contrast to a decrease in arterial pressure following SNP, hypertension and tachycardia occurred after the administration of KCN, with hyperventilation and an increase in packed cell volume. During infusion of SNP, increases in plasma cyanide concentrations were associated with an increase in arterial base deficit, plasma lactate and excess lactate and a decrease in oxygen consumption. The occurrence of lactic acidosis with SNP 1.5 mg kg$^{-1}$ suggests that this may be the maximum safe dose for short term infusion. However, all these changes reversed spontaneously following discontinuation of SNP, indicating that base deficit is an adequate metabolic monitor during administration of SNP.

The cardiovascular changes associated with i.v. sodium nitroprusside (SNP) have been well documented (Schlant, Tsagaris and Robertson, 1962; Ross and Cole, 1973; Wildsmith et al., 1973; Adams et al., 1974; Wang, Liu and Katz, 1977). Similarly, the effects of the drug on acid-base and blood-gas measurements have been studied in man (Wildsmith, Drummond and MacRae, 1975). Although the toxicity of nitroprusside has been ascribed to cyanide (Vesey and Cole, 1975), the contribution of this breakdown product to the hypotensive action of the drug has not been investigated. Indeed, there is some evidence that cyanide itself can produce various cardiovascular effects (Krasney, 1971; Barcroft, 1973; Liang and Huckabee, 1973) and increased cyanide concentrations resulting from abnormalities in its metabolism have been implicated as a possible cause of resistance to the hypotensive action of SNP (Davies et al., 1975a; Tremblay et al., 1977).

We have studied in dogs the cardiovascular effects of i.v. bolus injections of SNP and of an equivalent dose of potassium cyanide (KCN) and have recorded the changes produced in the blood-gas and acid-base state. Similarly, we have investigated the changes following i.v. infusion of SNP 1.5 mg kg$^{-1}$, our recommended maximum dose for man (Vesey, Cole and Simpson, 1975, 1976), at a constant rate over 1 h, to determine if this is free from evidence of cyanide toxicity (Simpson, 1978).

Since cyanide is associated with the development of histotoxic hypoxia, an attempt has been made to assess the adequacy of tissue oxygenation during nitroprusside infusion. The development of a progressive and irreversible metabolic acidosis has been recorded in several fatalities associated with i.v. SNP (Jack, 1974; Merrifield and Blundell, 1974; Davies et al., 1975b), and it is probable that the histotoxic effect of cyanide, producing an excess of lactate, is responsible for this acidosis. Measurements of plasma lactate and pyruvate have been carried out therefore, both during and after infusion of SNP and excess lactate has been derived subsequently from these results (using the formula of Huckabee (1958)). The simultaneous changes in oxygen consumption have been studied also, since this value would be expected to decrease during a hypoxic episode. The relationships of these variables to arterial base deficit have been examined to determine if measurement of the latter would provide a reliable indication of the development of SNP toxicity.

METHODS

The methods used have been described in detail elsewhere (Vesey et al., 1979). At the time intervals...
indicated, samples of mixed venous and arterial blood were obtained from the pulmonary and superficial femoral arteries. The samples were analysed immediately for pH, $P_{CO_2}$, $P_{O_2}$ (Instrumentation Laboratories 413 blood-gas analyser) and oxygen content (Lexington Instruments Lex-O$_2$-Con). Measurements of haemoglobin (cyanmethaemoglobin technique) and packed cell volume (microhaematocrit method) were made on all samples. Base excess or deficit was calculated from the values of pH and $P_{CO_2}$.

Plasma lactate and pyruvate estimations were carried out using commercially available enzymatic test combinations (Boehringer Corporation) and excess lactate was calculated from these results. Blood samples were withdrawn into precooled syringes, separated immediately at $0\, ^\circ C$ in a refrigerated centrifuge and an aliquot of the plasma added to perchloric acid $0.6$ mol litre$^{-1}$. The mixture was centrifuged, the supernatant stored at $4\, ^\circ C$ and the lactate determined within $24\, h$.

In all three groups of dogs, simultaneous recordings of arterial pressure and heart rate were accompanied by measurement of central venous pressure (CVP) (groups 1 and 2) or pulmonary artery pressure using a Swan–Ganz catheter (group 3). In groups 1 and 2, oxygen consumption was measured directly (Douglas bag technique) and cardiac output determined from the arterio-venous oxygen difference using the Fick principle. In group 3, cardiac output was measured by dye dilution using indocyanine green, and oxygen consumption was derived.

Measurements of oxygen consumption, cardiac output and plasma lactate were made in only three dogs in each of groups 1 and 2, but in all animals in group 3.

**RESULTS**

The mean concentrations of plasma and red cell cyanide and plasma thiocyanate, recorded in the three groups of dogs, have been discussed by Vesey and others (1979). Figure 1 shows arterial hypotension following administration of SNP both as a bolus dose (group 1) and as an infusion (group 3); potassium cyanide (KCN), on the other hand, resulted in a transient increase in arterial pressure. There was a sudden increase in CVP following the administration of KCN, but a minimal increase following SNP (fig. 2). This increase was associated with marked spontaneous hyperventilation (a normal response to KCN, since the dogs were not paralysed) and a corresponding reduction in the otherwise steady value of $P_{O_2}$ in group 3, pulmonary artery pressure decreased in parallel with systemic pressure, and these changes were sustained during the period of infusion of SNP. Bolus injections of both SNP and KCN produced changes in heart rate (fig. 3); infusion of SNP resulted in a smaller increase, which was maintained throughout the period of infusion. However comparisons between the groups are complicated by differences in baseline values. Slight increases in cardiac output occurred following administration of
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83

1200

150

| 100 |

.. KCN BOLUS DOSE

o o SNP BOLUS DOSE

• » SNP INFUSION

0 30 60 90 120 150 180 210 240

TIME (min)

Fig. 3. Mean heart rate in all three groups of dogs.

0.6

• • KCN BOLUS DOSE

o o SNP BOLUS DOSE

• » SNP INFUSION

0 30 60 90 120 150 180 210 240

TIME (min)

Fig. 4. Mean cardiac output in all three groups of dogs. In groups 1 and 2, measurement of cardiac output was made using the direct Fick principle, while in group 3, dye dilution with indocyanine green was used.

0 30 60 90 120 150 180 210 240

TIME (min)

Fig. 5. Mean values of arterial \( P_{\text{aO}_2} \) in all three groups.

SNP, both as a bolus dose and during infusion (fig. 4); in contrast, KCN produced a very large, but transient, increase in cardiac output although the validity of the Fick principle in such rapidly changing circumstances must be considered doubtful.

Although a significant increase in \( P_{\text{aO}_2} \) was observed following KCN (group 2) little change occurred following SNP (groups 1 and 3) (fig. 5). Although oxygen consumption was estimated in only three dogs from each of groups 1 and 2, those receiving potassium cyanide exhibited a decrease to approximately 50% of the initial value within 5 min of administration, followed by a rapid return to normal values. However, the results of oxygen consumption measurements in group 1 were inconclusive. The dogs in groups 1 and 2 showed an increase in plasma lactate, which returned subsequently to baseline values. The peak concentrations occurred later in the SNP group (20–40 min after administration) than in the KCN group (5–10 min). However, the dogs receiving SNP demonstrated only a 2–3-fold increase in lactate concentrations, in contrast to a 5–9-fold increase in the cyanide group. Pyruvate was not measured in group 1 or 2, precluding the calculation of excess lactate. The development of lactic acidosis in each of these two groups coincided, as might be expected, with an increase in arterial base deficit. The magnitude of the metabolic acidosis was related to the lactate concentrations observed; thus the KCN group developed a maximum base deficit of \( 7.3 \pm 1.65 \text{ mmol litre}^{-1} \) (mean ± SEM) and a peak increase in plasma lactate of \( 6.9 \pm 1.3 \text{ mmol litre}^{-1} \), compared with \( 2.5 \pm 0.75 \) and \( 1.95 \pm 0.49 \text{ mmol litre}^{-1} \) respectively in the SNP group.

A more comprehensive study of tissue oxygenation was carried out in the dogs in group 3. The relationship between plasma lactate and arterial base deficit, both during and after SNP infusion, is shown in figure 6 and regression analysis confirms a close correlation between these two variables (\( r = 0.95; P<0.001 \)). The two measurements most likely to indicate inadequate tissue oxygenation (excess lactate and oxygen consumption) are shown together in figure 7. A decrease in oxygen consumption was associated with an increase in excess lactate (\( P<0.01 \) for excess lactate and \( P<0.02 \) for oxygen consumption), both changes occurring during the infusion of SNP.

Both KCN and, to a lesser extent, SNP produced an increase in PCV (maximum increases above basal = \( 24.9 \pm 4.13\% \) and \( 9.1 \pm 1.7\% \), mean ± SEM, both 5 min after the bolus dose) although there was no statistically significant increase in the SNP group.

Discussion

The cardiovascular responses to SNP were similar to those reported previously (Adams et al., 1974). The hypotensive action of SNP was not associated with high concentrations of plasma cyanide, since the hypotension occurred more rapidly than the increase in plasma cyanide in groups 1 and 3.

The effect of SNP on cardiac output in dogs is not
as well defined as its hypotensive action. Ross and Cole (1973) demonstrated significant increases in cardiac output following infusion of SNP, whereas Adams and colleagues (1974) were unable to demonstrate any change under various anaesthetic conditions. More recently, both Wang, Liu and Katz (1977) and Michenfelder and Theye (1977) have shown that a significant decrease in cardiac output occurs following infusion of SNP. The results of the present study show that cardiac output increases following SNP, both as a bolus dose and as an infusion, although these changes are not statistically significant.

However, the dogs in group 3 appear to be in two distinct categories: in five, cardiac output was increased, while in the remainder it was decreased slightly or unchanged. Similarly, McDowall and his colleagues (1974) grouped their baboons depending upon the response to SNP. These results may be dependent upon individual variation and may, in part, explain the conflicting results of previous studies. Similar variations have been reported in studies in conscious man (Schlant, Tsagaris and Robertson, 1962; Franciosa et al., 1972). It is also possible that variation in cardiovascular response may result from the anaesthetic technique used; while Ross and Cole (1973) used urethane, other workers have used a variety of agents, including pentobarbitone, halothane and in particular nitrous oxide, which have cardiovascular effects of their own.

In those animals in which cardiac output increased it is noteworthy that this occurred after 45-60 min of infusion of SNP, suggesting that haemodynamic values do not stabilize as early as 2 min after commencement of infusion as stated previously (Adams et al., 1974). The very large, although transient, changes in cardiac output following injection of KCN confirm the findings of Liang and Huckabee (1973) and one may speculate that increases following administration of SNP may be mediated by cyanide, particularly since the increase in cardiac output after 45 min coincided with the maximum plasma HCN concentration. The well-documented increase in heart rate in response to SNP is evident from this study, but although cyanide itself produced a marked tachycardia this may not explain the effect of nitro-
prusside since changes occurred very rapidly. A decrease in stroke volume in all the dogs receiving SNP confirmed the findings of Adams and his colleagues (1974) and contrasted with the increase associated with the administration of cyanide.

The large increase in central venous pressure in the dogs receiving KCN was undoubtedly a result of the marked spontaneous hyperventilation and straining against the ventilator observed in these animals, a response to cyanide which is well documented (Krasney, 1971; Levine, 1975). This also explains the increase in $P_{aO_2}$ and the reduction in $P_{aCO_2}$ recorded in this group. The failure to demonstrate a significant reduction in $P_{aO_2}$ in either of the two groups of dogs receiving SNP is surprising in view of the findings of other workers, but this may be because the dog was lying in the lateral position during the study. Wildsmith, Drummond and MacRae (1975) noted a significant decrease in $P_{aO_2}$ in man and recommended an increase in inspired oxygen during the period of hypotension, and Adams and colleagues (1974) reported similar small decreases in dogs.

The large packed cell volumes in groups 1 and 2 were associated with large concentrations of plasma cyanide and may be a response to this. Increases in haematocrit or haemoglobin concentration as a result of hypoxia from rebreathing (Kramer and Luft, 1951) or infusion of cyanide (Liang and Huckabee, 1973) in the dog have been shown to result from release of splenic stores of red blood cells.

It would appear from the reported fatalities (Jack, 1974; Merrifield and Blundell, 1974; Davies et al., 1975b) that the toxicity of SNP is essentially a result of progressive and ultimately irreversible metabolic acidosis indistinguishable clinically from cyanide poisoning. We have stated elsewhere that 1.5 mg kg$^{-1}$ should be the maximum dose of sodium nitroprusside which may be administered over a short period (Vesey, Cole and Simpson, 1975, 1976). This dose, administered at a constant rate over 1 h to the dogs in group 3, produced increases in plasma lactate, which were associated with a maximum increase in arterial base deficit of 3.75 mmol litre$^{-1}$.

It is uncertain if the lactic acidosis was caused by hypotension or the production of cyanide since, in all the dogs studied, changes in lactate, base deficit and oxygen consumption returned to normal spontaneously following discontinuation of SNP. However, the mean changes in plasma lactate followed closely those of the mean plasma HCN, although examination of the individual lactate and plasma HCN values suggests a wide variation in individual response to increased cyanide concentrations. The peak increase in lactate concentrations of $2.38 \pm 0.34$ mmol litre$^{-1}$ (mean $\pm$ SEM) occurred at peak increase in the plasma HCN concentrations of $1.36 \pm 0.18$ $\mu$mol litre$^{-1}$ after 45–60 min infusion with SNP. The development of a significant excess lactate value during the period of infusion confirms that the base deficit and increased lactate concentration may result from some impairment of tissue oxygenation, and indeed a reduction in total body oxygen consumption was associated with these findings. Since the dog appears to metabolize HCN more rapidly than does man, the development of lactic acidosis suggests that SNP 1.5 mg kg$^{-1}$ for infusions of 1 h duration may be approaching the upper safe limit for man. Larger and more significant reversible changes in lactate and oxygen consumption occurred in the dogs receiving equivalent bolus doses of KCN and SNP.

The highly significant correlation between blood lactate and arterial base deficit, which occurred both during and after infusion of SNP ($r = 0.95, P < 0.001$), indicates that the simple and accessible measurement of changes in acid–base balance gives adequate clinical warning of the development of a metabolic acidosis associated with administration of SNP.

Aitken and others (1977) suggest that, in man, increasing lactic acidosis is associated with blood HCN concentrations greater than 20 $\mu$mol litre$^{-1}$ (53 $\mu$g%). Base deficit was at a maximum 45–180 min after peak cyanide concentrations were reached in four patients who received the highest doses of SNP (0.11–0.26 $\mu$mol kg$^{-1}$; 0.34–0.78 mg kg$^{-1}$), a finding which these authors attribute to delayed toxic effects of the drug. However, this differs from our findings in the dogs where both lactate and base deficit changed in parallel with the plasma cyanide concentrations. In addition there was no delayed increase in these during the 3 h following infusion. After bolus doses of KCN and SNP the greatest mean lactate and base deficit occurred within 10 and 20 min respectively of the peak blood cyanide concentrations and showed no subsequent increase during the next 3 h. After 15 min infusion with SNP in our dogs a mean increase in lactate of 1.2 mmol litre$^{-1}$ was associated with a plasma cyanide concentration of 0.62 $\mu$mol litre$^{-1}$. Thus some lactate production in man may be associated with $blood$ cyanide concentrations as low as 20 $\mu$mol litre$^{-1}$ (53 $\mu$g%; Aitken et al., 1977) or $plasma$ concentrations of 0.3 $\mu$mol litre$^{-1}$ of HCN. However, this insignificant degree of acidosis would not appear to justify reducing the maximum dose of SNP to as little as 0.5 mg kg$^{-1}$.
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REFERENCES

Physiological and metabolic effects of SNP and cyanide

Von Sodium Nitroprussid (SNP) und Potassium Zyanid wurden in zwei Gruppen von anästhesierten Hunden untersucht. In einer dritten Gruppe wurden die metabolischen Veränderungen studiert, die durch eine einständige, unveränderte, intravenöse Infusion von SNP 1,5 mg kg⁻¹ herbeigeführt wurden. Im Gegensatz zu einer Verminderung des arteriellen Drucks nach SNP, traten Hypertonie und Tachykardie nach Verabreichung von KCN auf, mit Hyperventilation und einem angereicherten Erythrozytenvolumen. Während der SNP-Infusion wurden die verstärkten Plasmazyanidkonzentrationen mit einer Vergrößerung des arteriellen Basisdefizits, Plasmalaktats und übermässig viel Laktat, und einer Verringerung im Sauerstoffverbrauch in Verbindung gebracht. Das Auftreten von laktischer Hyperazidität mit SNP 1,5 mg kg⁻¹ scheint darauf hinzuweisen, dass dies die Maximumdosis für eine ungefährliche Kurzinfusion ist. Wie dem auch sei, alle Änderungen dieser Art kehrten nach einer Unterbrechung der Verabreichung von SNP spontan ins Gegenteil um, damit wurde bewiesen, dass das Basisdefizit während der Verabreichung von SNP ein ausreichender metabolischer Monitor ist.

Algúnos efectos fisiológicos y metabólicos de nitroprusiato sodico y cianuro en el perro

Se han estudiado los cambios cardiovasculares y de base ácida tras la administración de dosis en bolo intravenosas equivalentes de nitroprusiato sódico (SNP) y cianuro potásico (KCN) en dos grupos de perros anestesiados. En un tercer grupo, se estudiaron los cambios metabólicos producidos por la infusión intravenosa de SNP 1,5 mg kg⁻¹ a una rapidez constante durante 1 h. En contraste con una disminución en la presión arterial tras la administración de SNP, la administración de KCN produjo hipertensión y taquicardia, con hiperventilación y aumento en el volumen de células compactas. Durante la infusión de SNP, aumentaron las concentraciones de cianuro en la plasma, lo cual se asoció con un aumento en la deficiencia arterial de base, lactato en la plasma y un exceso de lactato, y una disminución en el consumo de oxígeno. La ocurrencia de acidosis láctica con SNP 1,5 mg kg⁻¹ sugiere que ésta posiblemente sea la dosis máxima segura para infusiones de corto plazo. Sin embargo, todos estos cambios fueron invertidos espontáneamente después de suspenderse la administración de SNP, indicando que la deficiencia de base sirve adecuadamente como monitor metabólico durante la administración de SNP.