Clinical Toxicology

The metabolic effects of fatal cyanide poisoning

B.M. Singh, N. Coles, P. Lewis, R.A. Braithwaite¹, M. Natrass and M.G. FitzGerald

The General Hospital, Steelhouse Lane, Birmingham B4 6NH and ¹Regional Laboratory for Toxicology, Dudley Road Hospital, Birmingham B18 7QH, UK.

Summary: Metabolic and toxicological data were obtained during the first 24 hours following severe and eventually fatal cyanide poisoning. Initial blood cyanide concentrations were 804 $\mu\text{mol/l}$ but fell rapidly over 24 hours following cobalt edetate therapy to 15 $\mu\text{mol/l}$. However, plasma thiocyanate concentrations rose over 24 hours (147–267 $\mu\text{mol/l}$) suggesting continued tissue detoxification. The major metabolic abnormality was lactic acidosis (initial pH 7.21, blood lactate 17.5 mmol/l) which corrected over 12 hours. Despite high circulating insulin concentrations the responses of blood glucose, plasma non-esterified fatty acid, blood glycerol and 3-hydroxybutyrate suggested marked insulin resistance.

Introduction

A case of fatal cyanide poisoning, previously reported,¹ is described in which detailed toxicological and metabolic data were obtained. These metabolic sequelae are discussed.

Case report

A previously well 24 year old man was admitted as an emergency. The patient had been working alone in the bottom of a silver plating tank removing several inches of residue of silver cyanide sludge without protective clothing or respirator or supervision and was found unconscious in the sludge by his workmates. An immediate antidote of amyl nitrite was not administered. The air in the tank was subsequently found to contain 200 parts per million of hydrogen cyanide.

On arrival in casualty his hair and clothes were matted with a black compound. He had chemical burns on exposed skin which had the characteristic brick red colour of cyanide poisoning. There was a strong odour of bitter almonds. He was apnoeic and his pulse was 120 beats per minute, faintly palpable but with no recordable blood pressure. His pupils were fixed and dilated and he was flaccid with no response to pain. He underwent immediate endotracheal

intubation and an intravenous infusion was established through which 300 mg cobalt edetate together with 50 ml of 50% dextrose was administered at 1 and 2 min after arrival. Subsequent to the second dose the patient began spontaneous breathing but lapsed into apnoea by 7 minutes when a third dose of antidote was administered with no effect upon respiration although facial oedema developed. Mechanical ventilation was initiated.

Blood investigations after the initial resuscitation period revealed a haemoglobin of 16.5 g/dl, a leucocytosis of 20.4×10^9 cells/l, sodium 145 mmol/l, potassium 4.7 mmol/l, urea 6.9 mmol/l, glucose 18.7 mmol/l and arterial blood pH 7.08, P_{O_2} 68.5 kPa, P_{CO_2} 4.5 kPa and HCO_3^- 10 mmol/l on 100% inspired oxygen. An electrocardiogram showed antero-lateral ischaemia.

His skin was washed. A naso-gastric tube was passed and gastric lavage performed. A flow directed catheter was inserted into the pulmonary artery to monitor colloid fluid replacement therapy. Despite adequate volume replacement he required inotropic support to maintain his systolic blood pressure at 100 mmHg. He was anuric for 4 hours but subsequently entered a gross polyuric phase lasting 24 hours. An insulin infusion of short-acting human insulin of 6 units/h and increased to 12 units/h at 12 hours was initiated. No further glucose was administered. Other investigations were performed during the first 24 hours of admission (Table I).

At 24 hours he was no longer acidotic and his blood pressure and urine output were stable but an electro-

Correspondence: B.M. Singh, M.D., M.R.C.P., Department of Diabetes and Endocrinology, 9th Floor, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK.

Accepted: 27 June 1989

Table 1 Toxicological and metabolic data obtained during the first 24 h following cyanide poisoning

	1/2	2	4	<i>Time from arrival (h)</i>			<i>Reference range*</i>
				12	18	24	
Blood cyanide $\mu\text{mol/l}$	804	819	608	23	15	15	(<2)
Plasma thiocyanate $\mu\text{mol/l}$	NA	147	172	345	281	267	(10–70)
Blood pH	7.21	7.23	7.27	7.33	7.40	7.41	(7.38–7.46)
Plasma insulin mU/l	36	17	46	54	120	56	(<1–4.1)
Blood glucose mmol/l	23.6	21.4	22.6	44.5	13.6	17.1	(3.9–5.0)
Blood lactate mmol/l	17.5	13.0	5.4	3.8	2.4	2.2	(0.5–1.1)
Blood pyruvate mmol/l	0.32	0.34	0.40	0.37	0.18	0.15	(0.04–0.11)
Blood L/P ratio	55	38	14	10	13	15	(5.9–14.0)
Blood alanine mmol/l	0.64	0.57	0.47	0.52	0.34	0.24	(0.18–0.37)
Blood glycerol mmol/l	0.51	0.44	0.06	0.06	0.04	0.03	(0.05–0.09)
Plasma NEFA mmol/l	0.65	0.61	0.73	0.56	0.44	0.35	(0.43–1.00)
NEFA/glycerol ratio	1.3	1.4	12.2	9.3	11.0	11.7	(6.1–18.6)
Blood OHB mmol/l	0.11	0.09	0.05	0.03	0.04	0.03	(0.03–0.09)

Reference ranges for blood cyanide and thiocyanate concentrations were supplied by the Regional Laboratory for Toxicology, Dudley Road Hospital, Birmingham. Fasting hormone and metabolite reference values were obtained in 8 men (mean $\pm$ s.d.), age 22 ± 2 years.

OHB = 3-hydroxybutyrate; NA = not available, *non smokers; NEFA = non-esterified fatty acid. L/P = lactate pyruvate.

encephalogram failed to show any cerebral activity. Three days after his admission formal brain death testing was undertaken. This failed to show any brain stem activity and ventilation was discontinued after both kidneys had been donated for transplantation.¹

Discussion

The metabolic sequelae of cyanide poisoning are poorly documented in humans although lactic acidosis is recognized.² The marked acidosis in our case was due to excess lactate produced by anaerobic metabolism of glucose. With the paralysis of mitochondrial respiration, glycolysis is enhanced by the Pasteur effect in which allosteric ATP and citrate inhibition of phosphofructokinase is lost³ and re-oxidation of cytoplasmic NADH formed by triose oxidation occurs in the conversion of pyruvate to lactate.

Altered hepatic lactate metabolism as well as increased lactate production by other tissues contributes to lactate accumulation.⁴ It is well recognized that hepatic lactate and pyruvate uptake are diminished in acidosis by an effect upon their transport which is pH-dependent.⁵ Increased hepatic intracellular H^+ concentration also results in conversion of pyruvate to lactate by lactate dehydrogenase.⁶ Acidosis further impairs gluconeogenesis at the step between pyruvate and oxaloacetate⁵ and cyanide poisoning would also inhibit this reaction by decreasing intramitochondrial

ATP concentrations. The liver thus becomes a net lactate producer.⁶ Impairment of gluconeogenesis in our case is supported by elevated concentrations of the other gluconeogenic precursors alanine and glycerol.

Despite the severity of cyanide poisoning, near-normal initial non-esterified fatty acid (NEFA) concentrations might suggest that NEFA utilization proceeded and the high normal initial concentrations of 3-hydroxybutyrate (OHB) could indicate that NEFA activation to fatty acyl-CoA and intramitochondrial NEFA β -oxidation continued. However, OHB concentrations also depend upon peripheral utilization and this may have been impaired by lack of mitochondrial NAD^+ .⁷

During the first 24 hours NEFA and glycerol concentrations did show suppression and their ratios returned to normal, suggesting a normal lipolytic rate, but only at insulin concentrations indicative of gross insulin resistance.⁸ Similarly, OHB concentrations were resistant to suppression by insulin.⁸ Insulin infusion appeared to have little effect upon glucose metabolism.

In summary we report a case of fatal cyanide poisoning. The metabolic complications were lactic acidosis, a known association² but also a severe degree of insulin resistance in glucose, ketone and fatty acid metabolism. The correction of these metabolic abnormalities were refractory to the early detoxification of blood cyanide, intensive supportive therapy and insulin infusion. Extensive cellular damage occurred prior to onset of therapy highlighting the importance of preventative measures in occupational health.

References

1. Brown, P.W.G., Buckles, J.A.C., Jain, A.B. & McMaster, P. Successful cadaveric renal transplantation from a donor who died of cyanide poisoning. *Br Med J* 1987, **294**: 1325.
2. Graham, D.L., Laman, D., Theodore, J. & Robin, E. Acute cyanide poisoning complicated by lactic acidosis and pulmonary oedema. *Arch Int Med* 1977, **137**: 1051–1055.
3. Bloxham, D.P. & Lardy, H.A. Phosphofructokinase. In: Boyer, P.D. (ed.) *The Enzymes*, volume 8. Academic Press, New York, 1973, pp. 239–278.
4. Cohen, R.D. & Woods, H.F. Lactic acidosis revisited. *Diabetes* 1983, **32**: 181–191.
5. Schwab, A.J., Bracht, A. & Scholz, R. Transport of D-lactate in perfused rat liver. *Eur J Biochem* 1979, **102**: 537–547.
6. Fine, A., Brosnan, J.T. & Herzberg, G.R. Release of lactate by the liver in metabolic acidosis. *Metabolism* 1984, **33**: 393–396.
7. Sahlin, K. & Katz, A. The content of NADH in rat skeletal muscle at rest and after cyanide poisoning. *Biochem J* 1986, **239**: 245–248.
8. Hale, P.J., Wright, J.V. & Nattrass, M. Differences in insulin sensitivity between normal men and women. *Metabolism* 1985, **34**: 1133–1138.