Changes in Skeletal Muscle Oxygenation During Cyanide Toxicity

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Abstract

Background: Cyanide (CN) is highly toxic to animals and humans. [1] Although metabolic studies have been conducted during CN toxicity, none of the studies have addressed changes in tissue oxygenation (rSO_2). Thus, we evaluated changes in hamstring muscle rSO_2 during severe CN toxicity and following its reversal in rabbits.

Method: Twenty New-Zealand rabbits (3-4kg) were anesthetized, allowed to spontaneously breathe via a low-flow oxygen mask. We monitored blood CN, lactate levels, skeletal muscle (hamstring) rSO_2 (non-invasive regional oximetry system, Nonin Inc., Plymouth, MN), and arterial pH. After obtaining baseline control data, animals were started on an infusion of NaCN (0.55 mg/kg/hr). The infusion continued until the occurrence of severe CN toxicity as demonstrated by the occurrence of severe lactic acidosis, hypotension and or bradypnea. Following this the rabbits were randomly administered either a placebo or an antidote called sulfanegen sodium [2]. Hemodynamic and metabolic variables were monitored for an additional two hours in surviving rabbits.

Results: CN infusion resulted in severe significant toxicity in all the rabbits. This was accompanied by a significant reduction in skeletal rSO_2. Without the antidote, tissue oxygenation declined even further and the rabbits died. Following antidote administration there was an improvement in skeletal rSO_2 and reversal of lactic acidosis.

Discussion and Conclusion: Although CN impairs oxygen utilization in mitochondria, we were surprised to note a decline in skeletal rSO_2 during severe CN toxicity. This could be due to continued anaerobic metabolism resulting in severe lactic acidosis and desaturation within tissues. Reversal of CN toxicity resulted in gradual improvement in skeletal rSO_2.

References: 1. Baud FJ. Hum Exp Toxicol. 2007;26:191-201. 2) Brenner M, et al. Toxicol Appl Pharmacol. 2010;248:269-276.

Acknowledgements:

Sensors for regional SO_2 were provided by Nonin Medical Inc, Plymouth, MN

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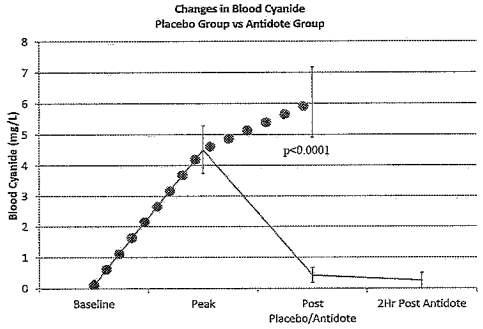
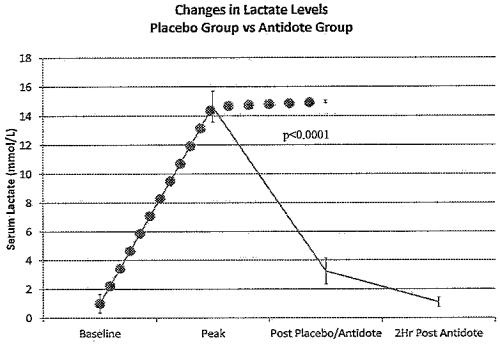
Introduction:

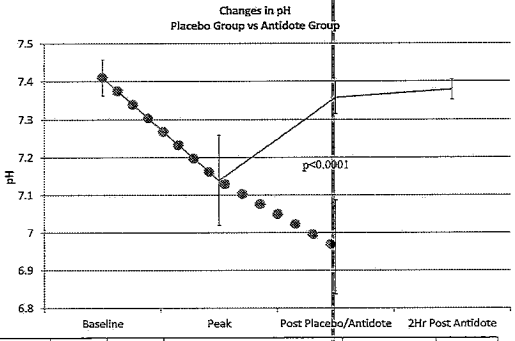
Cyanide (CN) is highly toxic to animals and humans. [1] Cyanide toxicity has been has been reported following smoke inhalation, industrial accidents, sodium nitroprusside overdose and could potentially occur as an act of bioterrorism. Although metabolic studies have been conducted during CN toxicity, none have addressed changes in tissue oxygenation (rSO_2). We report on skeletal muscle regional saturation of oxygen by using a non-invasive externally applied regional oximetry system- this measures the balance of oxygenated and deoxygenated hemoglobin in the skeletal muscle. [2]

Methods:

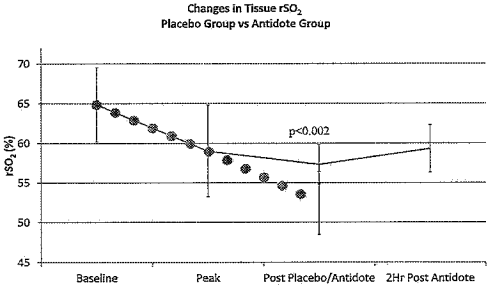
Twenty New-Zealand rabbits (3-4kg) were anesthetized, allowed to spontaneously breathe via a low-flow oxygen mask. Intravenous catheters were placed in both ears. We monitored blood CN, lactate levels, arterial pH and pO2, MAP, HR and skeletal muscle (hamstring) rSO_2 (non-invasive regional oximetry system, Nonin Inc., Plymouth, MN). After obtaining baseline control data, animals were started on an infusion of NaCN (0.55 mg/kg/hr). The infusion continued until the occurrence of severe CN toxicity as demonstrated by the occurrence of severe lactic acidosis, hypotension and or bradypnea. Following this the rabbits were randomly administered either a placebo or an antidote (IV) called sulfanegen sodium [2]. Hemodynamic and metabolic variables were monitored for an additional two hours in surviving rabbits. An independent samples t-test was performed to determine significance ($p<0.05$) of placebo vs antidote.

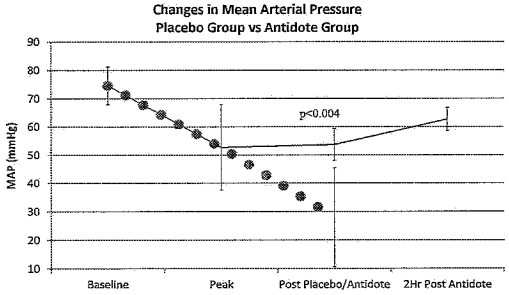






CN Plus Placebo
—CN Plus Antidote





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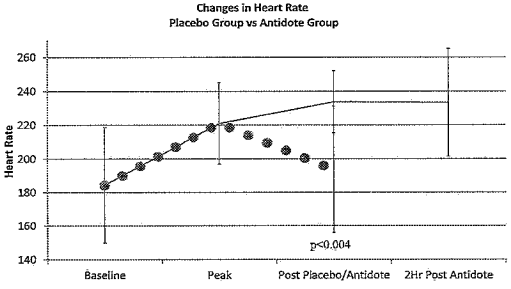

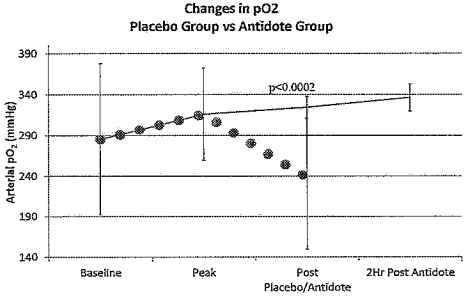

	Baseline	Peak	Post Placebo	/ Antidote	p value	2 Hr Post Antidote
Cyanide (mg/L)	0.102 (0.166)	4.509 (0.769)	6.038 (1.138)	0.4214 (0.245)	0.0001	0.250 (0.255)
Lactates (mmol/L)	1 (0.65)	14.64 (1.07)	14.97 (0.09)	3.24 (0.91)	0.0001	1.08 (0.34)
pH	7.41 (0.04)	7.14 (0.12)	6.96 (0.13)	7.36 (0.04)	0.0001	7.38 (0.03)
Arterial pO_2	285.25 (92.8)	316.1 (56.4)	238.3 (88.7)	324.5 (13.3)	0.004	336.4 (16.5)
Mean Arterial Pressure	74.6 (6.6)	52.7 (15.2)	28 (17.4)	53.7 (5.7)	0.0002	62.6 (4.1)
Heart Rate	184.3 (34.3)	221 (24.1)	193.6 (37.5)	233.7 (18.4)	0.004	233.3 (31.7)
Tissue rSO_2	64.9 (4.7)	59 (5.8)	52.4 (3.9)	57.3 (2.5)	0.002	59.3 (3.0)

Results:

CN infusion resulted in progressive increases in blood cyanide levels, accompanied by lactic acidosis. In addition, this was accompanied by an increase in heart rate and arterial pO_2. Mean arterial pressure and tissue rSO_2 were observed to progressively decline. Following administration of placebo no improvement was seen and all rabbits died. However, after the antidote there was an improvement in skeletal muscle rSO_2 and reversal of lactic acidosis. See figures for significance.

Discussion and Conclusion:

Acute CN toxicity results in lactic acidosis, systemic hypotension and tachycardia. For the first time, we demonstrate that during CN toxicity and subsequent reversal there are peripheral (skeletal muscle) oxygenation changes detectable by a non-invasive regional oximetry system. Significant differences were observed between the placebo and antidote groups ($p<0.002$). Although CN impairs oxygen utilization in mitochondria, we were surprised to note a decline in skeletal rSO2 during severe CN toxicity. This could be due to competition at the mitochondrial level in the face of continued anaerobic metabolism resulting in severe lactic acidosis and desaturation within tissues. Furthermore the antidote sulfanegen sodium was capable of reversal of cyanide toxicity in all ten rabbits.

References:

1. Baud FJ. Hum Exp Toxicol. 2007;26:191-201. 2) Brenner M, et al. Toxicol Appl Pharmacol. 2010;248:269-276.

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