

Lactate Clearance and Beta-Agonist-Induced Elevated Lactates in Asthma

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Citation

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Abstract

Background: Lactic acidosis occurs in asthma exacerbations at times and is felt to be secondary to B2-agonist use most of the time. It is also possible that subjects with decreased lactate clearance due to organ dysfunction are more susceptible to B2-agonist-induced lactic acidosis.

Objective: Profile acute asthma exacerbation patients with normal liver and hepatic function and lactic acidosis associated with B2-agonists use.

Study Design: Retrospective case series.

Methods: Subjects were selected for the series if they were being admitted for an asthma exacerbation from the ED, had an elevated lactate >4 mmol/L, and had no evidence of hepatic or renal dysfunction. The hospital course of these patients is described.

Results: Ten asthmatics (7 female), average age 54.7 ± 10.7 were admitted with lactates ranging from 4.5 to 8.7 mmoles/L after receiving initial albuterol treatments of at least 2 to 6 and usual care in the ED.

After treatment for acute asthma, all ten asthmatics improved and were discharged home over several days to a just over one week.

Conclusion: Asthmatics with B2-agonist-induced lactic acidosis can have normal hepatic and renal function and still develop the acidosis. This speaks against reduced lactate clearance as a contributing factor in B2-agonist-induced lactic acidosis in asthma.

INTRODUCTION

Lactic acidosis is often seen in emergency department and in hospitalized asthmatics (1-3). The etiology is thought to be B2-agonist therapy, but it is important for treating physicians to exclude type A lactic acidosis. Lactic acidosis due to drugs are categorized as type B -2 in the classification by Woods and Cohen, table 1 (4). Type A lactic acidosis is felt to result from increased lactate generation with or without a reduction in lactate clearance. With type A lactic acidosis the underlying cause needs to be identified and treated in order to prevent a poor outcome. In type A lactic acidosis due to sepsis, an elevation to 4 mmole/L or greater is indicative of severe sepsis (5). In contrast, B-2 lactic acidosis secondary to B2-agonist therapy is relatively benign and the primary treatment is reduction or discontinuation of the medication causing the acidosis.

Table 1

Types of Lactic Acidosis

Type A. Decreased tissue perfusion or reduced oxygen delivery or both.
Examples: Sepsis or severe anemia.

Type B. No evidence of decreased tissue perfusion or reduced oxygen delivery.

Type B-1 – Leukemia, lymphoma, AIDS

Type B-2 – Related to drugs (B₂-agonists, metformin) and toxins (methanol)

Type B-3 – Inborn errors of metabolism such as pyruvate dehydrogenase deficiency

In order to document an elevated lactate production with B2-agonist therapy in asthma in the absence of any clinically apparent factors which could alter lactate clearance, a retrospective cohort was created from patients admitted with a diagnosis of asthma and no evidence of hepatic or renal disease.

METHODS

Patients admitted to the hospital from the emergency department with an elevated lactate of greater than 4

mmol/L and an admitting diagnosis of asthma were identified. Those with normal hepatic and renal function were selected for the cohort.

RESULTS/HOSPITAL COURSE

From the emergency department, 10 patients were identified with elevated lactates of 4.5 to 8.7 mmol/L (normal: < 2 mmol/L). The asthmatics were predominantly female (7 of 10) and all were of Hispanic or African-American ethnicity. More than half were cigarette smokers, and the average age was 54 + 10.7 years. The BMI was 30.2 + 3.6 ranging 23 to 34. Demographic data and laboratory results are shown in table 2 including measures of hepatic and renal function. One patient was intubated and was subsequently extubated with full recovery. All patients had arterial blood gas lactate levels before discharge that were less than 3 mmol/L. No patient had pH reduction below 7.3 consistent with the acidosis.

All patients were treated initially with 2 to 6 albuterol treatments. Pre-hospital albuterol treatments were not quantified.

DISCUSSION

With the advent in the last decade of lactate values obtained by arterial blood gas analysis, elevated lactate levels are a common finding in admitted asthmatics and are seen every month in the ED, medical wards, and ICU. Although elevated lactate levels stimulate interest by consultants who evaluate asthmatics to make sure there is no evidence of hypoperfusion, it is such a common finding that most specialists see the patient and just continue total asthma treatment with some reduction in albuterol therapy. The lactate values usually become normal in one or two days. A reduction in albuterol B2-agonist therapy can also help in reducing the lactate level with alternate use of ipratropium bromide.

Lactate is normally synthesized at a rate of 20 mmol/kg body weight daily and cleared primarily by the liver (60%) or kidneys (20%) (6). Theoretically, most nucleated cells can metabolize some lactate to acetyl-CoA (5). The liver and kidneys can not only metabolize lactate to acetyl-CoA but can regenerate glucose from lactate via gluconeogenesis as well (Cori cycle: glucose to lactate to glucose). The major lactate synthetic organs (7) are the muscles and skin (25% each), brain (20%), intestine (10%), and red blood cells (20%). The red blood cells are the only major organ that make lactate but cannot clear lactate. When lactate levels are

elevated both skeletal muscle and the heart increase their metabolism of lactate.

Table 2

Admission lab values and serial lactate levels in 10 patients with a diagnosis of acute asthma

Characteristics	1	2	3	4	5	6	7	8	9	10
Age	59	60	49	33	62	44	58	60	69	46
Gender	F	F	F	F	F	M	F	F	M	M
Race	H	B	H	B	H	B	B	B	B	B
BP	154/78	91/52	123/68	151/80	143/80	154/87	141/96	111/73	125/72	135/84
P	140	81	94	110	89	125	70	82	116	97
RR	22	16	20	30	17	24	16	16	17	18
T	96.1	96	96.4	96	98	98	97	96	98	97.2
Best PEFR (l/min)	250	*	350	480	260	*	200	380	250	250
PEFR(A)	80	*	280	230	210	160	140	*	120	170
Smoker	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
TH (ALB)	3	2	5	6	6	3	3	4	5	6
TH(IPA)	0	2	0	3	2	3	3	3	2	3
AST	22	29	12	18	19	27	31	29	13	20
ALT	18	19	33	21	41	20	23	19	29	28
TB	0.7	0.2	0.3	0.2	0.3	1.3	0.2	0.2	0.3	0.2
Albumin	3.7	4	3.3	4	3.7	4.1	3.6	4	3.7	4
BUN	12	11	18	12	14	12	9	12	21	11
Cr	0.8	0.9	0.5	0.8	0.7	0.9	0.7	1.4	0.8	0.6
L(0)	1.7	3.4	*	*	2.4	3.37	*	3.4	1.7	*
L(a)	5.9	6.0	5.4	5.8	4.5	5.1	5.7	6.0	4.5	8.7
L(b)	2.6	1.8	2.4	1.7	1.6	1.6	2.3	2.1	2.5	2.2

F= female, M= male, H= hispanic, B= black, BP= blood pressure, P= pulse, RR= respiratory rate, T= temperature, PEFR= peak expiratory flow reading, liters/min. TH= number of treatments. ALB= albuterol, IPA= ipratropium, AST= aspartate aminotransferase, ALT= alanine aminotransferase, TB= total bilirubin, BUN= blood urea nitrogen, Cr= creatinine, L= lactate, (0)= pre-admission, (a) after admission nebulizations (b) post-acute asthma exacerbation, *= missing data

In this study we used a biased selection technique of only including subjects admitted from the ED with a diagnosis of asthma and elevated lactate levels. Blood gas analyses are generally only done when the ED physician considers possible admission because treatment is not working. In addition, no subject had any history of hepatic or renal disease that might have predisposed to problems with lactate clearance. The patients were readily identified with a simple query of recent years, and the patients improved with treatment for asthma, with subsequent home discharge. The elevated lactate levels were felt to be secondary to B2-agonist therapy for asthma and not reduced perfusion.

The mechanism of elevated lactate levels in asthmatics is unknown but presumably increased production of lactate is the issue as elegantly suggested by Rodrigo and Rodrigo (8). They took 18 asthmatic patients who were in the ED with an asthma exacerbation, obtained a baseline normal lactate level, and then treated them with 4800 ug of albuterol by metered dose inhaler over 2 hours. Four of 18 subjects developed a lactic acid level greater than 4 mmol/L. All patients did well clinically, were also treated with systemic steroids as needed and there was no evidence of hemodynamic instability during the hospital course (8). Therefore, intense albuterol treatment can induce a lactic acidosis in over 20% of patients, albeit most asthmatics will not develop a lactic acidosis with albuterol.

Several studies have been done in nonasthmatic

normal volunteers that suggest that increased production of lactate is secondary to B2-agonist stimulation. Normal volunteers were given B2-agonists after a baseline lactate was drawn (9-11). The stimulation results in elevated lactate levels in many nonasthmatic volunteers clearly suggesting increased production of lactate. The lactate clears when the stimulation is stopped. In addition, women given ritodrine (a Beta-agonist for premature labor) often develop a transient elevated lactate (12). There is no evidence that B2-agonists reduce hepatic or renal function resulting in decreased lactate clearance. In addition, there is some evidence that B2-agonists increase glycolysis resulting in increased pyruvate production which serves as a lactate precursor when not going down the tricarboxylic acid cycle (13,14).

CONCLUSIONS

Acute asthmatic patients with no evidence of hepatic or renal dysfunction can develop an acute and sometimes marked elevation of lactate after treatment with albuterol. The acidosis is transient and improves with reduction in albuterol therapy. This study suggests but does not prove that B2-agonists increase lactate production in acute asthma. Definitive proof would require determination of endogenous lactate production, turnover, and clearance using radioactive tracers.

A recently published teaching case posed the question, "Can Albuterol be Blamed for Lactic Acidosis?" (15). Our answer, "Absolutely!"

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