

### **SALMETEROL AND LACTIC ACIDOSIS: CLINICAL AND EDUCATIONAL ASPECTS**

*To the editor:* The article by Manara and colleagues reminds us of a rare but significant adverse effect of salmeterol.<sup>1</sup> Although the precise mechanism for elevated lactate levels (type B lactic acidosis) in patients with  $\beta_2$ -agonist overdose is not known, different hypotheses have been suggested. The explanation given by the authors is supported by an earlier observation made from healthy volunteers who had decreased glycogen content in muscle biopsies during infusions of the  $\beta$ -agonist epinephrine.<sup>2</sup> We would like to make three brief comments: one on mechanism, a second on clinical aspects, and a third on education and training.

The mechanism for increased lactate level observed in this patient with excessive  $\beta_2$ -agonist stimulation is likely due to poor oxygen extraction from a functionally shunted capillary bed. The new low-resistance circuit is formed due to arteriolar dilation, which allows blood to pass through the capillary bed without sufficient time for oxygen extraction, thus resulting in tissue hypoxia and venous hyperoxia.<sup>3</sup> This statement is supported by wide pulse pressure, as observed in this case. The elevated systolic pressure with reduced diastolic pressure is due to  $\beta_2$ -receptor-mediated vasodilation and enhanced inotropy.<sup>4</sup>

In clinical practice, hyperlactatemia is often attributed to underlying or comorbid illness(es). Sometimes the clinical picture may be challenging to

interpret, as seen in an outbreak of clenbuterol-containing heroin,<sup>5</sup> which was treated as cyanide poisoning before the causative agent was identified (mistaking the hypotension, profound hyperlactatemia, and venous hyperoxia). It is always important to consider less common causes of lactic acidosis and correlate the cause with the clinical picture and laboratory data. The increase in use of point-of-care analyzers in the emergency department or other critical care setting raises an additional concern about the method or the machine used and interfering substances in the specimen while interpreting a high lactate level, especially when the clinical picture is not consistent with the degree of elevation. For example, in ethylene glycol poisoning, there is an artifactual elevation of lactate due to the interference of glycolic acid, a metabolite of ethylene glycol when it cross-reacts with the enzyme L-lactate oxidase.<sup>6</sup> Therefore, physicians should be aware of this analytical interference in every case of severe metabolic acidosis with elevated lactate levels. Measurement of the “lactate gap”<sup>7</sup> using two different technologies helps distinguish true lactic acidosis.

As a teaching point, there is a wide differential diagnosis of the etiology of lactic acidosis;  $\beta_2$ -agonist overdose as a cause of hyperlactatemia may be considered, especially when it occurs in the absence of respiratory distress.

We look forward to further studies to find out why only a small number of patients experience this adverse effect and to explore genetic contribution for susceptibility.

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