Rasburicase-induced fatal respiratory arrest?

Urate oxidase is an endogenous enzyme found in most mammals but not in humans. Urate oxidase catalyzes the enzymatic oxidation of uric acid into allantoin, a metabolite that is 5–10 times more soluble in urine than uric acid. With complementary DNA technology it is possible to produce large quantities of the pure recombinant protein [1]. Rasburicase (RS), a recombinant form of urate oxidase, has been demonstrated to be superior to allopurinol in the control of uric acid production associated with acute leukemias and high-grade lymphomas (2).
Here we describe two cases of fatal respiratory arrest and death, while receiving RS as part of the antileukemic treatment.

**case 1**

A 51-year-old woman, with previous history of active smoking (20 cigarettes/day), allergy to codeine, and dyslipidemia, was admitted because of recent onset dyspnea. On physical examination, she was alert and oriented with cyanosis of the lips; temperature was 38.7°C; blood pressure was 120/50 mmHg; the heart rate was 120/min without murmurs, and the rest was normal. The most important laboratory values were as follows: leukocytes = 244 000 × 10^9/l, Hb = 7.4 g/dl; platelets = 34 000 × 10^9/l; uric acid = 13.45 mg/dl; and lactate dehydrogenase (LDH) = 2.479 U/l. X-rays films of the thorax were normal and electrocardiogram (ECG) showed a sinus rhythm at 120/min.

With the diagnosis of acute myelogenous leukemia (M5), treatment with oxygen, hydration, allopurinol, and hydroxyurea was started. Twelve hours later, RS (0.20 mg/kg/day) infusion was started and during the infusion the patient developed progressive dyspnea with cardiopulmonary arrest and death, despite cardiopulmonary resuscitation procedures.

**case 2**

A 51-year-old man, with history of active smoking (40 cigarettes/day), obesity, and gingivitis was admitted because of dyspnea and weakness. The physical examination showed an obese, febrile (38°C) patient, with face and eyelid edema, gingival hyperplasia, a heart rate of 112/min and systolic murmur, and edema of abdominal wall and lower extremities. Laboratory values were as follows: leukocytes = 168 900 × 10^9/l (8% blasts); Hb = 5 g/dl; platelets = 34 000 × 10^9/l; uric acid = 20.55 mg/dl; urea = 64 mg/dl; and LDH = 1.692 U/l. X-rays films of the thorax and ECG were normal.

Treatment with oxygen, hydration, allopurinol, prednisone, and hydroxyurea was started. Eighteen hours later (next morning), the first dose of RS was administered. The patient remained dyspneic, but with good oxygen saturation level. On the following morning, the second dose of RS was administered and during the infusion, dyspnea increased and cardiopulmonary arrest developed. Cardiopulmonary resuscitation was performed, but the patient remained in a coma. A computed tomography study of the brain was normal and the diagnosis of anoxic brain damage was established. The patient died 72 h later.

The development of severe adverse reactions to RS accounts for <1% of patients. The most serious adverse reactions attributed to RS were anaphylaxis, rash, hemolysis, and metahemoglobinemia. Other serious adverse reactions were fever, neutropenia with fever, respiratory distress, sepsis, neutropenia, and mucositis [2, 3].

Both fatal episodes accounted in two patients of the same age, with acute myelogenous leukaemia (M5) and active heavy smokers. We have no data on whether criteria for chronic bronchitis or bronchial hyperreactivity were present. Both patients were admitted with dyspnea without heart failure and normal X-rays films of the thorax.

Our hypothesis on the origin of the respiratory arrest was a severe bronchospasm, secondary to an RS-induced anaphylactic reaction, probably associated with tobacco-induced bronchial injury.

Massive pulmonary thromboembolism could be a possible cause, but there were no signs or symptoms of deep venous thrombosis, the patients had no acute chest pain, and the ECG pattern was not consistent with this.

Despite this being only a hypothesis, caution should be taken when RS is to be used in patients with previous history of heavy smoking, chronic bronchitis, or bronchial hyperreactivity. In case of severe hyperuricemia, reduced dose of RS could be used under close cardiopulmonary observation [4].

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doi:10.1093/annonc/mdl380

Published online 25 October 2006

Volume 18 | No. 2 | February 2007