Sepsis-Like Syndrome Caused by the Russian Medication Pyrogenal (*Salmonella typhi* Endotoxin)

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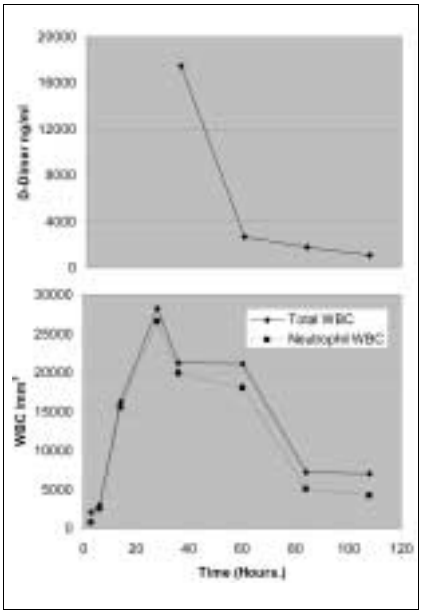
Many immigrants to Israel continue to use medications that they had taken in their previous countries, medications that are not always licensed in Israel. We recently cared for a patient who presented with a sepsis-like syndrome: severe headache, fever, hypotension and leukopenia that turned rapidly to marked leukocytosis. This reaction appeared 20 minutes after the intramuscular injection of a medication that turned out to be the Russian medication Pyrogenal, an extract of *Salmonella typhi* endotoxin.

Patient Description

A 29 year old woman presented to the emergency room with severe headache and vomiting that started 20 minutes after the intramuscular injection of a medication. The patient had immigrated to Israel from Russia 7 years earlier. She was married, had one son and had had six abortions, all of them at weeks 9–12 of gestation. She reported to the physicians at admission that the medication injected was Pergonal, a preparation that contains follicle-stimulating hormone and luteinizing hormone. In the emergency room, about 2 hours after the injection, she was found to be in distress, her blood pressure was 119/68 mmHg, pulse 118/minutes and temperature 38.3°C. No nuchal rigidity was found and the rest of the physical examination was normal. Blood count revealed leukopenia of 2,030/mm^3, neutrophils 37%, lymphocytes 56%, platelets 278,000/mm^3 and hemoglobin 11.7 g/dl. Chest X-rays and brain computerized tomography were normal; a lumbar puncture was considered but not performed. Gynecologic examination including vaginal ultrasound to rule out ovarian hyperstimulation was normal.

At 5 hours post-injection, hypotension was first recorded with a range of 85–90/45–68 mmHg and lasted for about 7 hours despite intravenous administration of 3 L saline. Her temperature ranged from 37 to 38.5°C during the first 24 hours. Leukocyte count changed dramatically: the leukopenia observed during the first 5 hours post-injection turned within 8 hours to leukocytosis of 16,000/mm^3, and at 28 hours post-injection it peaked to 28,000/mm^3 with 94% neutrophils [Figure]. On admission to our department 24 hours after referral to the emergency room, she complained of headache but no nuchal rigidity was found. Blood pressure, heart rate and temperature were normal. It was then discovered that the medication injected was Pyrogenal, which she had begun to take 20 days earlier during a visit to Russia. To treat her habitual abortions, she started a course of 10 intramuscular injections of Pyrogenal, starting at a dose of 10 μg with an increment of 10 μg every other day. She received the last dose of 100 μg prior to admission.

The hospitalization course was relatively mild. The figure shows the course of the leukocyte counts, and that of the D-dimer which was found to be very high, at 17,500 ng/ml (normal < 200 ng/ml), when it was first measured 36 hours after admission. As another manifestation of disseminated intravascular clotting, a nadir platelet count of 115,000/mm^3 was found at that time. Serum aspartate and alanine aminotransferase levels at 36 hours were 4.5 and 3 times of normal respectively, with a gradual decline over the next 3 days. All blood cultures were negative. A single dose of ceftriaxone was administered on the third day. The patient was discharged 6 days after admission.



Changes in the white blood cell and neutrophil counts, and in D-dimer concentration after intramuscular injection of 100 μg Pyrogenal (*Salmonella typhi* endotoxin).

Comment

Lipopolysaccharide, also known as endotoxin, has a major role in initiation of the septic process caused by gram-negative bacteria [1]. LPS is embedded in the outer membrane of the bacterial cell wall. It binds to macrophages, and through complex signal transduction pathways leads to production of cytokines (such as tumor necrosis factor) that mediate the cellular and organ damage observed in sepsis [1]. Leukocytosis and activation of the coagulation cascade appear, and through local inflammation and fibrin deposition con-

LPS = lipopolysaccharide

tribute to the tissue damage and organ failure [1].

Our patient presented with a sepsis-like syndrome characterized by fever and hypotension, initial leukopenia turning rapidly to marked leukocytosis, and evidence of DIC (high D-dimer and thrombocytopenia) caused by *Salmonella typhi* endotoxin. Previous reports of endotoxin administration to humans usually involved lower doses of the toxin. Michie et al. [2] administered *Escherichia coli* endotoxin intravenously to 13 healthy volunteers at a dose of 4 ng/kg. This dose was 400 times lower than that in our case. The authors mention that 2 hours post-injection the patients' temperature rose by 2°C, no reduction in blood pressure was observed, and leukocyte count rose to a mean of 13,000/mm^3 [2]. Administration of a higher endotoxin dose was described by Taveira da Silva et al. [3]. Intravenous self administration of 1 mg of salmonella endotoxin (about 10 times higher than our patient's dose) caused headache, vomiting, severe hypotension of 42/20 mmHg, and temperature of 40°C. After an initial leukopenia the patient had extreme leukocytosis with a peak of 37,000/mm^3 and a platelet count of 64,000/mm^3. He was treated with intravenous fluids and vasoactive amines but, in contrast to our patient, developed transient renal and pulmonary dysfunction. The milder course in our patient could be attributed to the lower dose used, the intramuscular route of administration, and possibly to the tolerance that she may have developed due to the escalating doses. These case descriptions demonstrate the major role of LPS in the production of septic shock.

Our patient was treated by the Russian medication Pyrogenal, manufactured by the Russian Academy of Medicine, Moscow (product leaflet). This *Salmonella typhi* endotoxin is used in Russia to manipulate the immune system for various indications, such as chronic arthritis, bronchial asthma, neoplastic diseases, neurosyphilis and tuberculosis [4]. This case underscores the risk that a therapy of unproven efficacy entails: simulated sepsis, potential life threat, and need for unnecessary diagnostic or therapeutic procedures.

Finally, the error that occurred because of the similarity of the drug names – Pergonal and Pyrogenal – is a source of much concern. In the United States, name confusion has been identified as the primary cause of about 25% of medication errors [5].

DIC = disseminated intravascular coagulation

References

1. Cohen J. The immunopathogenesis of sepsis. *Nature* 2002;420:885–91.
2. Michie HR, Manogue KR, Spriggs DR, et al. Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med* 1988;318:1481–6.
3. Taveira da Silva AMT, Kaulbach HC, Chuidian FS, Lambert DR, Suffredini AF, Danner RL. Shock and multiple organ dysfunction after self-administration of Salmonella endotoxin. *N Engl J Med* 1993;328:1457–60.
4. Malin DI. The place of pyrogen therapy in the modern treatment of schizophrenic patients. (Russian). *Zh Nevropatol Psikhiatr Im S S Korsakova* 1992;92:81–5.
5. Lambert BL, Chang KY, Lin SJ. Effect of orthographic and phonological similarity on false recognition of drug names. *Soc Sci Med* 2001;52:1843–57.

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