Serum Sickness–like Reaction Possibly Associated with Meropenem Use

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Serum sickness–like reactions most commonly occur secondary to drug administration. We describe a serum sickness–like reaction that was possibly associated with meropenem therapy.

In 1905, von Pirquet and Schick [1] characterized the classic syndrome of serum sickness after administration of heterologous antitoxin serum. Reactions with clinical features slightly different from those of classic serum sickness, with the source of antigen not being heterologous serum, are referred to as “serum sickness–like reactions” (SSLRs) [2]. Today, SSLRs occur most commonly secondary to drug administration [2–4]. This case report describes an SSLR that was possibly associated with receipt of meropenem therapy.

Case report. The patient was a 34-year-old man who had a ventriculoperitoneal shunt placed in 1982 for hydrocephalus secondary to a septum pellucidum cyst. He had no known drug allergies. In early January 1999, he began to complain of increased pain, swelling, redness, and tenderness along the subcutaneous course of his shunt. He was treated as an outpatient with a variety of orally administered antibiotics, including clarithromycin, cloxacillin, and amoxicillin-clavulanic acid. On 22 February, he presented to the hospital with neck edema and redness over the shunt, along with headache and fever. Intravenous vancomycin and cefotaxime were empirically started for a suspected shunt infection and possible meningitis.

A CSF specimen obtained by lumbar puncture grew Pseudomonas aeruginosa and Klebsiella pneumoniae on culture. The peritoneal end of the ventriculoperitoneal shunt was removed on 26 February because of its suspected perforation of the bowel, and an external ventricular drain was inserted. During the operation, the ventricular portion of the catheter was found to be very adherent and was left in situ. Culture of a sample of the tissue blocking the peritoneal segment of the shunt grew P. aeruginosa, as well as Enterobacter cloacae and Bacteroides fragilis (β-lactamase positive). Vancomycin and cefotaxime were discontinued, and meropenem (2 g iv q8h) was initiated on 25 February. Oral ciprofloxacin (750 mg b.i.d.) was added on 2 March. Meropenem was discontinued on 8 March, when the patient was discharged home with clinical improvement and a planned 2-month course of oral ciprofloxacin and metronidazole (500 mg b.i.d. for both). These were his only medications.

The patient was readmitted to the hospital on 20 April 1999 because of a recurrence of meningitis. His oral antibiotic therapy was discontinued, and the neurosurgical service empirically started administering vancomycin and cefotaxime (with intermittent ceftriaxone doses to accommodate a weekend leave) intravenously for 8 days, until 28 April. On 26 April, the remaining ventricular portion of the shunt was removed. When seen by the infectious diseases service on 27 April, the patient started receiving meropenem (2 g iv q8h) for a planned 2-week course of therapy. He was discharged from the hospital on 30 April with a home intravenous antibiotic program. The patient did well until 6 May, when he developed a pruritic rash in association with joint swelling. The next day he noticed the appearance of erythematous macular lesions on his skin, accompanied by erythema and swelling of his fingers. Meropenem was discontinued because of a suspected SSLR. A time line summarizing the patient’s antibiotic exposures is presented in figure 1.

The patient was seen in the emergency department on 9 May after having received a single dose of ceftazidime. He had a temperature of 37.9°C, a heart rate of 150 beats/min, and a respiratory rate of 20 breaths/min, without shortness of breath or wheezing. During physical examination, he was found to be mildly unwell with erythema multiforme and hand and finger edema. Facial edema, mucosal lesions, lymphadenopathy, hepatomegaly, and splenomegaly were not present. Laboratory values were within normal limits, with the exception of liver function test values, which were moderately elevated, with an alanine aminotransferase (ALT) level of 276 U/L (normal range, 10–40 U/L), an aspartate aminotransferase (AST) level of 132 U/L (normal range, 10–42 U/L), and an alkaline phosphatase...
level of 160 U/L (normal range, 18–113 U/L). The impression was that the patient had experienced an SSLR to meropenem. The following day (10 May), the patient started a 10-day course of prednisone (40 mg q.d.) and a 1-week course of orally administered ciprofloxacin to complete therapy for his infection.

On 17 May 1999, the patient reported that his symptoms had improved within 24–48 h of initiation of prednisone therapy, and there was no evidence of skin or joint manifestations of the reaction. However, his liver enzyme levels had increased (ALT level, 1288 U/L; AST level, 580 U/L; and alkaline phosphatase level, 163 U/L). By 31 May, these values had decreased to 213 U/L, 100 U/L, and 153 U/L, respectively. On 14 June, the patient reported mild persisting arthralgias of the hips, shoulders, and hands. He was instructed to take enteric-coated aspirin (650 mg t.i.d.) for symptomatic relief. When seen at a follow-up visit on 22 July, the arthralgias had resolved and the liver profile had improved (ALT level, 103 U/L; AST level, 83 U/L; and alkaline phosphatase level, 69 U/L). In September 1999, his ALT and AST levels were only slightly elevated. Diagnostic tests for immune complexes and serological tests for hepatitis B virus (hepatitis B surface antigen, surface antibody, and core antibody) and hepatitis C virus were performed during this period, and the results were found to be negative.

To investigate the potential role that meropenem played in this patient’s reaction, an in vitro lymphocyte cytotoxicity assay was performed. This technique has been previously reported by one of the authors (M.J.R.) to examine cross-reactivity between loracarbef and cefaclor [5]. The assay determines the viability of a patient’s lymphocytes when exposed to reactive drug metabolites generated by a murine microsomal system. Cell viability is compared with a control. The percentage of cell viability (± SEM) for our patient’s lymphocytes exposed to meropenem and rat liver microsomes was significantly lower (89.2% ± 1.78%; P < .05) than that of the control under the same conditions (100% ± 1.99%; P < .05, by analysis of variance).

Discussion. β-Lactam antibiotics are commonly implicated as causes of SSLRs [2–4], and the frequency of SSLRs is slightly greater in association with cefaclor use [6]. Our patient was suspected to have had an SSLR to meropenem. We conducted a review of the medical literature published from 1966 through October 2002 using MEDLINE; the review did not reveal reports about serum sickness or SSLRs associated with currently marketed carbapenem antibiotics, including imipenem and meropenem. A search conducted by AstaZeneca, Canada, of their worldwide safety database (updated October 2002) found no reports of meropenem-induced SSLRs (personal communication).

Heckbert et al. [7] found that, in a pediatric population, all but 1 of 11 cases of antibiotic-related serum sickness reactions occurred after receipt of multiple antibiotic treatments, especially among patients who had ≥6 courses. Our patient may have been at increased risk for an SSLR, given the frequency and duration of his antibiotic use over a period of ~4 months.

Serum sickness or SSLRs are typically characterized by fever, arthralgias, and cutaneous manifestations [3]. While receiving meropenem, our patient presented with low-grade fever, characteristic cutaneous manifestations, and compromised flexion at the proximal interphalangeal joints, followed by persisting arthralgias of the hands, hips, and shoulders. It is difficult to determine whether the patient’s elevated liver enzyme levels were part of the reaction, simply a transaminitis related to meropenem use [8], or a ciprofloxacin-induced hepatic reaction [9]. However, the return of the liver enzyme levels to baseline values coincident with the resolution of the patient’s symptoms would suggest that this was part of the drug reaction.

The typical interval from the commencement of drug therapy to the onset of clinical manifestations of serum sickness or SSLR is 8–14 days [3], but the onset may be delayed up to 3 weeks [10]. The reaction can occur with the first exposure and at an accelerated rate if the patient has been previously sensitized to the offending agent [10]. Our patient’s reaction developed on the ninth day of his second course of meropenem therapy. At the time of the reaction, he was not taking concurrent medications. Although an SSLR has been previously reported in association with use of ciprofloxacin and metronidazole [11, 12], these agents were started 65 and 59 days, respectively, before the onset of our patient’s reaction. Given that this was the patient’s second recent exposure to vanco-
mycin and cefotaxime, the 16-day time delay to reaction onset after therapy initiation also appears to be protracted, making them less likely causes.

Enhanced cellular sensitivity has been demonstrated to be a component of adverse reactions to a number of drugs, including antimicrobials, anticonvulsants, and antipsychotic agents. The use of cytotoxicity assays has been mainly limited to drug safety research, and precise estimates of their specificity, sensitivity, and predictive value for various drugs are currently unknown [13]. However, the lymphocyte cytotoxicity assay results for our patient indicate that his cells were markedly more sensitive to meropenem than were control cells. This observation, in addition to the patient’s symptoms, time course of presentation, and normal findings of medical work-up for other causes, strongly suggest that he had an SSLR to the carbapenem antibiotic meropenem. The incidence of this reaction is likely rare, given the lack of any previously published case reports of SSLRs to either imipenem or meropenem.

References