

A young infant with transient severe hypertriglyceridemia temporarily associated with meropenem administration

A case report and review of the literature

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Abstract

Background: Slight changes in the lipid profile can be observed over the acute phase of infectious diseases. Moreover, some anti-infective drugs can modify serum lipid concentrations, although antibiotics do not seem to have a relevant, direct, or acute effect on the lipid profile.

Methods: A 75-day-old breastfed Caucasian female, born at term after a regular pregnancy, was hospitalized for osteomyelitis. She was immediately treated with intravenous meropenem and vancomycin. Therapy was effective, but after 22 days of treatment, her blood was found to be viscous with a purple shade.

Results: A fasting blood sample showed serum triglycerides of 966 mg/dL, total cholesterol of 258 mg/dL, and high-density lipoprotein cholesterol of 15 mg/dL. Secondary causes of hyperlipidemia and primary hereditary disorders were ruled out. Thereafter, the possibility that antibiotics may have had a role in the hypertriglyceridemia was considered, and meropenem was discontinued. After 72 hours of meropenem discontinuation, a sharp modification of lipid variables was observed, and further testing showed a complete normalization of the lipid profile.

Conclusion: In this child with osteomyelitis, the increase in serum triglycerides appeared suddenly after 3 weeks of meropenem treatment and resolved quickly after meropenem discontinuation, thus highlighting the possible association between meropenem and lipid profile alterations. Monitoring the lipid profile should be considered in cases of long-term treatment with meropenem, and further studies on meropenem safety should include evaluation of the lipid profile.

Abbreviations: HDL = high-density lipoprotein, WBC = white blood cell count.

Keywords: antibiotics, hyperlipidemia, hypertriglyceridemia, meropenem, osteomyelitis

1. Introduction

For several years, it has been known that changes in the lipid profile can be observed over the course of infectious diseases as

Editor: Fadi Khasawneh.

The authors have no conflicts of interest to disclose.

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Medicine (2016) 95:38(e4872)

Received: 7 February 2016 / Received in final form: 30 July 2016 / Accepted: 23 August 2016

<http://dx.doi.org/10.1097/MD.0000000000004872>

part of a general metabolic response to infections. In general, during severe acute infection, serum concentrations of total cholesterol and high-density lipoprotein (HDL) cholesterol are reduced, whereas the serum concentrations of triglycerides are increased.^[1–3] However, the serum levels of all these parameters are usually only slightly modified and tend to normalize with healing after the acute phase of the disease. Moreover, some anti-infective drugs can modify serum lipid concentrations. The best example of this is represented by some highly active antiretroviral drugs that are currently administered to adults and children to treat HIV infection.^[4] Although it has been recently demonstrated that the early use of antibiotics in the prenatal and postnatal period can influence lipid metabolism through alterations of the intestinal microbiome,^[5] no relevant, direct, or acute effect on the lipid profile has been demonstrated. This paper reports a case of a young infant suffering from osteomyelitis who developed transient serum lipid alterations strictly associated with the administration of the recommended doses of meropenem.

2. Case

2.1. Presenting concerns

A 75-day-old Caucasian female born at term after a regular pregnancy, with weight and length within the normal range, was admitted to the emergency room with fever (maximal axillary temperature, 39.0°C), irritability, and poor feeding.

2.2. Clinical findings

Her medical and family histories were negative, and she did not have any comorbidities.

She had a septic appearance (i.e., axillary temperature 39°C, gray color, lethargy, and feeding intolerance) and showed evidence of a subcutaneous soft tissue mass overlying the middle and lower sternum and adjacent ribs on the left side.

Laboratory findings showed severe anemia (hemoglobin, 6.8 g/dL), a significantly increased white blood cell count (WBC; 32,000/mm³) with neutrophilia (65%), and a marked increase in both C-reactive protein and procalcitonin serum concentrations (17.6 mg/dL and 1.23 µg/dL, respectively).

Magnetic resonance imaging confirmed the diagnosis of rib osteomyelitis.

The infant, who continued to receive breast milk and did not receive any parenteral nutrition, was immediately treated with intravenous meropenem (100 mg/kg/d in 3 divided doses) and vancomycin (40 mg/kg/d in 3 divided doses). Meropenem dosage was the same recommended for meningitis due to the infant's septic conditions. Whole blood transfusion was initially added to eliminate anemia and restore normal circulation.

Therapy was rapidly effective. There was an evident improvement in her general clinical condition after a few days. After 1 week, hemoglobin returned to within normal range, and the WBC and acute phase reactant serum concentrations returned to normal.

After 22 days of treatment, when a venous sample was drawn for laboratory controls, the blood was found slightly lactescent as nonfat skim milk. The following day, a fasting blood sample was obtained again. After centrifugation, triglycerides in the serum were 966 mg/dL, total cholesterol was 258 mg/dL, and HDL cholesterol was 15 mg/dL.

2.3. Timeline

Table 1 summarizes the main clinical and laboratory findings in this 75-day-old infant with a diagnosis of osteomyelitis treated with meropenem and vancomycin.

Management of this case and its publication were approved by the Ethics Committee of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. Written informed consent was obtained from the patient's parents.

2.4. Diagnostic focus and assessment

Further lipid profile testing during the following days revealed similar values. The mother was instructed to breastfeed in sessions at least 4 hours apart, and blood samples were always obtained after 4 hours of fasting.

Secondary causes of hyperlipidemia, such as diabetes mellitus, hypothyroidism, renal failure, glycogen storage disease, lipodystrophy, lymphoma, systemic lupus erythematosus, and HIV infection, were ruled out.

Laboratory tests of the parents excluded primary hereditary disorders, including familial dyslipidemias.

2.5. Therapeutic focus and assessment

Because the lipid profile remained abnormal despite a normal WBC and acute phase reactants, the possibility was considered that antibiotics might have had a role in this adverse event. On the basis of data highlighting the role of methicillin-resistant *Staphylococcus aureus* as the main etiologic agent of osteomyelitis in the first years

of life,^[6,7] even if in absence of blood culture positivity in this initially septic infant, it was decided to stop meropenem and continue vancomycin.

After 72 hours of meropenem discontinuation, a sharp modification of the previously abnormal lipid variables was evident. Serum triglycerides were 152 mg/dL, total cholesterol 215 mg/dL, and HDL cholesterol 27 mg/dL.

2.6. Follow-up and outcomes

Italian government pharmacovigilance agency was immediately informed on the adverse event possibly related to meropenem use, and then the government agency informed the drug manufacturer. Vancomycin was stopped after 2 additional weeks. At the end of therapy and after 1 month, there was a complete normalization of the lipid profile, and laboratory test results were normal.

3. Discussion

In this child with osteomyelitis, a transient, relevant modification of the concentration of serum triglycerides was evident. The triglycerides were found to be up to 5 times higher than the maximum normal level of subjects of the same age and similar feeding pattern, whereas total cholesterol was increased and HDL cholesterol decreased. The increase in serum triglycerides appeared suddenly after almost 3 weeks of meropenem treatment and resolved quickly after meropenem discontinuation.

The clinical feature, especially the sudden onset and rapid ascent of serum triglycerides to well above the normal levels, excludes familial dyslipidemias.^[8] These diseases were also excluded by the examinations performed in the infant and her parents and by the lipid profile's rapid return to normal. A mutation in the *GPD1* gene, which encodes glycerol-3-phosphate dehydrogenase 1, is associated with moderate-to-severe transient hypertriglyceridemia in infancy that normalizes with age.^[9] However, in these cases, normalization occurs after years during late childhood or early adulthood. In addition, both the triglycerides and total cholesterol levels in the parents were found to be within normal limits, further supporting this conclusion.

Serum lipids can be derived from food and be transported from the gut to the bloodstream. A high-saturated fat diet can cause serum lipid alterations.^[8] However, the child was always breastfed and did not receive any intravenous lipid intake during the hospital stay. As previously reported, infections can be associated with mild-to-moderate changes in the lipid profile, but these variations usually begin in the early phase of the infectious disease as part of the whole picture leading to an increased synthesis of acute phase proteins, although they can persist during the convalescent phase.^[10] In this child, the triglyceride changes were severe and occurred only after 3 weeks from the disease onset, a result suggesting no relationship with the osteomyelitis. In contrast, the lipid profile changes were apparently associated with meropenem administration and rapidly resolved after the antibiotic was withdrawn.

Meropenem is a carbapenem antibiotic that is approved for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and pediatric bacterial meningitis in patients ≥ 3 months. However, meropenem is often prescribed off-label in neonates and younger infants who suffer from severe life-threatening suppurated bacterial infections^[11] and at doses in the range of those suggested for treatment of meningitis in older children,^[12] as occurred in this case. The

Table 1

Main clinical and laboratory findings in a 75-day-old female infant with a diagnosis of osteomyelitis.

Finding	Admission (October 26, 2015)	Day 7 (November 2, 2015)	Day 22 (November 17, 2015)	Day 23 (November 18, 2015)	Day 28 (November 23, 2015)	Day 35 (November 30, 2015)	Day 44 (December 9, 2015)	Day 78 (January 11, 2016)
Symptoms and signs	Fever, irritability, poor feeding, subcutaneous mass over the middle and lower sternum and adjacent ribs on the left side	None	None	None	None	None	None	None
Magnetic resonance imaging	Evidence of an osteochondral lesion of the seventh left rib (22 × 25 mm ²)				Decrease in the osteochondral lesion of the seventh left rib (9 × 19mm ²)			
Laboratory examinations								
WBC, cells/ μ L	32,000	15,130	14,110	N.p.	10,640	10,490	9430	9210
Neutrophils, %	65	27	21.2	N.p.	17.6	19.4	25	27
Hemoglobin, mg/dL	6.8	10.5	10.5	N.p.	9.2	9.6	10.6	11.2
CRP, mg/dL	17.6	0.8	0.04	N.p.	0.06	0.03	0.02	0.02
PCT, μ g/L	1.23	0.09	0.06	N.p.	0.06	0.04	0.02	0.02
Creatinine, mg/dL	0.13	0.12	0.14	N.p.	0.14	0.12	0.13	0.16
AST, U/L	30	29	30	N.p.	32	39	30	28
ALT, U/L	16	17	17	N.p.	18	25	18	19
TSH, mIU/L				N.p.		3		
Urine exam	Normal	Normal	Normal	N.p.	Normal	Normal	Normal	Normal
Lipid profile								
Triglyceride, mg/dL	115	N.p.	Slightly lactescent serum	966	753	152	134	90
Total cholesterol, mg/dL	196	N.p.		258	215	215	207	156
HDL cholesterol, mg/dL	30	N.p.		15	16	17	33	36
Parental lipid profile								
Mother								
Triglyceride, mg/dL					43			
Total cholesterol, mg/dL					200			
HDL cholesterol, mg/dL					76			
Father								
Triglyceride, mg/dL					116			
Total cholesterol, mg/dL					223			
HDL cholesterol, mg/dL					44			
Excluded diagnoses								

Table 1. continued

Finding	Admission (October 26, 2015)	Day 7 (November 2, 2015)	Day 22 (November 17, 2015)	Day 23 (November 18, 2015)	Day 28 (November 23, 2015)	Day 35 (November 30, 2015)	Day 44 (December 9, 2015)	Day 78 (January 11, 2016)
Anti-infective therapy	Meropenem + vancomycin	Meropenem + vancomycin	Meropenem + vancomycin	Meropenem + vancomycin	Meropenem + vancomycin	Vancomycin (meropenem stopped for 72 h)	None (vancomycin stopped for 48 h)	None
Diet	Exclusive breastfeeding	Exclusive breastfeeding	Exclusive breastfeeding	Exclusive breastfeeding	Exclusive breastfeeding	Exclusive breastfeeding	Exclusive breastfeeding	Exclusive breastfeeding

ALT = alanine transaminase, AST = aspartate transaminase, CRP = C-reactive protein, HDL = high-density lipoprotein, N.p. = not performed, PCT = procalcitonin, TSH = thyroid-stimulating hormone, WBC = white blood cell count.

Diabetes mellitus, hypothyroidism, renal failure, glycogen storage disease, lipodystrophy, lymphoma, systemic lupus erythematosus, and HIV infection

safety profile of meropenem has been studied in the past both in adults and in children.^[12–15] The drug has been found to be safe and well tolerated because no more than 3% of exposed subjects experience a drug-related adverse event.^[13] The gastrointestinal tolerability was considered excellent, and no risk of seizure, previously evidenced with other carbapenems, was demonstrated. Moreover, changes in the levels of biochemical markers, including indicators of renal^[13] and hepatic injury,^[14] have never been reported, even in subjects with renal or liver disease. However, all of these data have been collected in patients older than 3 months, and variability related to an infant's development is absent. A study to solve this problem and clarify the safety of meropenem in the first 3 months of life is in progress.^[15] This is the first report of transient hypertriglyceridemia associated with meropenem, and previous studies did not show an influence on lipid profile associated with meropenem use. Although it is not possible to understand from a single case insights on how meropenem administration caused hypertriglyceridemia, this case highlights that monitoring the lipid profile should be considered in cases of long-term treatment with meropenem, and further studies on the safety of meropenem should include evaluation of serum triglycerides and cholesterol.

4. Patient's parents' perspective

We were very worried when we were informed of the alteration in our baby's lipid profile. In particular, we were worried about the possibility that something was wrong with breastfeeding. We were confident in the pediatricians who followed our child, and we were very happy to discover that the lipid profile had returned to normal a few days after discontinuing meropenem.

5. Informed consent

The patient's parents provided their written informed consent for the publication of this study.

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