Hyperlipidemia Due to Rectal Phenobarbital Use: Case Report

Kadir Serafettin Tekgunduz⁎, Eda Kepenekli‡, and Yasar Demirelli†

⁎Ataturk University Medicine Faculty, Division of Neonatology, Turkey
‡Marmara University Medicine Faculty, Division of Pediatric Infectious Diseases, Turkey

Abstract
Treatment with hepatic enzyme-inducing antiepileptic drugs leads to increases in the levels of total cholesterol (TC) and triglyceride (TG). We report a case of a 10-month-old infant with hyperlipidemia due to use of rectal phenobarbital-paracetamol combination during echovirus infection. To the best of our knowledge, this is the first case reported in the literature of hyperlipidemia due to rectal phenobarbital use.

Introduction
Febrile illness in children younger than 36 months is common and has potentially serious consequences. As parents especially fear the possibility of febrile convulsion; they often administer antipyretics without consulting a physician. Some of these rectal antipyretics are combined with phenobarbital (e.g. Paranox®). Phenobarbital is an antiepileptic known to induce hepatic microsomal enzymes. Microsomal enzyme induction with exogenous drugs can alter the metabolism of bile acids, bilirubin, total cholesterol (TC), triglyceride (TG), and other endogenous molecules [1,2]. A 10-month-old infant presented with hyperlipidemia due to rectal phenobarbital-paracetamol combination (Paranox®), which was used by the parents to reduce fever related to enterovirus infection.

Case Report
The 10-month-old female weighing 10 kg infant presented to our emergency clinic with a five-day history of high fever. There were no previous hospital admissions. The infant was healthy, had received the recommended routine immunizations, and was taking no medications prior to the onset of fevers. Subsequent to the onset of fevers, the patient was treated with antipyretics. She appeared good, with a temperature of 38.8°C. Her physical examination was normal; she had a clear oral pharynx, and her tympanic membranes were normal. There was no significant hepatosplenomegaly, lymphadenopathy or skin rash. Cardiovascular and respiratory exams were unremarkable. Her abdomen was soft and nontender, and normoactive bowel sounds were noted. The neurological exam revealed an awake infant with normal tone, strength, and reflexes. There were no detectable cranial nerve abnormalities. Babinski signs were negative. The initial laboratory data showed normal hemoglobin (13 g/dl), thrombocyte count (365×10⁹/μL) and leukocyte count (10.2×10⁹/μL [neutrophils 34%, lymphocytes 59%, monocytes 7%]). Liver enzymes (aspartate aminotransferase [AST] 15 U/L, alanine aminotransferase [ALT] 41 U/L), renal function tests (urea 9 mg/dl, creatinine 0.2 mg/dl), electrolytes (Na 135 mmol/L, K 4.3 mmol/L, Ca 10.5 mg/dl) and acute phase reactants (C-reactive protein [CRP] 2.97 mg/L, procalcitonin 0.434 ng/ml) were normal.

The serum was grossly lipemic. Lipid profile estimation showed markedly increased TG (760 mg/dl) and TC (257 mg/dl) levels. Lumbar puncture was performed, and the cerebrospinal fluid (CSF) analysis was normal. No microorganism was isolated in blood, CSF or urine cultures. Chest X-rays and abdominal ultrasonography were normal. Blood samples were taken for viral serology. While investigating the cultures. Chest X-rays and abdominal ultrasonography were normal.

No microorganism was isolated in blood, CSF or urine. The serum was grossly lipemic. Lipid profile estimation showed markedly increased TG (760 mg/dl) and TC (257 mg/dl) levels. Lumbar puncture was performed, and the cerebrospinal fluid (CSF) analysis was normal. No microorganism was isolated in blood, CSF or urine cultures. Chest X-rays and abdominal ultrasonography were normal. Blood samples were taken for viral serology. While investigating the cultures. Chest X-rays and abdominal ultrasonography were normal.

Hyperlipidemia was eventually detected as positive, and the infant’s fever has resolved on the ninth day.

Discussion
Secondary causes of hyperlipidemia include hypothyroidism, nephrotic syndrome, biliary atresia, glycogen storage disease, Niemann-Pick disease, Tay-Sachs disease, systemic lupus erythematosus, hepatitis, and anorexia nervosa [3]. Certain medications exacerbate hyperlipidemia, including isotretinoin, thiazide diuretics, oral contraceptives, steroids, β-blockers, immunosuppressants, protease inhibitors used in the treatment of human immunodeficiency virus (HIV), and anticonvulsants [3-5]. Among these, only the use of anticonvulsant was determined in our patient. Because hyperlipidemia turned up spontaneously normal level, we didn’t need to investigate other causes.

Some authors have reported that hepatic enzyme-inducing antiepileptic drugs cause not only long-term increases in serum TC levels, but also short-term increases (over the first year of treatment) in serum levels of TC and TG [4,5]. Sönmez et al. [6] showed that plasma lipoprotein (α) levels were significantly increased during treatment with phenobarbital, carbamazepine, and sodium valproate, and they stated that the results of the studies concerning the effect of antiepileptic drugs on serum lipids are controversial. This is the first case in the literature in which hyperlipidemia was due to rectal phenobarbital use.

In our case, the development of hyperlipidemia in such a short time is remarkable. Yukawa et al. [7] reported that the result indicated that the mean volume of distribution/bioavailability in neonates and infants treated with rectal administration was similar to that obtained in a previous population pharmacokinetic study following intravenous administration [8]. The development of hyperlipidemiain a such short time may be attributed to the rapid increase in serum levels of the drug and the direct involvement of the liver.

In conclusion, the present case indicates that serum lipid profiles...
should be monitored carefully in children receiving phenobarbital.

References
1. Eirís JM, Lojo S, Del Río MC, Novo I, Bravo M, et al. (1995) Effects of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy. Neurology 45: 1155-1157.
2. Matsuda I, Higashi A, Inotsume N (1989) Physiologic and metabolic aspects of anticonvulsants. Pediatr Clin North Am 36: 1099-1111.
3. Behrman RE, Kliegman RM, Jenson HB (2011) Defects in Metabolism of Lipids, Greenbaum LA, Nelson Textbook of Pediatrics, (17thedn): 475-477
4. Luoma PV, Sotaniemi EA, Arranto AJ (1983) Serum LDL cholesterol, the LDL/HDL cholesterol ratio and liver microsomal enzyme induction evaluated by antipyrine kinetics. Scand J Clin Lab Invest 43: 671-675.
5. Isojärvi JI, Pakarinen AJ, Myllylä VV (1993) Serum lipid levels during carbamazepine medication. A prospective study. Arch Neurol 50: 590-593.
6. Sonmez FM, Demir E, Orem A, Yildirim S, Orhan F, et al. (2006) Effect of antiepileptic drugs on plasma lipids, lipoprotein (a), and liver enzymes. J Child Neurol 21: 70-74.
7. Yukawa E, Suematsu F, Yukawa M, Minemoto M (2005) Population pharmacokinetic investigation of phenobarbital by mixed effect modelling using routine clinical pharmacokinetic data in Japanese neonates and infants. J Clin Pharm Ther 30: 159-163.
8. Grasela TH Jr, Donn SM (1985) Neonatal population pharmacokinetics of phenobarbital derived from routine clinical data. Dev Pharmacol Ther 8: 374-383.