

Methotrexate/naproxen-associated severe hepatitis in a child with juvenile idiopathic arthritis

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ABSTRACT

Methotrexate (MTX) is a cornerstone in the treatment of juvenile idiopathic arthritis (JIA). Although associated with many mild adverse effects, the short and long-term safety of MTX in JIA has been excellent. While many JIA children treated with MTX develop liver enzyme abnormalities no cases of irreversible liver damage or of severe non-infectious hepatitis with Reye-like features have been reported in non-systemic JIA. We report a 2-year-old girl with oligoarthritis whose liver enzyme increased to greater than 45 times the upper limit of normal, and developed hypoglycemia and hyperammonemia after 10 months of MTX and naproxen therapy. An infectious and metabolic work-up for other causes was unremarkable. She recovered completely after folinic acid therapy; MTX and naproxen was not restarted. While very rare in JIA, MTX in synergism with naproxen can induce severe liver toxicity and it is important to screen children for liver enzyme abnormalities.

Introduction

Methotrexate (MTX) is a cornerstone in the treatment of children with juvenile idiopathic arthritis (JIA) (1). The overall safety profile of MTX is excellent (2). Cases of irreversible liver damage and cirrhosis have not been reported in children, although transient elevated liver enzymes are common (about 15% in various series) (1-8). Acute severe liver toxicity, observed rarely in the adult rheumatoid arthritis (RA) population (9, 10), has not been reported in children without systemic JIA. The frequency and severity of liver enzyme abnormalities are significantly less in children treated with naproxen as compared to salicylates (11-14). We describe a case of severe hepatitis associated with MTX in synergism with naproxen in a previously healthy child with JIA.

Case report

A Caucasian female was diagnosed with oligoarthritis JIA at 13 months of age. Initial therapy with naproxen and oral corticosteroids resulted only in a partial response. Three months after diagnosis oral MTX was started, 5 mg/week

(~12 mg/m²) with folic acid 0.5 mg/d. Due to a lack of significant response at 3 months, oral MTX was increased to 7.5 mg weekly (~17.5 mg/m²/week). Naprosyn was continued for symptoms of stiffness and pain. Routine laboratory examinations, including aspartate aminotransferase (AST) and albumin drawn every 6 weeks were normal until 8 months of therapy when she had an AST of 88 U/L (normal 10-55 U/L). One dose of MTX was skipped. At 10 months on the day she received MTX her AST was later found to be 2372 U/L. MTX and naproxen were then discontinued. Her cumulative dose of MTX was 282.5 mg (~71 mg/1.73 m²). She was not taking other medications or additives. She had mild upper respiratory symptoms with 2 episodes of morning emesis and was mildly lethargic. She was afebrile, anicteric with mild hepatomegaly. Three days later her AST increased to 2657 U/L, and alanine aminotransferase (ALT) was 5016 U/L (0-45 U/L), gamma-glutamyl transpeptidase (GGT) 237 U/L (0-35 U/L) and lactate dehydrogenase (LDH) 1540 U/L (140-320 U/L). She had hypoglycemia of 38 mg/dL and her ammonia level was mildly elevated on several occasions (68, 71, 93 umol/L – normal 11-38 umol/L). Her complete blood count, erythrocyte sedimentation rate, creatine phosphokinase, alkaline phosphatase, total bilirubin, albumin, international normalized ratio and prothrombin time were normal. The MTX serum level 3 days after the last dose, was lower than the limit for detection. Viral hepatitis, including hepatitis A, B and C, cytomegalovirus and Epstein-Barr virus, were excluded by serology. Alpha-1-antitrypsin, lactate and pyruvate levels were normal. Liver ultrasound revealed borderline enlargement but was otherwise normal. The patient was hospitalized and was treated with 10% intravenous dextrose solution and intravenous folinic acid, 5 mg every 6 hours for five days. A liver biopsy was considered; however, by day 5 of admission her ammonia and glucose level had normalized without need for intravenous therapy and liver enzymes were improving. By discharge (after 8 days) AST was 71 U/L, ALT 399 U/L, GGT 156 U/L and LDH 291 U/L.

Methotrexate was not resumed despite later complete normalization of liver enzymes and she has not had further elevations in her liver enzymes. Later work-up for additional metabolic causes of liver toxicity including organic acids, blood and urine acylcarnitine and amino acid profiles was negative.

Discussion

We described a child with oligoarthritis JIA treated with MTX and naproxen who developed severe hepatitis with hypoglycemia and hyperammonemia, without severe encephalopathy and coagulation abnormalities. This is the first case of severe hepatitis associated with MTX and naproxen we could find in a pediatric JIA patient without systemic arthritis. The marked elevation in liver enzymes (ALT > 100 times normal, AST > 45 times normal) far exceed the usual MTX or naproxen-associated liver enzyme increases (3-5, 11). The most likely etiology was MTX toxicity in synergism with naproxen, perhaps triggered by a virus, although no virus of those typically causing hepatitis was detected. While naproxen and MTX can alter each other's drug kinetics (15), a study by Ortiz *et al.* did not show a correlation between concurrent use of both medications and elevated liver enzymes (16). In addition while liver enzyme abnormalities are commonly seen during salicylate treatment of JIA (especially systemic) or rheumatic fever, these are much less common in response to naproxen (11-14). It is not clear whether the oral administration of a relatively high dose of MTX (17.5 mg/m²/week), usually administered parenterally to maximize absorption (17), had an effect on the development or the degree of hepatitis due to the first pass effect in the liver. Polymorphisms in folate carriers and polyglutamation enzymes (not checked in this patient) have been shown to affect intracellular MTX and metabolite concentrations (18). We did not find an occult metabolic disorder as a predisposing factor. A liver biopsy was not obtained since the patient improved rapidly after the start of folinic acid therapy while a biopsy was contemplated. A retrospective study has shown that folinic acid

given the day after MTX might reduce adverse effects, including liver enzyme abnormalities, without decreasing the effect of MTX (19). Intracellular hepatic polyglutamate metabolites of MTX have been shown to deplete hepatic folate stores, a process reversible with folinic acid therapy (20). Folinic acid was therefore administered to antagonize the intracellular polyglutamate metabolites of MTX and not to clear circulating MTX, since MTX serum levels were already undetectable. The rapid improvement after folinic acid repletion further supports the association of MTX and hepatitis.

Our patient recovered completely and 3.5 years after the event there is no clinical or biochemical evidence of chronic liver damage. Formal guidelines for the frequency of liver enzyme testing in MTX have not been established for JIA since no cases of irreversible liver damage have been reported in children (2-8). While no large cost benefit studies have been done in JIA and therefore there is no consensus on the frequency of liver enzyme testing, there is a consensus on the need to periodically test these enzymes. A recent study of 89 patients in one center found that testing at 3-month intervals detected abnormalities as often as monthly testing (16). Our patient was relatively asymptomatic and without routine testing her hepatitis may have only been discovered later and if not from another undiscovered cause may have resulted in damage.

While extremely rare, severe hepatitis may occur during MTX treatment of JIA, perhaps in synergism with NSAID therapy, and it is important to continue to routinely screen children for liver enzyme abnormalities.

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