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Case Report

NITROFURANTOIN-INDUCED ACUTE LIVER DAMAGE IN PREGNANCY

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This article presents a rare case of acute toxic hepatitis in thirty-one-year old primigravida. In the 36th week of gestation, the patient was introduced nitrofurantoin 100 mg a day due to symptoms of dysuria and enterococcus isolated from urine culture. After induced delivery at term because of hypertension, repeated laboratory findings showed increased aspartate aminotransferase (AST) and *alanine aminotransferase* (ALT) and negative hepatitis C and B markers. The patient was subicteric at the time. Coagulation and complete blood count values were within the normal range. Nitrofurantoin therapy was discontinued. Abdominal ultrasound was normal with the exception of a slight hepatomegaly without any lesions, focal or diffuse. Given that discontinuation of nitrofurantoin and introduction of methylprednisolon therapy significantly lowered liver enzyme levels, restoring most of them to normal, we concluded that this was probably the case of toxic liver damage caused by nitrofurantoin.

KEY WORDS: *antibiotic, hepatotoxicity, pregnant woman, therapy*

Nitrofurantoin (NF) is a synthetic antibiotic which belongs to the nitrofuran group with nitrofurazon. It inhibits numerous bacterial enzymes involved in DNA and RNA synthesis, as well as carbohydrate metabolism and other metabolic pathways. It is clinically useful against a wide spectrum of gram-positive (*Staphylococcus*, *Streptococcus*, *Enterococcus*) and gram-negative (*E. coli*, *Serratia* sp., *Enterobacter*, *Klebsiella* and *Citrobacter*) bacteria. As such, NF is used widely in treatment and prophylaxis of recurrent urinary tract infections in pregnancy and in general gynaecology (1).

Different xenobiotics, including drugs, may cause liver damage that usually resembles either acute hepatitis, cholestatic liver disease or mixed hepatitis and cholestasis. However, drug-induced liver injury can mimic all forms of acute and chronic hepatobiliary diseases (2).

It has become customary to divide liver diseases in pregnancy into those which coincide with pregnancy and chronic liver disease preceding pregnancy. Toxic drug-induced hepatitis in pregnancy belongs to the first category. On the other hand, there are liver changes induced by pregnancy, which disappear after delivery such as hepatocellular damage caused by severe preeclampsia, eclampsia, and/or the HELLP syndrome (from: Hemolysis, Elevated Liver and a Low Platelet).

This article presents a rare case of acute toxic hepatitis in pregnancy. After excluding all other factors, we narrowed its cause down to nitrofurantoin.

Case presentation

Thirty one-year old primigravida was admitted to the pregnancy ward in the 38th week of gestation for check up and pregnancy termination. Termination

was indicated due to elevated blood pressure (140/95 mm Hg to 160/100 mm Hg) without proteinuria or oedema. On admittance, the patient had irregular contractions and was dilated 4 cm to 5 cm. Ultrasound check up showed foetus presentating head first, with normal biophysical profile, and normal Doppler sonography of the foetal and maternal circulation. Anamnesis showed allergy to penicillin and family history of hypertonia. During the second trimester of pregnancy, the patient was treated with cefalexin 2x1.0 g due to *E. coli* isolated from urine culture. From the 34th week of gestation onward she was taking atenolol 1x25 mg prescribed by primary care gynaecologist to treat slightly elevated blood pressure. However, blood pressure was never above 150/95 mm Hg. Coagulation, liver function, complete blood count (CBC), electrolytes, creatinine, and blood uric acid were all within normal ranges during pregnancy. Repeated urine culture was sterile as well. In the 36th week of gestation, the patient started to receive daily doses of 1x100 mg of nitrofurantoin (Belupo, Croatia) due to symptoms of dysuria and enterococcus isolated from urine culture. Excipients were as follows: maize starch, talc, magnesium stearate, carmellose sodium, titanium dioxide (E171), tartrazine (E102), indigo carmine (E132), and gelatine. The patient was taking nitrofurantoin for 10 days.

After admittance to the hospital, laboratory tests showed elevated liver enzymes with normal CBC and coagulogram, without haemolysis (Table 1). Also, no jaundice or itching was detected. Because of the elevated blood pressure (150/100 mm Hg), elevated liver enzymes, 37 weeks of gestation, and favourable genital finding, delivery was induced with amniotomy and oxytocin infusion (Novartis Pharma Stein AG, Switzerland), 5 IU of oxytocin in 500 mL physiological saline at 30 mL h^{-1}. A live, eutrophic male child weighing 2880 g and 48 cm long, was delivered with Apgar score 10/10. Manual exploration of the uterus was performed to remove remaining placenta and the patient was intravenously receiving anaesthetics alfentanil (Janssen Pharmaceutica NV, Belgium), 1x1 mg and propofol 1 % (Fresenius Kabi Austria GmbH, Austria), 1x200 mg. The patient received amoxicillin 1x1.2 mg iv, (Pliva Hrvatska, Croatia) as prophylaxis. Repeated laboratory findings the following day showed increased AST and ALT values, negative hepatitis C and B markers, and subicterus. NF therapy was discontinued.

Since we identified several signs of liver failure such as permanent elevation of liver enzymes and subicterus, the patient was transferred to the intensive care unit. There she was repeatedly tested for liver enzymes. Coagulation and CBC were within the

Table 1 *Results of blood analysis after patient's admittance to hospital*

Parameters	Days					Normal ranges
	1st		2nd	7th	11th	
	17:00 h	21:00 h	7:00 h			
platelets x 10^9 / L^{-1}	209	206	195	352		150 to 350
D-dimer / µg L^{-1}	253		**313**	**284**		50 to 228
AST / U L^{-1}	420	434	846	**73**	36	11 to 38
ALT / U L^{-1}	**861**	**940**	**1425**	**551**	**241**	12 to 44
LDH / U L^{-1}			**665**	231		0 to 240
gamma-GT / U L^{-1}			45	57		11 to 53
alkaline phosphatase / U L^{-1}			**273**	**153**		45 to 127
glucose / mmol L^{-1}	5.2					3.8 to 6.0
urea / mmol L^{-1}	5.4					3.0 to 8.0
creatinine / µmol L^{-1}	87					75 to 125
uric acid / µmol L^{-1}	347		423	263		140 to 420
total bilirubin / mmol L^{-1}			**20.8**	10.4		3.0 to 17.0
direct bilirubin / mmol L^{-1}			**8.0**	2.4		0.0 to 3.4
sodium / mmol L^{-1}	134					135 to 150
potassium / mmol L^{-1}	4.2					3.8 to 5.2
chloride / mmol L^{-1}	103					95 to 105

AST: aspartate aminotranspherase; ALT: alanine aminotranspherase; LDH: lactate dehydrogenase; gamma-GT: gamma-glutamyl transpeptidase
Bolded values are out of the normal range

normal range. Abdominal ultrasound was normal with the exception of a slight hepatomegaly without any lesions, focal or diffuse. Methylprednisolone (Pharmacia Upjohn, USA) therapy, 80 mg per day was introduced with crystalloid, colloid, and 5 % glucose infusions. Given that discontinuation of NF and the above mentioned therapy significantly lowered liver enzyme levels, restoring most of them to normal, we concluded that this was probably the case of toxic liver damage caused by NF. With improved liver function, the patient was transferred back to the obstetrics and gynaecology ward (Table 1).

The course of postpartum period was normal, and the patient was discharged with normal blood pressure. However, a regular check up with a hepatologist was strongly recommended.

DISCUSSION

Being a member of a nitroaryl drug group, nitrofurantoin is a lipophilic xenobiotic. Consequently, it is readily metabolised by cytochrome P450 before elimination. One of the enzymes involved in nitroaryl reduction is NADPH-cytochrome P450 reductase localised mainly in the hepatic endoplasmic reticulum. Oxidation and reduction of nitroaryls depend on the NADPH conditions under which this oxidative system catalyses both enzymatic reactions. Therefore, oxidative and reductive pathways may occur as competitive and simultaneous processes, and the toxicity of lipophilic nitroaryls associated with oxidative stress may be a consequence of relative contributions from both metabolic pathways (3).

Nitrofurantoin is effective in eliminating both Gram-negative and Gram-positive pathogens from the urinary tract. Rapid absorption and excretion by kidneys gives NF its therapeutic value as a urinary antibacterial drug. Its half life ranges from 20 min to 1 h (3). The risk of adverse reactions to NF increases with age, and is more common in women than in men (89 % vs. 11 %) (4). In patients with normal renal function, systemic accumulation of the drug is scarce. However, patients with creatinine clearance of 35 mL min^{-1} to 40 mL min^{-1} or a clinically significant elevation of serum creatinine should not receive NF (5). For this reason, patients receiving long-term NF therapy are routinely monitored for changes in renal function (6).

NF crosses the placental barrier and can cause haemolytic anaemia of the foetus due to its immature erythrocyte enzyme system (7).

The most common adverse events associated with NF include nausea, headache, and flatulence (4). Although rare, serious adverse events in patients receiving long-term (>6 months), low-dose NF prophylaxis have also been reported. These include chronic pulmonary reactions, hepatic injury, peripheral neuropathy, and hypersensitivity to NF (4, 8-12). Here we report the case of acute liver damage caused by administration of NF. Previous studies indicate that hepatotoxicity is the most lethal NF-related adverse reaction (8-12). NF probably produces massive oxidative stress in hepatocytes, due to the nitroreductive metabolism of the drug (13). However, cases have been reported of immune-mediated liver injury (14, 15). This supported by lupus erythematosus-like presentation, autoantibodies against nuclear antigen and smooth muscle, and by hypergammaglobulinaemia. In general, determining the cause of hepatic toxicity is complex because this requires liver biopsy and drug rechallenge.

Our patient was taking NF for ten days. This may be too short a period for a hepatotoxic reaction to develop. She had normal creatinine clearance; there were no signs of haemolytic anaemia in either the mother or the child, and the mother's liver enzyme levels declined after discontinuation of NF. We can conclude that NF was responsible for acute liver damage either by direct action or as a result of pregnancy-related metabolic changes. Considering the incidence of liver damage in the HELPP syndrome or preeclampsia and/or eclampsia, assessment of the liver function and patient's general condition is strongly recommended before administering NF to pregnant women.

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Sažetak

AKUTNO OŠTEĆENJE JETRE UZROKOVANO PRIMJENOM NITROFURANTOINA U TRUDNOĆI

Autori prikazuju rijedak slučaj akutnog oštećenja jetre - akutni toksični hepatitis u 31-godišnje primigravide. U 36. tjednu trudnoće zbog dizuričnih smetnji i dokazanog enterokoka u urinokulturi ordiniran je nitrofurantoin 1x100 mg. Nakon terminski induciranoga poroda zbog hipertenzije, ponovljene laboratorijske pretrage upućuju na značajno povišenje vrijednosti jetrenih enzima uz negativne markere na C i B-hepatitis te subikterus. Koagulogram i crvena krvna slika bili su uredni. Nitrofurantoin se isključuje iz terapije. Abdominalni ultrazvuk upućuje na hepatomegaliju bez fokalnih ili difuznih oštećenja.
Nakon isključenja nitrofurantoina iz terapije uz metilprednizolon, vrijednosti jetrenih enzima se normaliziraju, što potvrđuje slučaj toksičnog oštećenja jetre uzrokovanog nitrofurantoinom.

KLJUČNE RIJEČI: *antibiotik, gravidne žene, hepatotoksičnost, terapija*

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