Dipyrone-Induced Oligohydramnios and Ductus Arteriosus Restriction

Amir Weintraub MD and David Mankuta MD MHA

Department of Obstetrics and Gynecology, Hadassah University Hospital and Hebrew University-Hadassah Medical School, Jerusalem, Israel

Key words: dipyrone, non-steroidal anti-inflammatory drugs, oligohydramnios, ductus arteriosus restriction

IMAJ 2006;8:722–723

Dipyrone (Optalgin®) is a non-steroidal anti-inflammatory drug that inhibits cyclooxygenase-1 and cyclooxygenase-2 activity, thereby reducing the production of prostaglandin E2 and E1. This effect is not unique to pregnant women or fetuses but occurs widely in adults, particularly in patients with contracted intravascular fluid volume as a result of congestive heart failure, cirrhosis, diuretic use, or restricted sodium intake. All these clinical situations are at increased risk for NSAID-related changes in renal function. The drug is widely used in many countries as an analgetic and antipyretic agent, especially in some parts of Europe, South America and Asia. It was banned in the United States by the Food and Drug Administration in 1977 because of a possible association with agranulocytosis. In contrast to other NSAIDs, precautions regarding the use of dipyrone during pregnancy are not well defined and information on its safety in pregnancy is scarce. A weak association with Wilms' tumor was found in children of women who took dipyrone during pregnancy [1]. Other suggested adverse effects are leukemia and neural tube defects found in mice. The association of NSAIDs with oligohydramnios was described in a series of patients who took indomethacin [2], and in only two case reports of dipyrone use. We report another case of dipyrone-associated oligohydramnios with fetal ductus arteriosus restriction.

Patient Description

A 26 year old woman in the 35th week of her first pregnancy was admitted with an E*scherichia coli* urinary tract infection. Her past medical history was uneventful. Her pregnancy was also uneventful, except for a positive triple test. All sonographic studies during pregnancy were normal, including amniotic fluid evaluated 8 days before admission to the hospital. Three days before her index admission she took dipyrone (Optalgin®, V-Talgin®, Phanalgin®), 6 g a day for 3 days, and papaverine HCL to relieve her urinary symptoms. Her physical examination was normal except for left flank tenderness. She was normotensive. Her kidney function tests were within normal values for pregnant women; urea 3.0 mmol/L (normal non-pregnant values 3.3–6.5 mmol/L), creatinine 44 µmol/L (normal non-pregnant 60–106 µmol/L), uric acid 184 µmol/L (normal 150–380 µmol/L). Complete blood count was normal as were blood electrolytes.

Obstetric ultrasound examination revealed oligohydramnios with an amniotic fluid index of 40 mm (normal 50–240 mm) and restricted ductus arteriosus. Analgesic treatment was replaced with paracetamol, and antibiotic treatment with intravenous cefuroxime was initiated. Serial fetal sonographic examinations showed an improvement in ductus arteriosus width and in amniotic fluid volume 2 days after dipyrone cessation, which gradually returned to normal (AFI 140 mm) within 1 week. A normal healthy baby was vaginally born in the 40th week of her pregnancy.

Comment

We describe a case of oligohydramnios that might have been caused by dipyrone use. In this case, oligohydramnios and ductus arteriosus narrowing occurred following the use of the drug and resolved soon after its discontinuation. This case adds to two previously described cases and this report is the first to describe narrowing of the ductus arteriosus in such circumstances [3,4]. Catalan et al. [3] reported a case of a term pregnant woman who suffered from renal colic treated with high dose dipyrone and who developed oligohydramnios 60 hours after treatment initiation. Thirty-five hours after dipyrone was discontinued the AFI returned to normal. In the second report, Sanchez-de-la-Nieta and colleagues [4] described a healthy 21 year old woman who developed maternal acute renal failure, rash and oligohydramnios (AFI 20 mm) 10 days after taking dipyrone, 1.5–3 g a day for 10 days, to relieve her back pain. Following treatment with intravenous fluids and dipyrone discontinuation the rash disappeared and blood analyses and the AFI returned to normal (AFI 60 mm).

Dipyrone associated with renal failure during pregnancy may be explained by two possible mechanisms: a) reversible renal ischemia secondary to inhibition of prostaglandin synthesis, and b) acute tubulointerstitial nephritis. Both cases, as well as ours, suggest a possible effect of the drug on fetal kidney function, reflected by the reduction in amniotic fluid index. The two previous case reports mention the use of high dose magnesium dipyrone, whereas in our patient the compound used was sodium dipyrone. Cases of agranulocytosis and aplastic anemia were reported with the sodium compound but we are not aware of differences in effect between magnesium and sodium on the ductus arteriousus or fetal kidneys.

In all cases described, including the present report, dipyrone withdrawal was associated with a dramatic improvement in the amniotic fluid volume. In these cases, the mechanism of oligohydramnios is probably related to the reduced produc-

NSAID = non-steroidal anti-inflammatory drug

AFI = amniotic fluid index

tion of prostaglandins, which are essential for maintaining renal blood flow during intrauterine life. The existence of a patent ductus arteriosus during pregnancy is also prostaglandin-dependent. PGE_2 is involved in the regulation of sodium reabsorption and acts as a counter-regulatory factor under conditions of increased sodium reabsorption. PGI_2 (and possibly PGE_2) increases potassium secretion mainly by stimulating secretion of renin and activating the renin-angiotensin system, which leads to increased secretion of aldosterone. In addition, this vasodilatory prostaglandin increases renal blood flow and glomerular filtration rate. In healthy hydrated individuals, renal prostaglandins do not play a major role in sodium and water homeostasis. Under conditions of decreased renal perfusion, the production of renal prostaglandins serves as an important compensatory mechanism. Increased salt and water retention is a mechanism that causes blood pressure increase during therapy with NSAIDs in adults. Perhaps a similar mechanism reduces the glomerular filtration rate in fetuses, resulting in oligohydramnios. The exact mechanism of oligohydramnios with these drugs is unknown. It could be related to fetal oliguria due to the increase of arginine vasopressin in the fetal collecting duct induced by prostaglandin inhibition, as has been shown in animal models.

In our patient, the dose of self-administered sodium dypirone was high, and part of the drug probably entered the fetal circulation transplacentally. Sodium dypirone can induce two different forms of acute renal failure: a) reversible renal ischemia secondary to inhibition of prostaglandin synthesis, appearing 3–7 days after initiation of therapy when drug levels inhibit prostaglandin synthesis; and b) acute tubulointerstitial nephritis. In our patient two fetal effects were seen: oligohydramnios and the constriction of the ductus arteriosus. In our patient as well as in the two patients previously reported, high doses of dipyrone were used by pregnant women. In one report, acute renal failure occurred in the mother together with oligohydramnios in the fetus [3]. In our case as in one other case report, maternal renal function was normal. The present report is the first to describe an effect on the ductus arteriosus. In all three case reports the withdrawal of dypirone was associated with an increase of maternal renal function and reduced fetal effects. We suggest that dipyrone is a possible cause for both adverse side effects [5]. Prior studies have not evaluated the function of the ductus. Our case report suggests a close relationship between restriction of the ductus size and oligohydramnios and may shed light on the mechanism of the latter.

In summary, prior case reports have shown an association between dipyrone use and oligohydramnios. In our case, oligohydramnios was also associated with restriction of the ductus arteriosus; both were reversible. Because of this possible association, we recommend that dipyrone be used with caution. Since all cases were induced by high doses of dipyrone, it is feasible that low dosage and limited length of usage should be practiced until further safety studies are performed. We recommend prescribing other analgesic drugs – for example, acetaminophen (Tylenol®, Acamol®, Paracetamol®) or morphine derivatives in cases of more severe pain – that have few long-term side effects on the fetus. In cases where inadvertent high dosages are used in the third trimester we recommend evaluation of the width of the ductus arteriosus, the amniotic fluid volume, maternal renal function, and complete blood counts.

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Correspondence: Dr. D. Mankuta, Dept. of Obstetrics and Gynecology, Hebrew University Hospital, P.O. Box 12000, Jerusalem 91120, Israel.
Phone: (972-2) 677-6484
Fax: (972-2) 579-1070
email: mankuta@yahoo.com