

# Mesalazine as a cause of fetal anemia and hydrops fetalis

## A case report

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### Abstract

**Rationale:** Mesalazine and its prodrug sulfasalazine are both used for inflammatory bowel disease. Sulfasalazine has been associated with hematological side-effects such as aplastic and hemolytic anemia in patients, but also in fetuses after intrauterine exposure. To our knowledge, we describe the first case of a fetus with severe anemia, and subsequent hydrops, where this drug was found at concentrations in the fetus corresponding to those in the mother and most likely responsible for the fetal condition.

**Patient concerns:** A uniparous woman was referred at 31 weeks of gestation due to a hydropic fetus with massive ascites and cardiomegaly.

**Diagnoses:** The patient had Crohn's disease and was thus treated with 4 g mesalazine daily. The fetus had severe anemia with an initial hemoglobin level of 51 g/L.

**Interventions:** The maternal medication was discontinued and four intrauterine erythrocyte transfusions were given during three weeks. Plasma samples were drawn from mother and fetus during cordocentesis for later analysis of mesalazine.

**Outcomes:** A healthy baby was born after 37 full weeks of gestation. Plasma levels of mesalazine were non-conspicuous in neither mother nor fetus. The mesalazine half-life in the fetus (37 h) was half that of the mother (80 h), both considerably longer than previously reported (about 19 h).

**Lessons:** A causal relationship must be suspected between the fetal anemia and the maternal use of mesalazine. This fetal side-effect should be considered in pregnant women on mesalazine (and its prodrug sulfasalazine).

**Abbreviation:** Hb = hemoglobin.

**Keywords:** adverse drug reaction, cordocentesis, fetal anemia, inflammatory bowel disease, intrauterine diagnosis, mesalazine, pharmacokinetics

## 1. Introduction

According to the Swedish Medical Birth Register 1302 pregnancies were reported exposed to sulfasalazine between 1973 and 2012, and 2072 to mesalazine, but these numbers may be underestimated. These 2 drugs have the same indications and sulfasalazine is cleaved to sulfapyridine and mesalazine (5-aminosalicylic acid) by the colonic microbiota.<sup>[1]</sup> For the majority of patients the indications are

maternal intestinal inflammatory disorders, that is, Crohn disease or ulcerative colitis with a prevalence estimated to 1% of the total population. Common side effects include headache, tinnitus, and fever but also hematological effects like leucopenia and thrombocytopenia have been reported. In laboratory animal set ups, the risk for fetal malformation seems low but still this drug should be carefully monitored and preferably abstained during pregnancy (Category C). Already in 1984 "bone marrow necrosis" was reported by Van de Pette et al<sup>[2]</sup> in a male patient on sulfasalazine and 2 years later Zwi and Becroft<sup>[3]</sup> described a case of fetal loss due to "aplastic anemia" with unknown etiology even though this patient was on sulfasalazine which was discontinued early in pregnancy. In a case report published in 2004 by Bokström et al<sup>[4]</sup> the association between fetal anemia requiring fetal transfusion and sulfasalazine was strongly suspected but no pharmacological studies were undertaken. Thus, fetal pharmacological side effects in pregnant women on sulfasalazine are not that well documented. Here, we report a case where the causality between maternal medication of mesalazine and fetal anemia, based on the clinical course and fetal and maternal levels of the drug, is considered likely.

## 2. Case report

The patient was a 43-year-old Caucasian uniparous trigravida, suffering from Crohn disease and on medication with mesalazine (Pentasa) 4 g/d. She was referred at 31 weeks of gestation with a hydropic fetus with massive ascites, suffering from cardiomegaly with elevated peak velocity (55 cm/s) in the middle cerebral artery and opted for intrauterine cordocentesis and subsequent transfusion. Infectious or chromosomal etiologies had already

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*Established facts: Severe fetal anemia may lead to hydrops fetalis; mesalazine is known to have hematological side effects. Novel insights: Mesalazine does pass the placenta; fetal plasma concentrations equal maternal levels; and this may lead to serious fetal side effects.*

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**Table 1****Maternal and fetal plasma concentrations of mesalazine measured by LC-HRMS.**

Time after dose, h	Maternal plasma conc., ng/mL	Fetal plasma conc., ng/mL
12.5	3.89	3.48
162	1.08	0.22
282	ND	ND

LC-HRMS=liquid chromatography coupled to high-resolution mass spectrometry, ND=not detectable.

been ruled out. She did not carry any erythrocyte antibodies and according to the pediatric cardiologist the enlarged fetal heart was not the primary cause of the hydrops. The hemoglobin (Hb) level at cordocentesis revealed a value of 51 g/L (ref.  $191 \pm 22^{[5]}$ ) and platelets  $94 \times 10^9/L$  ( $203 \pm 58.6^{[6]}$ ). Sixty milliliters of fresh, packed, and irrigated 0 rhesus blood group, D antigen negative red blood cells was given and samples were sent for hematological indices and liver enzymes. The blood-count came back and revealed schistocytosis which may indicate hemolysis. As there was a suspicion that this was due to the mother's medication, the referring unit was contacted and instructed to discontinue her medication. This was, however, not accomplished and 1 week later at her second visit at the Center of Fetal Medicine, the fetal Hb at cordocentesis was 61 g/L ( $185 \pm 20^{[5]}$ ) and platelets  $88 \times 10^9/L$ . A transfusion of 70 mL blood was given to the fetus and the maternal medication was withdrawn. The patient consented to extra sampling of both maternal and fetal blood for future analysis of mesalazine. Maternal and fetal blood was analyzed for mesalazine at the Department of Clinical Pharmacology at the Karolinska University Hospital. At the third transfusion at 33 weeks, the Hb level was 87 g/L and platelets  $80 \times 10^9/L$  and 90 mL blood was given. At 34 completed weeks the Hb count finally was 123 g/L ( $196 \pm 21^{[5]}$ ) and platelets  $149 \times 10^9/L$ , thus only 30 mL was transfused. So to summarize, in total 250 mL of packed erythrocytes were given at 4 occasions during a 3-week course. The massive fetal ascites, depicted by the abdominal circumference, measured +34% at 32 weeks. At 34 weeks, when the ascites was almost not visible, the abdominal circumference measured only +1.5%.

The course afterward was uneventful and she had a caesarean section, due to breech presentation, at 37 completed weeks and delivered a healthy infant, Apgar 7–8–9, weight 3100 g, and a Hb level of 154 g/L. Due to a transfusion-mediated low hematopoiesis, 3 top-up transfusions had to be administered, the first at 3 weeks postpartum.

This case was eventually reported as a suspected adverse drug reaction to the Swedish Medical Products Agency (Läkemedelsverket). The relationship between the intrauterine exposure of mesalazine and the fetal anemia was considered to be likely related to the drug.

### 2.1. Pharmacological analysis

Maternal and fetal plasma was analyzed by a specially developed ad hoc method utilizing liquid chromatography coupled to high-resolution mass spectrometry. Mesalazine pure substance was kindly provided by Cambrex AB (Karlskoga, Sweden). Measured concentrations are presented in Table 1.

Half-lives calculated from the first 2 measurements were 80 h for the mother and 37 h for the fetus.

### 3. Discussion

As can be seen in Table 1, fetal plasma levels of mesalazine were similar to maternal plasma levels 12 h post dose but the fetal half-life of the drug in the fetus was shorter than the half-life of the drug in the mother. No therapeutic range has been established for mesalazine. However, in a pharmacokinetic study by Wilding et al,<sup>[7]</sup> the plasma concentration 12 h post dose was between 100 and 200 ng/mL after a single dose of 1.5 g of mesalazine given as micropellets (similar to Pentasa) to healthy volunteers. The terminal half-life of mesalazine was estimated to 19.5 h, considerably shorter than in our patient and her fetus. By measuring mesalazine in both maternal and fetal plasma, we could exclude toxic accumulation in neither mother nor fetus. After cessation of the suspected culprit drug and fetal transfusions, a rapid resolution of hydrops fetalis and recovery of fetal Hb levels took place. However, the concentration–effect relationships between mesalazine and/or sulfasalazine exposure and various hematopoietic side effects is not fully understood.<sup>[1]</sup> Immunological mechanisms cannot be excluded. Numerous drugs have been associated with different antibody-mediated hemolytic mechanisms. Among them, sulfasalazine and the structural analog to mesalazine, the antimycobacterial agent 4-aminosalicylic acid, have been associated with immune hemolytic anemia with or without positive drug-induced antiglobulin tests.<sup>[8]</sup> Most cases of antenatal drug-induced anemia have been described with drugs causing oxidative stress to the erythrocytes. In the sulfasalazine case described by Bokström et al, immune-related mechanisms were suspected, however, not extensively investigated.<sup>[4]</sup> In the present case, a causal relationship between maternal mesalazine treatment and the fetal anemia must be suspected, whatever the exact mechanism.

### 4. Conclusion

We describe a case of fetal hydrops likely related to the maternal medication of mesalazine without achieving supratherapeutic levels in neither mother nor fetus. An association between maternal mesalazine treatment and fetal anemia must, therefore, be suspected and this should be considered in pregnant women on this medication.

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