Paracetamol Treatment for Patent Ductus Arteriosus, an Apparent Association with Acute Hemolysis in Three Preterm Infants: Case Series

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Established Facts and Novel Insights

- Paracetamol is a safe and effective therapy for hemodynamically significant patent ductus arteriosus (hsPDA). This report describes three preterm infants who were treated with paracetamol for hsPDA and developed acute hemolysis. As this side effect of paracetamol has not been reported previously and many preterm infants receive paracetamol for PDA closure, we advocate awareness.

Keywords
Case series · Hemolysis · Paracetamol · Patent ductus arteriosus · Preterm infants

Abstract
We report three preterm infants who were treated with paracetamol for hemodynamically significant patent ductus arteriosus and developed acute hemolysis. No other apparent cause of acute hemolysis was found during Neonatal Intensive Care Unit hospitalization. All three infants were born within 1 year. As this side effect of paracetamol has not been reported previously and many preterm infants receive paracetamol for PDA closure, we advocate awareness. We cannot be sure whether the hemolysis occurred due to an underlying cause that was augmented by paracetamol or whether the drug itself caused acute hemolysis in these preterm infants.

Introduction/Literature Review

Emerging evidence indicates that paracetamol is a safe and effective therapy for hemodynamically significant patent ductus arteriosus (hsPDA), with reports that it is being used increasingly in many neonatal intensive care units (NICUs) [1]. The safety profile of paracetamol has been found to be better than that of indomethacin and ibuprofen, with a lower rate of adverse gastrointestinal and renal effects [2] and no detrimental effect on cerebral oxygenation [3].

This report describes three preterm infants who were treated with paracetamol for hsPDA and developed acute hemolysis. The objective was to evaluate what is known in the medical literature as well as possible mechanisms for these findings.
**Case 1**

A female infant was delivered at 31 weeks of gestation with a birth weight of 1,116 grams. She needed continuous positive airway pressure for respiratory distress syndrome. Routine blood tests included direct Coombs test (DCT), which was negative, and glucose-6-phosphate dehydrogenase (G6PD) 15.8 Ug/Hb (N >10). At 3 days of age, a harsh systolic murmur was heard. Echocardiography showed hemodynamically significant patent ductus arteriosus (hsPDA), and intravenous (IV) paracetamol (S.A.L.F. 10 mg/mL) therapy was initiated at a dose of 60 mg/kg/day. Since repeat echocardiography showed no change in PDA diameter, with signs compatible with hsPDA, IV paracetamol was continued for 7 days with significant clinical and echocardiographic improvement. A day after treatment ended, her oxygen requirements increased, together with respiratory distress and tachycardia. Blood tests revealed a low hematocrit of 27.8% which was substantially lower than the hematocrit measured 2 days before and reticulocytes of 19% (Fig. 1). As total parental nutrition (TPN) was still being administered, blood chemistry revealed phosphate of 6.3 mg/dL and triglycerides of 95 mg/dL, both normal for age. Peripheral blood smear demonstrated mild spherocytosis, no elliptocytosis, no schistocytes, and markedly elevated bilirubin. Blood cultures and urine examination for cytomegalovirus (CMV) were negative. Liver enzymes were within normal range for age, lactate dehydrogenase (LDH) was 512 U/L (normal <225 U/L), and paracetamol serum levels were within normal range, 10 mg/L (normal <50 mg/L). As blood smear revealed only mild spherocytosis, mean corpuscular hemoglobin concentration divided by mean corpuscular volume was 0.32, and the eosin-5-maleimide binding test was 92.4%, excluding hereditary spherocytosis. She was treated with packed red blood cells (PRBCs), which resulted in clinical and laboratory stabilization. No other hemolytic crises occurred before discharge. A careful family history did not disclose any history of hemolytic crises. Blood tests including DCT, parvovirus B19, human immunodeficiency virus, syphilis, rubella, smear, blood, and urine cultures were normal. Abdominal and head ultrasound did not show bleeding (Table 1).

**Case 2**

A male infant was delivered at 27 weeks of gestation, with a birth weight of 1,020 grams. After birth, blood tests included DCT which was negative and G6PD levels were 17.2 Ug/Hb (normal >10). On day 8 of life, TPN was stopped successfully. A heart murmur was first auscultated at the age of 9 days. Echocardiography showed hsPDA, and paracetamol therapy, at a dose of 60 mg/kg/day, per os (100 mg/mL), was initiated. As echocardiography after 3 days of treatment still showed an hsPDA, therapy was continued 2 additional days. Echocardiography post-treatment showed a small, insignificant PDA with hematocrit of 32.5% and reticulocyte count of 2.3%. Three days after paracetamol was stopped, palor, tachypnea, and tachycardia were noticed. Hematocrit decreased to 21.2% with 22% reticulocytes, together with increased bilirubin level, which prompted phototherapy (Fig. 1). A thorough hemolytic investigation including peripheral blood smear demonstrated no elliptocytosis or schistocytes. Blood cultures and urinalysis for CMV were negative. Blood chemistry was within normal range for age, except for elevated LDH (Table 1). Paracetamol serum levels were within the normal range at 14 mg/L (normal <50 mg/dL). The infant was treated with PRBC, with stabilization of his hematocrit until home discharge.

**Case 3**

A female infant was delivered at 29 weeks of gestation, with a birth weight of 1,180 grams. Blood tests after birth included DCT, which was negative. G6PD levels were 13.9 Ug/Hb (normal >10). At 7 days, when oral nutrition consisted of 120 cc/kg/day, TPN was stopped successfully. At 9 days of age, after increased respiratory distress and harsh systolic murmur on physical examination, echocardiography demonstrated an hsPDA. A course of IV paracetamol (S.A.L.F. 10 mg/mL), 60 mg/kg/day, was initiated. Approximately 48 h later, hematocrit was decreased from 29.4% to 22.1%, with concomitant reticulocytosis and hyperbilirubinemia (Fig. 1), combined with increased respiratory demands and respiratory distress, indicating acute hemolysis. A thorough hemolytic investigation including peripheral blood smear demonstrated no elliptocytosis, no schistocytes, occasional spherocytes. Blood cultures and urinalysis for CMV were negative. Blood chemistry was within normal range for age except for elevated LDH (Table 1). Paracetamol serum levels were within normal range at 12 mg/dL (normal <50 mg/dL). The infant was treated with PRBC, with stabilization of his hematocrit until home discharge.

**Discussion/Conclusion**

In this case series, we report a possible adverse drug reaction (ADR) of acute hemolysis coinciding with paracetamol treatment for hsPDA, with no other specific cause for hemolysis found after extensive evaluation. The frequent use of off-label medications together

Table 1. Summary of the 3 preterm infants who reacted with acute hemolysis associated with paracetamol treatment

| Variable          | Case 1 | Case 2 | Case 3 |
|-------------------|--------|--------|--------|
| Gestational age, weeks | 31     | 27     | 29     |
| Gravidity, parity  | G1 P0  | G1 P0  | G3 P2  |
| IV/PO             | IV     | PO     | IV     |
| Paracetamol total dosage, mg/kg | 360    | 294    | 101    |
| Paracetamol per dose, mg/kg   | 15     | 15     | 15     |
| Bilirubin, mg/dL         | 17.3   | 15.7   | 16.7   |
| LDH U/L (normal <225 U/L) | 512    | 487    | 617    |
| Phosphatase, mg/dL       | 6.3    | 5.9    | 6.9    |
| Triglycerides, mg/dL     | 95     | 162    | 141    |
| Phototherapy, days       | 5      | 4      | 7      |

PO, per os.
with developmental changes that occur in children from birth to adolescence results in an elevated risk for ADRs [4]. The Naranjo scale is a systematic assessment of the likelihood of an ADR, which is well validated in children [5]. We analyzed our 3 cases using the Naranjo scale and found a score of 5, which is compatible with probable ADR (Table 2). All three infants were treated within 1 year (August 2019–August 2020) and were among 17 preterm infants who were treated with paracetamol for hsPDA during this period. No other apparent cause of

Table 2. Naranjo questions for the ADR of paracetamol in the case series (total score = 5, probable ADR)

| Question                                                                 | Yes | No | Unknown |
|--------------------------------------------------------------------------|-----|----|---------|
| 1) Are there previous conclusive reports of this reaction?               | X   |    |         |
| 2) Did the adverse event appear after the drug was given?                |     | X  |         |
| 3) Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? | X   |    |         |
| 4) Did the adverse reaction reappear upon re-administering the drug?    |     | X  |         |
| 5) Were there other possible causes for the reaction?                    |     | X  |         |
| 6) Did the adverse reaction reappear upon administration of placebo?    |     |    | X       |
| 7) Was the drug detected in the blood or other fluids in toxic concentrations? | X   |    |         |
| 8) Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose? | X   |    |         |
| 9) Did the patient have a similar reaction to the drug or a related agent in the past? | X   |    |         |
| 10) Was the adverse event confirmed by any other objective evidence?     |     |    | X       |

Fig. 1. Hemoglobin, reticulocytes and bilirubin values before during and after the hemolytic events.
acute hemolysis in these infants was found during NICU hospitalization. As we were unsure about the exact mechanism of the hemolysis and as paracetamol is a vital therapy for fever during childhood, we instruct parents and pediatricians to give paracetamol under close supervision for signs of hemolysis. Follow-up with pediatricians in the outpatient setting did not reveal a recurrence of this reaction, even though all 3 infants received paracetamol for fever associated with childhood illnesses at 8–12 months of age.

Hemolysis in the neonate can originate from immune or nonimmune conditions. As our cases were all DCT negative, maternal diseases such as lupus or enzyme deficiencies of the infant’s red blood cells or hemoglobinopathies are possible. However, we did not find any of these conditions. Another hypothesis for our findings could be that paracetamol has been shown to cause depletion of cellular glutathione, one of the major anti-oxidant systems [6]. Thus, paracetamol may decrease the free radical eliminating capacity of the glutathione peroxidase system, especially in preterm infants where the glutathione peroxidase system is reduced [7], leading to hemolysis. Furthermore, in vitro studies showed that vitamin E supplementation in rats exposed to toxic doses of paracetamol, ameliorated hemolysis, and increased glutathione levels [8]. Therefore, low levels of vitamin E in preterm infants might expose them to hemolysis when paracetamol is given. Although we did not measure serum levels of vitamin E in these 3 infants, all preterm infants in our NICU receive vitamin E through either parental or enteral nutrition. Risks of hemolysis after short-term administration of paracetamol in children with G6PD deficiency have been described [9]; however, this association was refuted in a recent study [9]. In our three cases, paracetamol was prescribed as recommended and blood levels were within the normal range. Therefore, the hemolysis did not occur because of any violation of the common practice of treatment. We suggest that other studies are needed to establish whether paracetamol treatment is associated with hemolysis or whether other predisposing factors are responsible for this undesirable side effect. We could not attribute the decreased hematocrit in these preterm infants to blood drawn for laboratory tests, as the difference was very abrupt, within a few days, together with signs and symptoms of hemolysis.

There are laboratory tests that may detect hemolysis before clinical signs are apparent. Urinalysis showing hemoglobin in the absence of intact red cells can be a good marker of hemolysis. Also, absent serum haptoglobin will help substantiate brisk hemolysis. If co-oximetry is available, elevated carboxy hemoglobin levels can identify and quantify hemolysis in preterm infants. Also, for any NICUs that use noninvasive end tidal carbon monoxide assessment, this may be the simplest and most reproducible means of identifying and quantifying hemolysis in this group of patients. We did not use these tests in our 3 infants, as we were not aware of the hemolysis until clinical signs were apparent.

We are aware that the efficacy and safety of paracetamol were tested in large, randomized, controlled studies, and it is a commonly used drug [1]. A recent Cochrane study analyzed 916 infants who were included in randomized trials [2], and the side effect of hemolysis was not reported. Therefore, we are very cautiously reporting our observation in these 3 preterm infants and are not recommending anything, but simply noting this association and advocating awareness. As our cases were followed to 18 months of age, we were able to eliminate hereditary hemolytic causes for our observations and permanent paracetamol toxicity in these 3 preterm infants. We can only suggest that the hemolysis was due to a probable ADR of paracetamol which might have been related to their young age and low anti-oxidant system. However, confirmation of this speculation will need to await additional reports, similar to ours.

**Statement of Ethics**

This study was reviewed and approved by the Institutional Review Board of Meir Medical Center and conducted in accordance with the ethical and humane principles of research established by the Declaration of Helsinki (decision reference number: Me-2018-024). Written informed consent was obtained from all parents. The parents of the infants described in this paper gave written consent for the inclusion of material pertaining to themselves and to their child. They acknowledge that they cannot be identified via the paper, and that they have been fully anonymized by the authors.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Sofia Bauer-Rusek, Dr. Nava Samra, and Dr. Shmuel Arnon contributed to conception and design, contributed to analysis of cases, drafted the manuscript, critically revised the manuscript, and gave final approval. Dr. Shiran Moore contributed to the conception and design, critically revised the manuscript, and gave final approval.

Data Availability Statement

Data are available and will be given upon request.

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