Ranitidine-induced Thrombocytopenia in a Neonate – A Case Report and Review of Literature

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Thrombocytopenia (platelet count $<150 \times 10^9/L$) regularly occurs in newborns but is especially observed in critically ill neonates. We describe the case of a small for gestational age (SGA) neonate, who showed an unexpected, severe thrombocytopenia ($8 \times 10^9/L$) at day 5 of life. The thrombocytopenia recovered completely after cessation of ranitidine (0.5 mg/kg/6 hr), which was started in a context of feeding difficulties. Other causes of neonatal thrombocytopenia were ruled out. Besides a brief report on a cimetidine-induced thrombocytopenia over 25 years ago, no other neonatal or pediatric cases of H_2 antagonist-induced thrombocytopenia have been reported to date, although being widely used in routine care. Moreover, several adult cases have been published. In general, neonatal thrombocytopenia, although one of the most frequent hematological conditions in newborns, is only rarely attributed to an adverse drug reaction. Clinicians should be aware of the risks for adverse reactions, especially in routinely used drugs and in critically ill patients.

ABBREVIATIONS ADR, adverse drug reaction; DITP, drug-induced immune thrombocytopenia; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; SGA, small for gestational age

KEYWORDS adverse drug reaction; drug-induced thrombocytopenia; ranitidine; thrombocytopenia

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Introduction

Thrombocytopenia in children, which is defined as a platelet count of $<150 \times 10^9/L$, occurs in 1% to 5% of all newborns and is one of the most common neonatal hematological abnormalities.¹ Among sick infants, thrombocytopenia is even more frequent, affecting up to 35% of newborns admitted to neonatal intensive care units (NICU).^{2,3} Mild depletion with spontaneous recuperation is most common and seen after transiently impaired platelet production such as in placental insufficiency or fetal hypoxia. Nevertheless, 5% to 25% will have severe thrombocytopenia ($<50 \times 10^9/L$), requiring urgent diagnosis and treatment.^{1,3}

Many causes for thrombocytopenia in neonates have been identified, most often being classified according to the timing of onset. Early-onset thrombocytopenia manifests within 72 hours of life and is mainly caused by prenatal factors, such as fetal hypoxia (as occurring in preeclampsia, diabetes, or intrauterine growth restriction), and perinatal asphyxia or infection.^{1,3–6} Neonatal alloimmune thrombocytopenia, caused by transplacental passage of maternal antiplatelet antibodies, represents another important entity in early-onset thrombocytopenia.⁷ Although it is believed that many cases remain clinically silent, it is estimated to occur in 1.5/1000 neonates and may cause possibly lethal thrombocytopenia.⁸ Late-onset thrombocytopenia occurs later than 3 days of life and over 80% of cases are caused by sepsis or necrotizing enterocolitis (NEC).⁹

Although often overlooked, also drug-induced immune thrombocytopenia (DITP) must be considered in patients with an unexplained low platelet count. Not only US Food and Drug Administration or government approved drugs, but also vaccines, alternative or herbal remedies, nutritional supplements, and food or beverages may cause immune-mediated thrombocytopenia.¹⁰ In a systematic review, Reese et al¹¹ identified 31 approved drugs, 2 vaccines, and 1 food with definite or probable evidence for an association with thrombocytopenia in children. Carbamazepine, hepatitis B vaccine, phenytoin, and trimethoprim/sulfamethoxazole were reported most frequently.¹¹

Case

We present the case of a late preterm (gestational age 36 weeks and 5 days) male infant, born from non-consanguineous, healthy Caucasian parents. During this primigravid pregnancy, maternal diabetes mellitus and hypertension occurred for which a low dose of daily insulin and antihypertensive drugs (labetalol 100 mg every 8 hours) were started, respectively, after 30 and 33 weeks of gestation. Progressive maternal hypertension with reduced cardiotocographic variability occurred for which the boy was delivered at a postmenstrual age of 36 weeks and 5 days by caesarian section. As maternal screening was negative, no group B streptococcal antibiotic prophylaxis was given before surgery. The boy was born small for gestational age (SGA) with a

Figure. Thrombocyte counts of our patient over the first 2 weeks of life (values $\times 10^9/L$ mentioned at each marker). A mild early-onset thrombocytopenia (1) was observed, presumably because of being born small for gestational age, with spontaneous recuperation at day 3 of life (2). At day 3, ranitidine (0.5 mg/kg/6 hr) was initiated, followed by a severe thrombocytopenia ($8 \times 10^9/L$) with only minimal recuperation after platelet transfusion (3), but fast and complete recovery after ranitidine cessation at day 6 (4).

weight of 1.8 kg (<3rd percentile), a length of 45.5 cm (10th percentile) and a head circumference of 30.5 cm (5th percentile). Minimal newborn resuscitation was needed with good cardiorespiratory response to inflation breaths with 30% oxygen, followed by continuous ventilations with positive end-expiratory pressure. Apgar scores were 6 and 8 after 5 and 10 minutes.

He was transported to the neonatal unit where cardiopulmonary monitoring remained stable and oxygen delivery into the incubator could be phased out in the first 36 hours of life. Chest radiography showed symmetrical diffuse ground glass lungs, compatible with low grade infant respiratory distress syndrome. A venous umbilical line was inserted for reliable administration of fluids without heparin infusion.

In addition to parenteral nutrition, minimal enteral feeding with preterm formula (PreNAN Stage 2, Nestle, Vevey, Switzerland) was initiated from day 1 onwards. Increasing the fraction of enteral feeding was however challenging. Gastric emptying was negligible with aspiration of large residual volumes, although only 3 mL per feeding was given over a nasogastric tube. Abdominal examination remained normal (supple, not distended, normal peristalsis), and an abdominal radiography revealed no obstruction, malrotation, or perforation signs. Meconium passed in the first 24 hours of life, and subsequent stools were normal and came daily. Blood samples in the first 3 days of life revealed hyperbilirubinemia (5.61 mg/dL after 24 hours), clinically and biochemically responding well after phototherapy. A transient renal insufficiency (serum creatinine of 1.2 mg/dL on day 3) caused slightly decreased diuresis

(1.3 mL/kg/hr) during 24 hours but recovered fully with intravenous fluid administration.

After 3 days, enteral feeding did not improve and infant formula was temporarily switched to an extensive hydrolysate (Nutramigen, Mead Johnson Nutrition, Chicago, IL). As prophylaxis for stress ulcer and hoping to stimulate gastric emptying, intravenous ranitidine (Zantac, GlaxoSmithKline, Brentford, UK) 0.5 mg/kg every 6 hours was initiated. Around the same time, peripheral edema became apparent and respiratory effort increased again. There was mild hypoalbuminemia with proteinuria (below nephrotic range) but no arterial hypertension nor abnormalities on renal ultrasonography. Although an early-onset thrombocytopenia resolved spontaneously by day 3, only 48 hours later, a severe thrombocytopenia of $8 \times 10^9/L$ was found (Figure). There were no signs of liver failure or disseminated intravascular coagulation and no purpura, other bleeding symptoms, or ultrasonographic evidence of intraventricular hemorrhage were found. A deep venous thrombosis on the central venous catheter was excluded by cardiac ultrasonography. Chest radiography showed infant respiratory distress syndrome deterioration requiring high flow nasal cannula from day 6 onwards. Although there were no clinical nor biochemical signs of sepsis or infection, broad spectrum prophylactic antibiotics (ampicillin 50 mg/kg every 8 hours and amikacin 15 mg/kg every 36 hours) were started. A platelet transfusion (10 mL/kg , corresponding to an estimated total of 4.5×10^{11} platelets) was given, with minimal recuperation of thrombocytopenia ($26 \times 10^9/L$ on days 6 and 7).

At this time, ranitidine, which was started 3 days

earlier, was suspected to be causative in this acute and severe thrombocytopenia. After ranitidine cessation on day 6, platelets rose to $44 \times 10^9/L$ on day 8, to $95 \times 10^9/L$ on day 10, and completely normalized to $179 \times 10^9/L$ on day 12. Testing for drug-dependent antiplatelet antibodies was not done, nor were thrombopoietin concentrations or immature platelet fractions assessed.

Both edema and respiratory distress progressively resolved a few days after a single administration of albumin and diuretics on day 8. It was believed that the occurrence of hypoalbuminemia and edema was secondary to a brief episode of acute kidney injury caused by a combination of prematurity and prenatal maternal hypertension and possibly aggravated by nutritional insufficiency and neonatal stress. The boy developed well during his further stay and growth was sufficient on preterm formula. He was discharged from our hospital at the age of 37 days (postmenstrual age of 42 weeks).

Discussion

Neonatal thrombocytopenia is a life-threatening condition, especially when it occurs in a newborn intensive care unit, and appropriate diagnosis and treatment is often urgently needed. Almost 75% of neonatal thrombocytopenia occurs in the first 72 hours of life,¹² and our patient too experienced a mild thrombocytopenia in the first 48 hours of life ($87\text{--}110 \times 10^9/L$). Such thrombocytopenia is commonly seen in SGA infants,^{1,3,4,12} with even evidence for a (linear) relation between platelet counts and birth weight centile.^{4,13} Typically, thrombocytopenia onset in SGA infants is early (<72 hours after birth), only a minority of patients (5%) require platelet transfusion, and no infants are yet reported with a platelet count $<20 \times 10^9/L$.¹³ Additional risk factors for thrombocytopenia were present in our patient, such as maternal diabetes and pre-eclampsia, which causes neonatal platelet depletion in up to 30%.¹⁴ As was expected, the initial platelet depletion in our patient resolved spontaneously, and platelet count was found to be normal at 72 hours of life. Subsequently, most causes of early-onset thrombocytopenia were ruled out for the severe thrombocytopenia that followed on day 5 (i.e., neonatal alloimmune thrombocytopenia).

In our case, there was a perfect chronological order (Figure) of ranitidine initiation with unexpected and severe thrombocytopenia and prompt and full platelet count recuperation after cessation of it, moreover within a duration as described in previous cases.¹⁵ The nature of the recovery phase is in contrast with thrombocytopenia caused by sepsis or NEC. As in our patient, such ill patients may too show a thrombocytopenia after 72 hours of life, often progressing rapidly and severe (platelet count $<30 \times 10^9/L$). Yet, such cases typically take over 1 week to recover platelet levels above $50 \times 10^9/L$.⁴ Furthermore, any signs of neonatal sepsis or NEC were missing in our case. The distinct course of rapid

and complete recovery and absence of recurrence, unless there is repeated exposure, is typical for DITP and may aid in clinical decision-making.¹¹ Intentional re-exposure to ranitidine to confirm an immune-mediated thrombocytopenia was considered ethically impossible in our patient. As such, a definite level of evidence for likelihood of an adverse drug reaction (ADR; level 1), as described by Naranjo et al¹⁶ and used in systematic reviews by George et al¹⁷ and Reese et al,¹¹ could not be established. Since ranitidine is renally cleared, the transient acute kidney failure in our patient is likely to have been an aggravating factor in the ADR in addition to being born SGA. Although cases are mostly described in adults, previous authors already advised H_2 receptor antagonists dose reduction in the presence of low glomerular filtration rate.¹⁸

As this case illustrates, in the differentiation of ADRs from possible confounding reactions, complex clinical pharmacological pathways, and many covariates that may explain inter- and intraindividual variability are often in play, especially in a predisposed population such as in NICU.¹⁹ Recently, a new ADR algorithm for infants in NICUs was developed,^{19,20} specifically to correct for confounding factors associated with organ dysfunction, immaturity, and underlying diseases, which are not taken into account when using the standard Naranjo scale. When calculating this revised score for our case (total = 9), a “probable” ADR was assessed.

Drug exposure as a cause for thrombocytopenia has often been overlooked, especially in pediatrics and neonatology. It is easily assumed that chances for drug-related interactions and complications only become relevant when many medications are used, which more frequently is the case in elderly or patients with chronic health problems.¹¹ The opposite, however, is true, as children and newborns may even be at increased risk for ADRs. The largely undiscovered field of developmental pharmacology, with lack of randomized controlled trials in vulnerable populations, leaves many voids in our knowledge of neonatal and pediatric pharmacokinetics and pharmacodynamics.²¹ Subsequently, abundant off-label prescription is common practice in this field (as was the case in our patient), which may compromise drug safety and efficacy and increase ADR likelihood.

Not many studies have accurately estimated the incidence of neonatal ADR, and large regional variability and selectivity in reporting is presumed to be present. In an older study conducted by Aranda et al²² in 1982, an NICU ADR incidence of 30% was found. Le et al²³ found an annual incidence of 0.4% to 2.3% in their pediatric population, although ADRs were more common in the NICU. This higher risk in neonates was confirmed by Kunac et al²⁴ who found the highest ADR number (41% of total) and rate (49 per 100 admissions) among the NICU population in their pediatric cohort. In a recent prospective study by Belén Rivas et al,²⁵ 17% of

neonates were found to experience an ADR. None of those studies reported H₂ antagonist associated ADRs.

Although many adult cases of DITP have been described, cases are reported seldom in pediatrics and—even rarer—in neonates. Illustratively, no neonatal DITP reports were registered in a large French pharmacovigilance database between 1986 and 2012.²⁷ When extensively reviewing scientific literature databases, we only found a handful of newborn patients with DITP. Vancomycin-induced thrombocytopenia was reported in 2 newborns, presenting with early-onset²⁷ and late-onset sepsis.²⁸ In another critically ill neonate, pantoprazole-induced DITP was described.²⁹ Also after a continuous glucagon infusion for treating intractable hypoglycemia, thrombocytopenia once occurred in a newborn.³⁰ Indomethacin^{31,32} and ibuprofen,^{31–34} both universally used to induce pharmacological closure of the arterial duct, were shown to cause DITP in a handful of neonates. Heparin-induced thrombocytopenia is often regarded as a unique entity, as drug-specific antibodies may lead to mild thrombocytopenia but paradoxically also cause platelet activation and thrombin production.³⁵ In neonatology too, heparin-induced DITP is especially observed in association with thrombosis or following cardiac surgery.^{36–39} Neonatal DITP may also occur in the absence of drug-use. Cow's milk-induced thrombocytopenia was for example reported in a newborn with congenital absent radius syndrome,⁴⁰ a condition itself associated with transient thrombocytopenia in infancy. Cow's milk-induced thrombocytopenia was also shown in another report in the absence of this syndrome.⁴¹

The above-mentioned drugs, sporadically causing DITP in newborns, are nonetheless frequently used in (intensive) neonatology units worldwide. Especially vancomycin consistently appears in the top 20 of most used neonatal drugs in the United States,^{42,43} but also in European countries such as Germany⁴⁴ and Estonia.⁴⁵ Indomethacin is among the top drugs used in the United States,^{42,43} whereas in Europe ibuprofen is more common.⁴⁵ Of other drugs known to cause DITP in children,¹¹ also acetaminophen, rifampicin, ceftriaxone, sulfamethoxazole/trimethoprim, and phenytoin are among the 100 most frequently used medications in NICUs in the United States.⁴²

Drug-induced thrombocytopenia caused by H₂ antagonists is a rare phenomenon. A variety of case reports of DITP in adult patients taking H₂ antagonists has been described. Wade et al¹⁵ extensively reviewed 29 of these cases. The toxic effect of H₂ antagonists in adults was especially shown in cimetidine, but a handful of patients taking ranitidine or famotidine has been described too. It was striking that critically ill patients were affected more often, and increased length of stay was especially observed in those patients on intensive care units. We found only 1 brief report, published in 1988, of a 6-day-old newborn with

a possible cimetidine-induced thrombocytopenia.⁴⁶ To our knowledge, no other neonatal or pediatrics cases with thrombocytopenia after H₂ antagonist use have been described yet. Also, in an extensive systematic review of 74 pediatric DITP cases, no other patients with H₂ antagonists were reported.¹¹ This may come as a surprise, as ranitidine is frequently used in children and newborns. It even has a reported exposure of 52 to 72 per 1000 infants in NICUs in the United States and ranks thus among the top 20 of most frequently used drugs.^{42,43} Although prevalence numbers may be underestimated as not all cases are detected or published, ranitidine-induced thrombocytopenia can be regarded as a very rare condition, which nonetheless requires urgent recognition and prompt action. Clinicians should be aware of the risks for (unexpected) adverse reactions, especially in routinely used drugs and in critically ill patients. Case reports as these may aid in expanding our knowledge of rare pharmacological complications and in the prevention of its occurrence.

Conclusion

Neonatal thrombocytopenia is a frequent hematological abnormality and has a variety of causes. In rare cases, thrombocytopenia may be caused by an ADR, supposedly immune-mediated. Although H₂ antagonists are widely used in pediatrics and neonatology, we describe the first case of severe ranitidine-induced thrombocytopenia in a neonate. Clinicians should be aware of the risks for (unexpected) adverse effects, especially in routinely used drugs and critically ill patients. Because of their age-specific, but largely undiscovered pharmacokinetic and pharmacodynamic characteristics, neonates and children carry an increased risk for adverse effects. Case reports as these aid in expanding our knowledge of ADRs and in the prevention of its occurrence.

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