

CASE REPORT

Prolonged prostaglandin E1 therapy in a neonate with pulmonary atresia and ventricular septal defect and the development of antral foveolar hyperplasia and hypertrophic pyloric stenosis

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Abstract

Prostaglandin E1 (alprostadil) is widely used for maintaining the patency of ductus arteriosus in ductus-dependent congenital heart defects in neonates to improve oxygenation. Among more common side effects are fever, rash, apnoea, diarrhoea, jitteriness, and flushing. More severe side effects are brown fat necrosis, cortical hyperostosis, and gastric outlet obstruction, most commonly the result of antral foveolar hyperplasia or hypertrophic pyloric stenosis. We report on an infant with a ductus-dependent congenital heart defect who developed symptoms and sonographic evidence of focal foveolar hyperplasia and hypertrophic pyloric stenosis after prolonged treatment with prostaglandin E1. Gastrointestinal symptoms persisted after corrective cardiac surgery, and pyloromyotomy was required. Study of the case and of available literature showed an association between the total dose of prostaglandin E1 administered and duration of treatment and the development of gastric outlet obstruction. We conclude that if patients are treated with a prostaglandin E1 infusion, careful monitoring for symptoms and signs of gastric outlet obstruction is required.

Key words: *Alprostadil, focal foveolar hyperplasia, gastric outlet obstruction, hypertrophic pyloric stenosis, neonates, prostaglandin E1*

Introduction

Prostaglandin E1 (alprostadil) at a therapeutic dose of 0.05 µg per kilogram per minute is widely used for maintaining the patency of ductus arteriosus in ductus-dependent congenital heart defects in neonates. The most common side effects are apnoea, abdominal

distension, bradycardia, enterocolitis, hypotension, vomiting, fever, and skin rash (1). Prostaglandin E1 is usually administered before corrective heart surgery, but long-term prostaglandin E1 infusion (i.e. more than 120 hours) has recently been associated with certain complications, such as brown fat necrosis, pseudo-Bartter syndrome, cortical hyperostosis, and

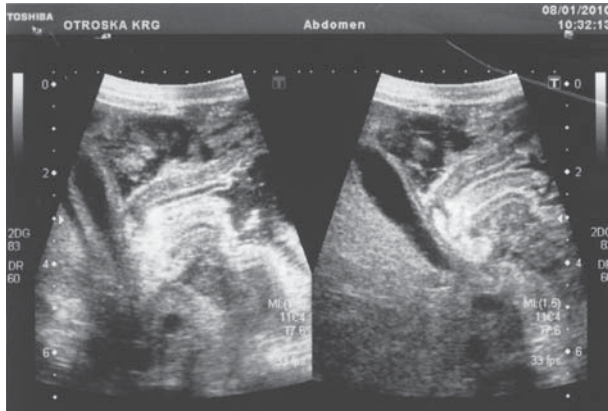


Figure 1. Longitudinal ultrasound images (left and right) of the pylorus on day 44 (2 days after cardiac operation and discontinuation of alprostadil). There is an elongation of the pyloric channel with moderately thickened pyloric musculature.

gastric outlet obstruction (GOO) (2,3). Prostaglandin E1 has many effects on gastrointestinal function, ranging from cytoprotection, trophic action, enteral pooling, and gut motility (3). It induces proliferation of the gastric mucosa in the antral region, leading to antral foveolar hyperplasia, which obstructs gastric emptying and can lead to pyloric stenosis (4,5).

Infantile hypertrophic pyloric stenosis (IHPS) is a condition in infants when the pyloric musculature becomes abnormally thickened and functions as a gastric outlet obstruction, which in turn leads to projectile non-bilious vomiting. It is usually not present at birth but manifests itself in the first few weeks of life (6). The aetiology of the condition has not yet

been fully elucidated, and postnatal precipitating factors have been poorly defined (7). The diagnosis of IHPS is clinical, with the diagnosis usually suspected based on the presentation of projectile vomiting, failure to thrive, and acid–base disturbances. Sometimes, a characteristic olive mass in the upper right abdomen can be palpated. The diagnosis is confirmed by sonographic findings of a thickened pyloric musculature (6). We report on an infant who developed focal foveolar hyperplasia and hypertrophic pyloric stenosis after prolonged treatment with prostaglandin E1.

Case report

A girl with a birth weight of 3200 g was born at 41 weeks gestational age after an uneventful pregnancy and vaginal delivery. The labour was induced because of decelerations on cardiotocography. The Apgar score was 9 after both 1 and 5 minutes. A few hours after birth she developed respiratory distress with saturation around 88% on 100% oxygen. A cardiac ultrasound (US) showed pulmonary atresia with a ventricular septal defect (VSD). Genetic analysis later confirmed 22q11.2 microdeletion. She was given intravenous prostaglandin E1 (alprostadil) at a dose of 0.05 µg/kg/min, which was later tapered down to 0.01–0.015 µg/kg/min. Cardiac catheterization revealed non-confluent central pulmonary arteries. The right pulmonary artery was supplied by a single major aorto-pulmonary collateral artery arising from the descending thoracic aorta, while the left pulmonary artery was supplied by a patent ductus arteriosus.

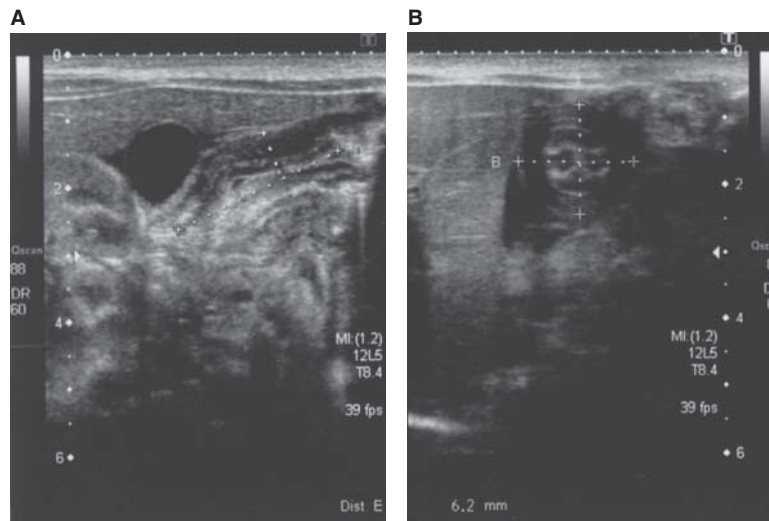


Figure 2. A: Longitudinal ultrasound image of the pylorus on day 47 (5 days after cardiac surgery when the patient vomited a large amount of non-bilious gastric content) showing elongated pyloric channel and thickened pyloric musculature. B: Transverse ultrasound image of the antropyloric region showing marked antral mucosal hypertrophy.



Figure 3. Transverse ultrasound image of the pylorus after pyloromyotomy, with antral mucosal thickening still present.

Surgical unifocalization of the central pulmonary arteries was deferred, and in the meantime prostaglandin E1 infusion was continued in order to secure perfusion of the left pulmonary artery. An attempt of discontinuation of prostaglandin E1 therapy on the 13th day was not successful, so prostaglandin E1 therapy was restarted 2 days later and was continued for another 3 weeks until she was successfully operated. She received prostaglandin E1 for 40 days in total with a total dose of 2848 µg. Until her heart surgery she was bottle-fed with calorically enriched milk formula and additionally through a nasogastric tube. There were no problems with her feeding during

the prolonged prostaglandin E1 therapy until the last few days before surgery, when non-bilious vomiting of small amounts of mucus was occasionally detected. No ultrasound of abdomen was performed. Heart surgery was carried out on the 42nd day after delivery. An abdominal ultrasound was performed on the second postoperative day because of distended abdomen. US showed an elongation of the pyloric channel, with moderately thickened pyloric musculature (Figure 1). Milk formula was then given again on the fifth day after surgery, after which she vomited a large amount of non-bilious gastric content. A repeat abdominal US showed elongated and thickened pyloric musculature (Figure 2A) with marked antral mucosal hypertrophy which caused a gastric outlet obstruction (Figure 2B). Abdominal palpation revealed a typical olive-like resistance in the upper right part of the abdomen. Pyloromyotomy was performed (Figure 3). Six hours after surgery the patient was once again put on milk formula, which she tolerated well. A control abdominal US 1 week after abdominal surgery showed improvement (Figure 4). The patient was fed normally and was gaining weight. A control examination after 1 month was normal.

Discussion

IHPS is a common paediatric surgical condition, presenting after birth with projectile vomiting. Its aetiology remains poorly understood (7). In our patient, clinical signs of IHPS presented after she had been treated for a prolonged period of time with prostaglandin E1 for a congenital cyanotic heart defect. The diagnosis of IHPS was based on the

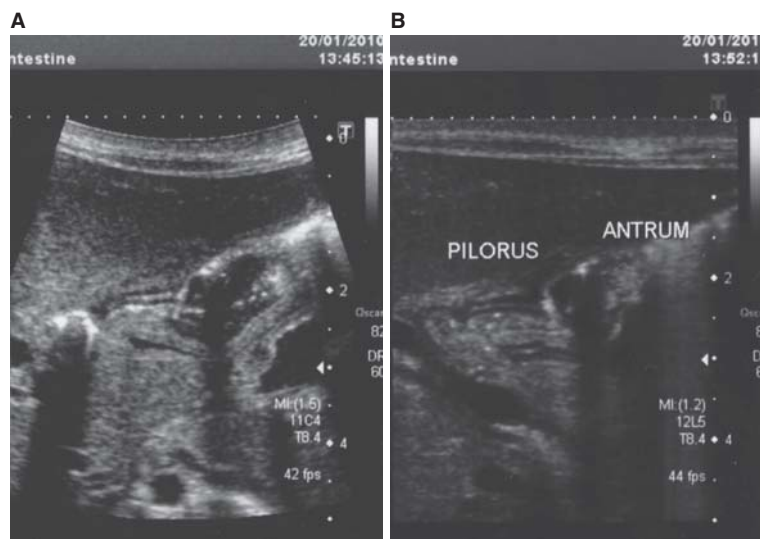


Figure 4. Longitudinal ultrasound image of pylorus and antrum performed on day 58 showing diminished pylorus wall thickness.

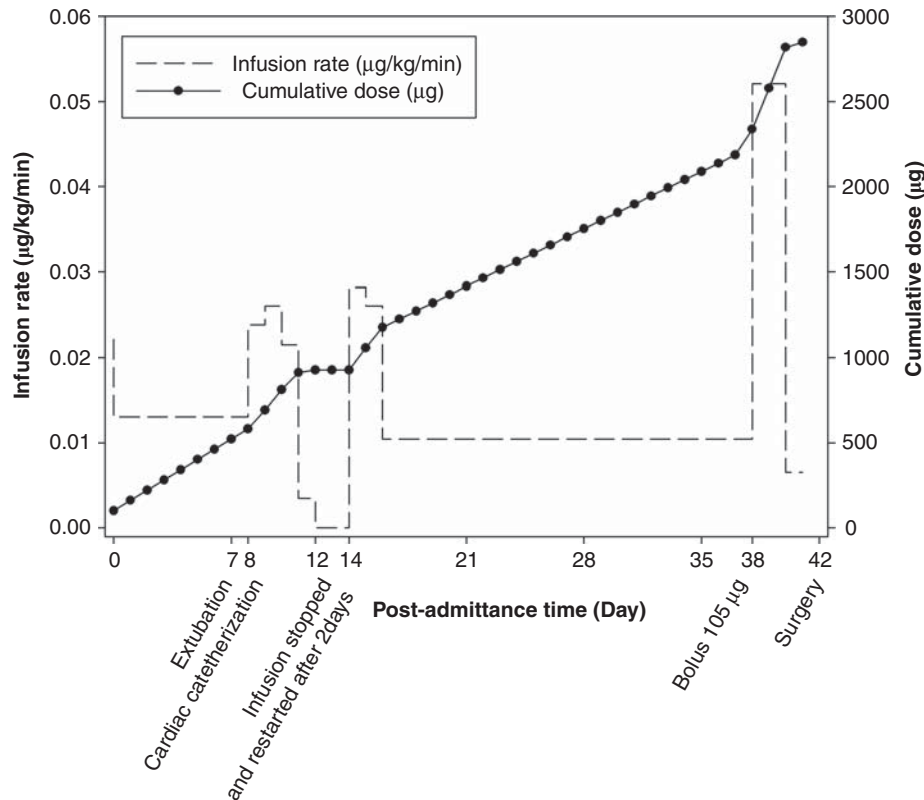


Figure 5. Prostaglandin E1 infusion rate and cumulative doses. Day 7, extubation; day 8, cardiac catheterization; day 12, infusion stopped and then restarted after 2 days; day 38, bolus dose of 105 µg of prostaglandin E1; day 42, surgery.

presentation with projectile vomiting and on the clinical examination with the palpation of a characteristic olive mass and was confirmed with sonographic finding of a thickened pyloric musculature. Our patient developed IHPS after having been treated with prostaglandin E1 for 40 days with a cumulative dose of 2848 µg. The development of abdominal distension in a patient treated with a similar cumulative dose to ours has previously been reported (8). Total doses in excess of 1560 µg/kg have been implicated in the development of focal foveolar hyperplasia (2). However, as seen above, cumulative doses at which symptoms developed were very different from case to case, which is why we believe that future research should focus more on the association between total doses of prostaglandin E1 administered and the development of specific side effects of treatment.

Furthermore, GOO in our patient was caused by both focal foveolar hyperplasia (FFH) and IHPS. It is only the second report to show that both entities can appear simultaneously (9). However, ours is the first case reported in which both entities appeared as a side effect of prostaglandin E1 therapy. This is an important fact to consider, because it affects the choice of therapy for GOO in neonates. If only FFH is present, discontinuation of therapy is usually

enough, but the presence of IHPS requires surgical treatment (6,10). In addition, we postulate that IHPS developed secondarily due to the invagination of FFH into the pylorus. These findings are supported by sequential US images, which were recorded at different intervals during the development and subsequent resolution of the condition. After pyloromyotomy had been performed, the gastric outlet was no longer obstructed, even though FFH persisted for some time after treatment. This confirms previous findings that FFH can resolve spontaneously after cessation of treatment (10).

In addition, a previous study established an association between the duration of prostaglandin E1 therapy and the cumulative dose and the development of GOO in neonates (5). Our case supports that association, both in terms of total dose required for the development of GOO, as well as the duration of treatment. Our patient was treated for 40 days, which is in accordance with data from two studies showing that patients with GOO received prostaglandin E1 infusion for 272–1109 hours and 23 days, respectively (5,11). The symptoms in our patient persisted even after the cessation of prostaglandin E1 therapy, which further confirms the presence of IHPS. There are reports to suggest that there

is a decrease of gastrointestinal symptoms after the discontinuation of prostaglandin E1 infusion, but in those cases, the pyloric musculature was not thickened and the symptoms were the result of FFH, which does not necessarily require an operative procedure (2,10).

On the other hand, a case report showed signs of GOO in a patient with cyanotic heart disease in the absence of prostaglandin E1 therapy, thus raising the question if prostaglandin E1 alone is responsible for the development of GOO or if hypoxia associated with such heart defects also may play a role (12). Given that, in our case, the cause for GOO was an anatomical lesion and, in the above-mentioned case report, the radiologic findings did not show muscle hypertrophy, we hypothesize that prostaglandin E1 causes GOO through a different mechanism than hypoxia. One possible explanation is that it exerts a direct effect on the gastric musculature, while hypoxia simply causes pyloric spasm due to ischaemia. However, not enough data are as yet available to reach a definitive conclusion.

As seen from our case (Figure 5), gastrointestinal symptoms became clinically manifest after the patient received a higher than recommended single dose of prostaglandin E1 (240 µg). There is not enough evidence to conclude if the bolus alone had the adverse effect, or if GOO was already present because of the prolonged treatment and the overdose simply coincided with the occurrence of symptoms.

In conclusion, our case report, as well as previous studies, shows that GOO is a possible side effect of prostaglandin E1 therapy in neonates and can be caused by both FFH and IHPS appearing simultaneously. In fact, FFH can be the cause of IHPS due to its invagination in the pylorus. Therefore, we recommend that even if prostaglandin E1 is administered at the recommended dose of 0.05 µg/kg/min newborns are monitored for the presence of gastric outlet obstruction. We also recommend that IHPS is the first condition to be ruled out as the cause of GOO as it can be present in parallel with FFH. If that is the

case, the gastrointestinal symptoms will not resolve spontaneously after cessation of treatment and an operative procedure will anyhow be required.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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