Case Report

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Hemolytic Anemia and Other Side Effects of Para-amino Benzoic Acid in an 8-Year-Old Girl

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Abstract

Background: Para-amino benzoic acid (PABA) is an important ingredient used as a structure moiety in drugs with wide range of therapeutic uses; however, its safety and possible side effects in young children have not been determined.

Case Presentation: An 8-year-old girl was admitted to the emergency department for paleness, jaundice, abdominal pain and nausea associated with Hemoglubin (Hb) =4.5 g/dl, reticulocytes = 6%, corrected reticulocytes = 1.8%, Lactate Dehydrogenase (LDH) = 1893 IU/L, and Total bilirubin =12 mg/dl with direct bilirubin = 0.7 mg/dl. The patient had received a prescription for PABA, in order to fade out some facial hypopigmented macules, for 120 days prior to her admission. Within 120 days of starting the PABA, the patient had developed new onset abdominal pain following each meal, weight gain, paleness, and jaundice. The PABA was discontinued on the day of admission. Hematologic evaluation revealed no evidence of autoimmune hemolytic anemia, glucose 6 phosphate dehydrogenase (G6PD) deficiency, red blood cell (RBC) membrane defects, or hemoglubinopathy. Moreover, hepatologic evaluation revealed no evidence of acute or chronic viral hepatitis, autoimmune or metabolic disorders at admission. During the admission, her transaminase and gama glutamil transpeptidase (GGT) levels increased more than 5 times without any elevation in international normalized ratio (INR) or alkaline phosphatase. Moreover, abdominal ultrasonography revealed acalculous cholecystitis. Her Hb, Hct (Hematocrit), reticulocytes, liver enzymes, bilirubin, and gallbladder ultrasonography completely normalized 2 months after discontinuation of PABA.

Conclusion: This report represented the first documented case of hemolytic anemia and hepatotoxicity in a child underwent PABA therapy, highlighting the need for clinician awareness about potential hemolytic anemia and hepatotoxicity of oral PABA particularly among children.

Key words: Hemolytic anemia, Hepatotoxicity, Para-Amino Benzoic Acid

Introduction

Para-amino benzoic acid (PABA) is an intermediate substance in the synthesis of folate by bacteria, plants, and fungi (1). Besides, many bacteria, including those found in the human intestinal tract such as E.coli produce PABA (2, 3). Moreover, there are some food sources delivered PABA to human like grains, wheat, rice, egg, chicken, and lamb liver. Although the potassium salt of PABA is used as a drug in fibrotic skin disorders (4, 5), some studies claimed that PABA has many other health and therapeutic benefits for human (6). PABA is probably safe in adults when consumed at a dosage up to 400 mg daily and possible side effects at this dosage are minor, including skin rash and loss of appetite; however, higher doses may lead to some severe damages (7-9). In this report, an eight year old girl with severe hemolytic anemia and some other side effects associated with orally PABA usage was presented.

Case report

A young girl (eight years old) with no positive past medical history presented to the emergency department of the hospital with abdominal pain, nausea, severe paleness, and jaundice. She had a dark complexion and her parents noticed her discoloration lately. There was no history

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of specific food consumption, additive, drug or substance, no history of blood transfusion, and no exposure to any poison, toxin, chemicals, bite or an injection. The condition was associated with yellowish discoloration of the urine; however, no discoloration in the feces was noticed. On presentation, her mother denied any previous consumption of a drug or chemicals by the patient. Moreover, this combination of symptoms never happened in her before. The patient had nausea and abdominal pain but not vomiting, diarrhea, constipation, fever, cough, sore throat, or nasal discharge. Furthermore, she had not any recent history of respiratory tract or any other infection. Her routine vaccination profile was complete. Her parents had not any consanguineous relationship; however, they divorced a few years ago and the patient lived with his father. There was no family history of anemia or any other disease. She was a febrile on admission with normal vital signs. She was completely alert with no specific distress. On physical examination, she had bilateral sclera icterus and jaundiced skin in addition to paleness. There were no lymphadenopathy or skin rashes. Abdominal exam was unremarkable without distension, tenderness, or hepatosplenomegaly, with no classical stigmata of chronic liver disease. Her other physical examination findings were unremarkable too, except a few hypopigmented macules less than 5 mm which were found on lateral side of her eyes. Laboratory studies showed mild leukocytosis (13400/mm3) with 80% PMN, 2% Band, 15% lymphocytes, 2% monocytes, and 11% Eosinophils. Her Hb was 4.5 g/dl with Hct = 13.7, RBC = 1.590.000/mm3, reticulocyte count = 6%, and normal RBC Indexes. In her PBS, there were some microspherocytes, polychomasia, and nucleated RBCs. Her platelet count was normal. Her aspartate transaminse (AST), alanine transaminase (ALT), alkaline phosphatase (Alk phos), prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR) were in normal ranges; however, lactate dehydrogenase (LDH) = 1893 IU/L, total bilirubin (Tbil), and direct bilirubin (Dbil) were 12 mg/dl and 0.7 mg/dl; respectively. BUN, creatinine, and serum electrolytes were normal. Direct and indirect coombs, screening antibody, and autoantibody were checked in two different labs and all were negative. G6PD was sufficient. The serum ceroloplasmin, osmotic fragility test, and Hb electrophoresis were also normal. The urinalysis was yellowish because of bilirubin, but other findings were normal. She received one unit of packed cell on the night of admission and another unit on the next day.

With further questioning of her mother on the next day, she finally admitted that her daughter has consumed one 500 mg PABA capsule daily for the last 120 days for her facial hypopigmented macules until the admission day. Besides, during PABA taking, the patient had experienced one episode of cutaneous jaundice, complained of right upper quadrant (RUQ) pain following each meal and had about 8 Kilograms weight gain which were unnoticed.

At that night, she complained of severe right upper quadrant (RUQ) pain with some nausea. Her physical exam revealed severe RUQ, epigastric tenderness, and ranitidine ordered for her. On the next morning, following gastrointestinal consultation, she got NPO and her laboratory studies revealed the following results: ALT = 198 IU/L, AST= 129 IU/L, Tbil = 1.1 mg/dl, INR = 1, Gama glutamyl Transferase (GGT) = 150 U/L, Alk phos = 530 IU/L, Amylase = 65 IU/L, and Lipase = 98 IU/L. Besides, viral hepatitis serologies were negative for hepatitis B surface Ag (HBs Ag), hepatitis B core Ab (HBc Ab), and hepatitis C virus Ab (HCV Ab). Evaluation for other acute viral infections, including ebstein barr virus viral capsid antigen (EBV VCA) antibody

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(including IgM, IgG) and cyto megalo virus (CMV) Ab (including IgM, IgG) were negative. Human immunodeficiency virus (HIV) antibody, anti nuclear antibody, anti double strand DNA, C3, C4 and CH50 were negative too. Immunoglobulins (including IgM, IgG and IgA) were normal. Thyroid stimulating hormone level (TSH) was higher than normal; however, free T4 was in normal range. In abdominal ultrasonograghy, gallbladder (GB) was highly distended with thickened wall and lots of sludge without any calculous. In color doppler ultrasonography, GB wall was hyperemic and there was tenderness with probe compression over GB (Ultrasonographic Morphy sign) in favor of acalculous cholecystitis. Therefore, IV pentoprazol and antibiotics (Cefotaxim, Amikacin and Metronidazol) started for her and NPO condition continued. After 3 days of NPO, her RUQ pain was relieved. Repeat abdominal ultrasonography revealed decreased inflammation of GB with some reduction in the wall thickness. After 2 days, she discharged with stable Hb, Hct, Reticulocyte count = 1% and normal amylase and Lipase. Oral pentoprazol and metronidazol were prescribed for her. The patient's parents were instructed never to re-challenge her with PABA and to report it as a medication adverse reaction in the future. In follow up visit in the following week, she was stable with no pain and had normal laboratory tests. In the next follow up visit, approximately 2 months after discontinuing PABA, the patient's was well, without any abdominal pain or jaundice, and lost 3 Kg of weight. Her patient's AST, ALT, Alk phos, Lipase, Amylase, Tbili, and Dbili were normal. Furthermore, her G6PD was normal; her TSH was slightly higher than normal with normal free T4. Moreover, her abdominal ultrasonography showed completely nomalization.

Discussion

In the present study, following effects were observed in an eight-year-old girl who took PABA on a daily basis at a dose of 17 mg/kg for 120 days:

1- A prominent hemolytic anemia (Hb = 4.5 g/dl, indirect hyperbilirubinemia = 11.3 mg/dl, corrected reticulocyte: 1.8%, and LDH= 1893 IU/L) at admission.

2- Hepatotoxicity with significant rises in liver function tests (AST, ALT, GGT, Tbil, and Dbil) during admission period.

3- A significant indirect hyperbilirubinemia with acalculous cholecystitis.

4- More than 25% weight gain during 4 month period of PABA taking.

5- A subclinical hypothyroidism.

PABA is frequently used as a building block in the design of drugs or drug candidates as well as a structure moiety in drugs. These drugs have a wide range of therapeutic uses such as sun-screening, antibacterial, antineoplastic, local anesthetics, anticonvulsant, antiarrhythmic, antiemetic, gastrokinetic, psychotic, neuroleptic, and migraine prophylactic (10). Moreover, despite many claims made about benefits of PABA for depression, infertility, vitiligo, etc as an oral supplement (6), the number of documented controlled studies for these types of PABA application in humans is really limited. For instance, one of the most studied orally PABA supplement is the potassium salt of PABA, known as POTABA, which has been used for the treatment of Pyronie's disease in adult patients with scleroderma and is well tolerated (11,12). In the present case, PABA was prescribed by a physician for treating a few facial hypopigmented macules. The daily dose of PABA was 500 mg (about 17 mg/kg of her body weight) and the duration of prescription was 120 days.

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In review of literature, just a report on a probably safe orally PABA dose in adults could be found, which was 400 mg daily (7). It seems that safety of PABA usage in young children has not been determined yet. A few studies, by the late of 1990s, reported fibrinolytic and direct anticoagulant activities as well as antithrombotic effects of PABA injection in rats and rabbits (13, 14). In studies animals, PABA at 1.5 mg/kg animal's body weight had a high anticoagulant activity and pronounced antithrombotic effect, without any side effects; however, at 3 mg/kg, PABA induced hemolysis of erythrocytes in about half of cases and decreased the number of thrombocytes by 20% (13, 14). In our case, a pronounced hemolytic anemia was also observed following PABA consumption; however, neither bleeding manifestation nor diathesis was observed clinically or para clinically (the patient's platelets count, PT, PTT, and INR were in normal ranges throughout her admission). This discrepancy concerning PABA side effects could be probably explained by the following reasons. First of all, the findings in animal phase of reserch may not be approved in the human phase all the time. Secondly, the route of PABA usage was different in this case in comparison to the studies on animals. Thirdly, the dose and duration of PABA usage were totally different between previous studies and this study.

There has been one report on a woman with severe hepatotoxicity who took 12 gram PABA on a daily basis (8). However, a study on rats in Taiwan didn't report any increase in ALT or AST after prescribing different doses of PABA orally (50 to 500 mg/kg of birth weight) for 4 weeks, (15). It is noteworthy to mention that the rising of ALT, AST, and GGT in our case occurred during her admission that can be probably due to high bilirubin concentration induced by RBC hemolysis and not the direct result of PABA consumption.

Neither weight gain nor any organ weight gain was mentioned in Taiwan study on rats following PABA feeding at different doses (15). With regard to significant weight gain in our case during 4 months of taking PABA and then losing of about 3 kilograms of her weight following 2 months of discontinuing the drug, it seems that emerging this side effect may probably need more time of PABA taking.

In our patient, significant indirect hyperbilirubinemia as well as abdominal pain and acalculous cholecystitis were observed during her admission. These effects may be attributed to the prominent RBC hemolysis, because the severity of rising in bilirubin level decreased gradually during admission (following discontinuation of PABA and reduction of the related RBC hemolysis). Besides, the colicky abdominal pain disappeared and the severity of ultrasonographic signs of cholecystitis decreased as well. Moreover, in the follow up visit 2 months later, all of the patient’s abdominal complaints relieved and her ultrasonographic findings of acalculous cholecystitis disappeared too. These PABA's side effects were not reported previously in the literature review.

In laboratory studies, the patient had a subclinical hypothyroidism at admission (normal free T4 and increasing in TSH) which continued to a lower level following two months of oral PABA discontinuation. A study in Japan indicated that administration of orally PABA to rats for two weeks led to elevation of the animals' TSH level (16). However, it should pointed out that we didn't have any baseline laboratory tests about free T4 and TSH levels of the patient before consuming PABA. Therefore, our findings on PABA side effects should be interpreted cautiously.

A case study indicated that daily consumption of 8 gram PABA could cause vitiligo (9), though no new local hypopimentation, , hyperpigmentation, and skin rashes was observed in the during

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patient's examination. In contrast, another case report mentioned skin rashes following low doses of PABA (up to orally 400mg daily) (7).

Ultimately, it should be admitted that there was an important pitfall in this case report, because PABA or its metabolites concentration couldn't be measured at the patient's serum, plasma, RBC level, or urine due to lack of access to a standard kit or tool for measuring PABA at any reference labs throughout the city.

Conclusion

In summary, the present case was the first case report of taking high dose of PABA for a long time in a young child and all of the findings should be approved by more accurate molecular or cellular laboratory tests at least at animal levels in order to be explained biologically.

Conflicts of interest

The authors declare no conflict of interest.

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