Homozygous glucose-6-phosphate dehydrogenase deficiency and propacetamol-induced hemolysis

We report an observation of a young Comorian G6PD-deficient woman who presented a hemolytic crisis after each of four parenteral administrations of a usual dose of propacetamol (the prodrug of acetaminophen).

Glucose-6-phosphate dehydrogenase (G6PD) X-linked hereditary deficiency is the most common of all clinically significant enzyme defects: more than 200 million people are G6PD-deficient in the world.[1,2] While many drugs are well known to provoke hemolytic anemia in G6PD deficiency, acetaminophen's imputability is still discussed. We report the case of a 28-year old nulliparous Comorian woman, in France since 1995, with homozygous G6PD deficiency, who presented a hemolytic crisis after each intravenous injection of propacetamol (the prodrug of acetaminophen) at a usual dose.

Mrs A. was admitted to the gastroenterology unit of Laveran Military Hospital because of a hepatic abscess. The organism responsible for the hepatic abscess remained unknown but amoebiasis was ruled out. She had been operated two months earlier for gallbladder cancer. The hepatic abscess was treated successfully by antibiotics but she had a reversible toxic agranulocytosis caused by cefotaxim.

One week after the antibiotics were stopped, strong headaches without fever lead to administration of normal doses of propacetamol. The patient developed hemolytic anemia (hemoglobin = 9 g/dL; haptoglobin < 0.08 g/L, reticulocytes = 10×6 10^9/L). A diagnosis of malaria was excluded by a negative QBC® test. Mrs A did not show clinical evidence of infection or fever, but had mild biological inflammation (C reactive protein: 62 mg/L). Biological exploration showed a negative Coombs' test, no

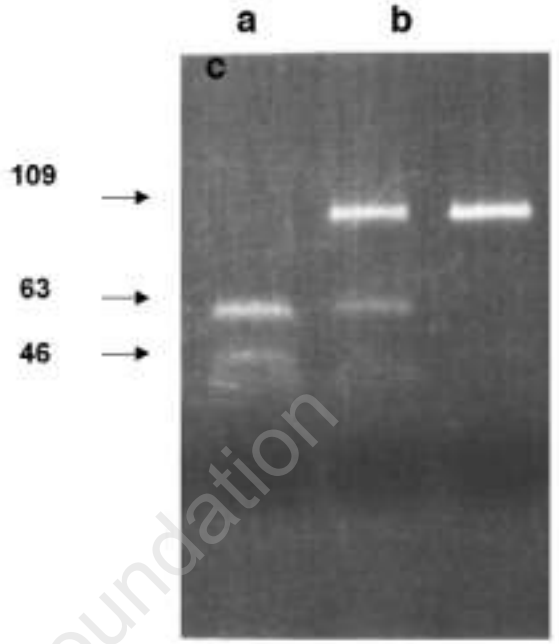

Figure 1. Characterization of the G6PD A- (202 G→A) variant: enzymatic restriction by NlaIII of the polymerase chain reaction fragment containing exons 3 and 4.
a: Propositus: homozygous mutation.
b: heterozygous control.
c: normal control.

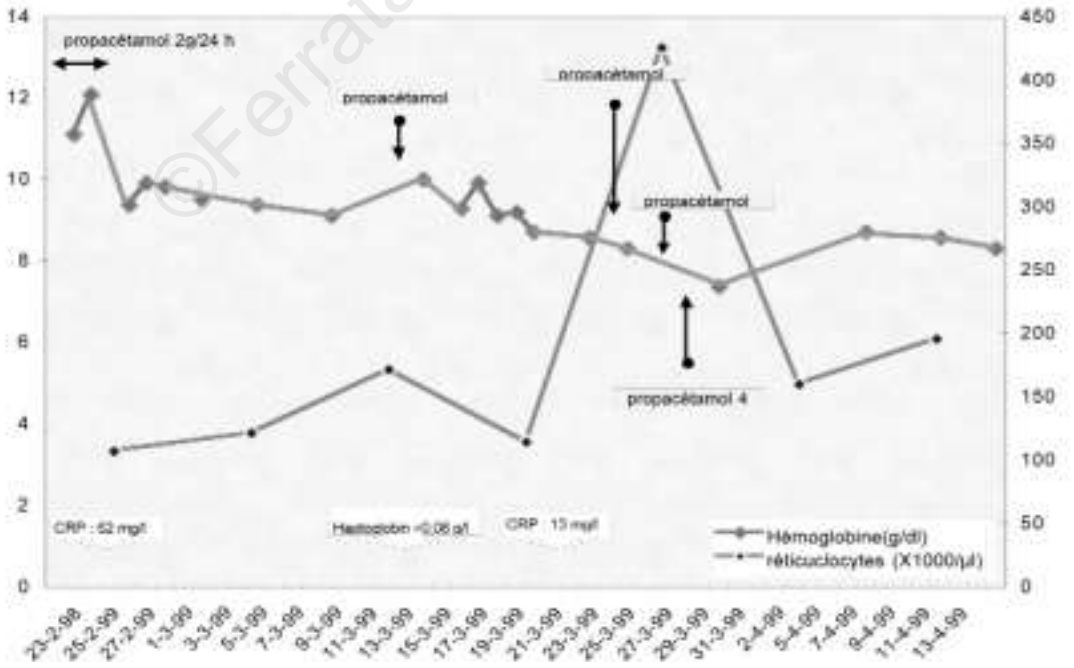

Figure 2. Evolution of hemoglobin and reticulocyte count.

hemoglobinopathy (hemoglobin was studied by electrophoresis and by high performance liquid chromatography), normal pyruvate kinase erythrocyte activity but a G6PD activity in erythrocytes (Randox reagent PD410) of 4.9% of normal, i.e. 7.37 mU/10^9 RBC (normal range 150–300). Molecular study of the G6PD gene was performed by restriction analysis following polymerase chain reaction,[3] and showed homozygosity for the mutations 202 A → G and 376 G → A (G6PD A-variant) (Figure 1).

Because acetaminophen is not considered as a hemolytic drug, it was continued. Each readministration of propacetamol led to a hemolytic crisis (4 times). The most severe hemolysis occurred after the last administration of propacetamol (6g). Haemoglobin concentration reached a nadir of 7.4 g/dL, reticulocyte count a peak of 425×10^9/L.

At this time, no fever, no clinical or biological infection, nor liver disease was found. Mrs. A. showed only a very mild inflammation with C reactive protein concentration of 13 mg/L. Figure 2 shows the evolution of hemoglobin and reticulocyte count. Several authors[1,2,4,5] consider that infections are the most common cause of hemolysis in patients with G6PD deficiency, that normal doses of acetaminophen have no hemolytic effect and can be safety administered to G6PD deficient patients. In our observation, Mrs. A. has only received propacetamol and low molecular weight heparin. During the first hemolytic episode, an inflammatory component cannot be neglected because C reactive protein was 62 mg/L but after the other administrations of propacetamol, this molecule was the only potential cause of hemolysis. We cannot find any differences between the G6PD deficient children described in reference 5 and our patient. During hospitalization our patient had no signs of any liver disease, cytolysis, or hepatic insufficiency (albumin and factor V were in normal ranges).

Propacetamol-induced hemolysis was declared to the French Regional Pharmacovigilance Center of Marseilles (declaration number MA99-608). According to their criteria, this institution considered that propacetamol-induced hemolysis had occurred at normal doses and that the intensity of hemolysis was dose-dependent. Therefore, this drug should be used with caution in G6PD-deficient patients and should be stopped if a hemolytic crisis appears.

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