Life-Threatening Hemolysis Caused by Dipyrone Overdose in a Patient with Glucose-6-Phophate Dehydrogenase Deficiency

Antopolsky M MD, Salameh S MD, Goldshtein B MD, Stalnikovicz R MD

Emergency Department, Hadassah University Hospital at Mt. Scopus, Jerusalem, Israel

Abstract

We describe a patient with glucose-6-phosphate dehydrogenase (G6PD) deficiency who presented with life-threatening hemolysis caused by an overdose of dipyrone. The literature on pyrazolone-induced hemolysis in G6PD-deficient patients is reviewed. Although the routine use of dipyrone very rarely causes hemolysis, even in G6PD-deficient individuals, the risk apparently increases with an overdose. Patients who present with a dipyrone overdose and known or suspected G6PD deficiency should be admitted for observation for at least 48 hours from the time of drug ingestion.

MeSH Words: dipyrone, G6PD deficiency, overdose

Introduction

Dipyrone (Optalgin in Israel; Metamizole or Analgin in many European and South-American countries) is one of the most widely used over-the-counter analgesics. It was initially thought to be contraindicated in the presence of glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is relevant to Israel given the high incidence of the disease that has been reported in certain populations [1]. However, more recent guidelines endorsed by the Israel Medical Association [2] advocate the free use of dipyrone by G6PD-deficient individuals.

Dipyrone overdose is often encountered in emergency departments (EDs) in the context of suicide attempts or self-directed overtreatment of pain. In the only large series of dipyrone overdose reported in the literature [3], the outcome was found to be generally benign. Thus, asymptomatic patients with dipyrone overdose are generally discharged after decontamination (when necessary) if the findings on general and psychiatric examination are negative. The aim of this study was to describe a case that raises concerns regarding the universal implementation of this practice.

Case Report

A 17-year-old boy was admitted to our ED following a suicide attempt by ingestion of 30g (60 pills) dipyrone (Optalgin) approximately 24 hours earlier. His previous medical history was unremarkable, with the exception of G6PD deficiency, found on routine testing in infancy, without any significant episode of hemolysis.

Besides psychological distress, the patient was asymptomatic .No jaundice was observed on physical examination and his abdomen was soft and non-tender. Blood parameters were within normal range for our laboratory (Table 1), although on reassessment, mild anemia (11.3 g %) was noted. The patient was discharged after psychiatric consultation.

Four days later, the patient returned to the ED because of extreme fatigue, vomiting and jaundice. He reported that a few hours after discharge at the index visit, he began to feel ill, with nausea, loss of appetite and fatigue. He stayed in bed for the next three days, but the symptoms only worsened, and he vomited several times. The patient and his parents denied intake of any other medicines, either therapeutically or with suicide intent, during this time. Moreover, the psychiatrist stated that the psychological problem that led to the suicide attempt had been solved.

On admission, the patient was conscious and alert but weak, with prominent jaundice. The physical examination was otherwise normal. Laboratory work-up (summarized in Table 1) demonstrated severe hemolysis and acute renal failure. The patient was admitted to the intensive care unit of our hospital and later transferred to that of a tertiary medical center. He was treated with repeated blood transfusions, intravenous fluids and plasmapheresis. The hemolysis gradually resolved and the hemoglobin levels and renal function stabilized and then improved (Table 1). On follow-up two months later, hemoglobin measured 14.2 g%, and renal function was normal.

Table 1. Results of laboratory investigation in a G6PD-deficient patient with dipyrone overdose

	1st ED visit 24h after ingestion	2nd ED visit 5d after ingestion	6d after ingestion	At discharge	At 2-mo follow-up
Hemoglobin, g%	11.3	9.9	6.8	8.7	**14.2**
Reticulocyte count, %	-	-	6.17	4	-
Total bilirubin, µmol/L	13	74	82	9	-
Unconjugated bilirubin, µmol/L	-	53	-	-	-
Lactate dehy-drogenase, IU/L		9955	15165	2628	-
Creatinine, µmol/L	94	380	420	320	92

Discussion

Dipyrone (Optalgin, Metamizole, Analgin) is a pyrazolone derivative used as an analgesic and antipyretic. It was first synthesized by the German company Hoechst AG in 1920 and has been in worldwide use since 1922. Reports of cases of dipyrone-induced agranulocytosis, a serious and potentially fatal complication, led to the withdrawal of the drug in several countries. Today, dipyrone is offered as a prescription drug in Germany and over the counter in Spain, Russia, India, Israel and Latin America. It is banned in the USA and many European countries.

Our search of the literature yielded two large studies on dipyrone [3] and on the pyrazolone family of analgesics [4] that were based on information from poison-control centers. Neither reported any cases of hemolysis. They did not address the issue of G6PD deficiency. In one case report published over 20 years ago [5], severe hemolysis occurred in a G6PD-deficient infant after administration of another pyrazolonic drug. Herman and Ben-Meir [6], in a 1975 survey of general practice with G6PD-deficient patients, reported 85 challenges with dipyrone that resulted in only one case of overt hemolysis. More recently, a laboratory study by Ciftci et al. [7] showed that metamizole had a significant inhibitory effect on the activity of G6PD enzyme both *in vivo* (in rats) and *in vitro*.

On the basis of these findings and the case presented here, we conclude that dipyrone has a low potential for causing hemolysis, even in G6PD-deficient individuals (in whom it is consequently not contraindicated). However, the risk apparently increases when an overdose of

the drug is taken. Therefore, until more extensive pharmacologic studies are performed, we propose that in cases of dipyrone overdose, patients with known or suspected (on the basis of ethnic origin) G6PD deficiency should be admitted for observation for at least 48 hours from ingestion of the drug, with serial testing for hemoglobin, bilirubin, and lactate dehydrogenase levels.

References

1. Oppenheim A, Jury CL, Rund D, Vulliamy TJ, Luzzatto L. G6PD Mediterranean accounts for the high prevalence of G6PD deficiency in Kurdish Jews. Hum Genet 1993; 91(3):293-294.
2. Clinical Guidelines on Medical Treatment in G6PD-deficient individuals [in Hebrew]. Israel Medical Association, 2003.
3. Bentur Y, Cohen O. Dipyrone overdose. J Toxicol Clin Toxicol 2004; 42(3):261–265.
4. Okonek S, Reinecke HJ. Acute toxicity of pyrazolones. Am J Med 1983; 75:94-98.
5. Sansone G, Reali S, Sansone R, Allegranza F. Acute hemolytic anemia induced by a pyrazolonic drug in a child with glucose-6-phosphate dehydrogenase deficiency. Acta Haematol 1984; 72(4):285.
6. Herman J, Ben-Meir S. Overt hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency: a survey in general practice. Isr J Med Sci. 1975 Apr; 11(4):340-346.
7. Ciftci M, Ozmen I, Buyukokuroglu ME, Pence S, Kufrevioglu OI. Effects of metamizol and magnesium sulfate on enzyme activity of glucose 6-phosphate dehydrogenase from human erythrocyte in vitro and rat erythrocyte in vivo. Clin Biochem 2001 Jun; 34(4):297-302.

Competing Interests: None

Funding: None

This manuscript has been peer reviewed.

Correspondence:

Dr. Meir Antopolsky
Emergency Department
Hadassah University Hosputal at Mt. Scopus
Jersalem, Israel 91120
Tel: (972)-2-5844333
Fax: (972)-2-5844176
Email: mimosa4@netvision.net.il