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Ciprofloxacin-induced acute haemolytic anaemia in a patient with glucose-6-phosphate dehydrogenase Mediterranean deficiency: a case report

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Dear Editor,

Glucose-6-phosphate dehydrogenase (G6PD) deficiency was discovered while investigating the development of haemolysis in patients who had received primaquine, and subsequently, several drugs have been linked to acute haemolysis in G6PD-deficient individuals [1]. Whether a specific drug directly causes haemolytic crisis in G6PD-deficient patients is often difficult to establish. Haemolysis following ciprofloxacin therapy has been described; however, definitive evidence for such an association is still lacking [2]. Haemolytic reactions to ciprofloxacin have been observed only in a few, isolated cases and currently there are no published reports on an association between the two [3]. Therefore, ciprofloxacin is not usually included in the lists of unsafe drugs in G6PD deficiency (see e.g. [4]). Herein, we report a patient developing intravascular haemolysis secondary to G6PD Mediterranean deficiency associated with ciprofloxacin administration.

An 88-year-old woman of Sicilian origin presented with nausea, vomiting and diarrhoea seven days after completion

of her first cycle of chemotherapy for colon cancer with capecitabine and irinotecan [5]. Colorectal cancer was diagnosed as pT4, N2, Mx, R1, V1, L1 about a year before and was initially treated with capecitabine monotherapy until the disease progressed. Past medical history included arterial hypertension, well controlled with daily administration of bisoprolol 5 mg, lercanidipine 20 mg and irbesartan 300 mg, and G6PD Mediterranean deficiency with intermittent acute haemolytic crises. The last haemolytic episode occurred about 3 years ago and was probably triggered by influenza. At the time of colorectal cancer diagnosis, G6PDH activity was 16 U/10¹² erythrocytes (normal range 146–376); an indirect Coombs test was negative. On physical examination at admission, the patient was dehydrated; however, blood pressure, heart rate and respiratory rate were normal. Body temperature was 36.8°C. White blood cell count was 12,950/μL (normal range 4,800–10,800) and haemoglobin was 11.1 g/dL (normal range 12.0–18.0). Platelets, mean corpuscular volume and mean corpuscular haemoglobin content of erythrocytes were normal as were blood glucose, serum creatinine and blood gas analyses. Symptomatic treatment was initiated with metoclopramide 10 mg administered intravenously every 8 h and with intravenous infusion of 5% glucose and normal saline solutions for re-hydration. The second day, the patient became sub-febrile with body temperature rising to 37.9°C. C-reactive protein was 9.14 mg/dL (normal range 0–0.5), and urine and chest X-ray were normal. Diarrhoea persisted. As the patient had no dyspnoea or cough, empiric antibiotic therapy was initiated with intravenous ciprofloxacin 500 mg daily. After the second dose of ciprofloxacin, she developed shortness of breath and became cyanotic on days 3 and 4. Laboratory testing showed that her haematocrit had dropped to 17.7%, haemoglobin was 6.4 g/dL, lactate dehydrogenase

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rose from 560 on admission to 1155 U/L (normal range 200–479), total bilirubin was 35.4 mg/dL (normal range 0.2–1.4) and haptoglobin was 27 mg/dL (normal range 36–195). Blood and stool cultures remained normal. The patient was treated supportively with intravenous hydration and red cell transfusion. Ciprofloxacin was discontinued and replaced with piperacillin 2 g/tazobactam 0.25 g given intravenously every 8 h for additional 8 days as empiric antibiotic treatment of chemotherapy-associated febrile diarrhoea. Enteral nutrition was changed to intravenous for a total of 16 days. The elderly patient was discharged on day 30 with haematocrit of 33.6% and haemoglobin of 11.5 g/dL; lactate dehydrogenase returned to 512 U/L. Renal function remained unaffected and icterus had normalised.

Antibiotic drugs classically involved in acute intravascular haemolysis of G6PD deficiency include sulfamethoxazole, nitrofurantoin and chloramphenicol [6]. Other drugs could precipitate haemolysis under particular circumstances such as fever, keto-acidosis or use at high doses including trimetoprim and streptomycin [6–8]. Additional anti-infectious agents able to trigger haemolysis in G6PD deficiency include some antimalarial drugs, especially primaquine [9].

The fluoroquinolones have become an increasingly popular class of antibiotics for use in a variety of infections, with ciprofloxacin probably being most frequently marketed and prescribed in the past. Ofloxacin has been reported to be safe in G6PDH deficiency [10]. Haemolytic anaemia is listed among significant adverse reactions at low frequencies (less than 1%), however, not consistently associated with G6PD deficiency (e.g. norfloxacin [11], ciprofloxacin [12]). Ciprofloxacin is classified as being unsafe in G6PD deficiency by the “Italian Favism-G6PD Deficiency Association” in the Mediterranean region and in Asia; however, haemolytic reactions to this substance have been reported only in few unpublished cases [3]. Accordingly, fluoroquinolones as triggers of acute haemolytic anaemia in G6PD deficiency are only infrequently mentioned in point-of-care manuals or text books [4].

The patient with G6PD Mediterranean deficiency presented here underwent repeated cycles of chemotherapy with capecitabine without any haemolytic problems. A few days after completion of capecitabine/irinotecan, however, she developed non-infective acute diarrhoea, known as typical toxicity of irinotecan, which can be associated with cholinergic symptoms and even be life-threatening. If persisting for more than 48 h, treatment recommendations for such a type of diarrhoea include hospitalisation and administration of ciprofloxacin, in particular when fever develops, as what happened in the case of our patient. The adverse haemolytic event appeared after ciprofloxacin was administered and improved when the drug was discontinued and changed to an alternative antibiotic. No other changes in medication had been made. Fever may have caused the

adverse event, but this is unlikely as the patient's temperature rose to 37.9°C only, and additional signs of infectious disease were absent. The Naranjo probability scale, thus, demonstrated a probable likelihood that ciprofloxacin was the cause of acute haemolysis in our patient [13].

Although acute haemolytic episodes in G6PD deficiency usually occur in male patients because of X-linked inheritance [1], haemolysis can also occur especially in elderly female heterozygous patients because of lyonization and oligoclonality of the bone marrow in old age [14].

A warning is included in the Italian package insert about ciprofloxacin as a potentially unsafe drug in G6PD deficiency [15] but not in package inserts in other European countries or the US [16]. At least in Europe and Asia, package inserts should uniformly warn that ciprofloxacin may be unsafe in G6PD deficiency. We also suggest that mention should be made in point-of-care manuals or text books of ciprofloxacin as a possible trigger of acute haemolytic anaemia in G6PD deficiency, which may be of relevance also when prescribing ciprofloxacin in pregnant women.

References

- Cappellini MD, Fiorelli G (2008) Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 371:64–74
- Luzzatto L, Metha A, Vulliamy T (2001) Glucose 6-phosphate dehydrogenase deficiency. In: Scriver CR, Beaudet AL, Sly WS et al (eds) *The metabolic and molecular bases of inherited disease*, 8th edn. McGraw-Hill, Columbus, pp 4517–4553
- Associazione Italiana di Favismo-Deficit di G6PD (2009) <http://www.g6pd.org/favism/english/index.mvc?pgid=avoid>. Accessed 11 December 2009
- Glader B (2009) Diagnosis and treatment of glucose-6-phosphate dehydrogenase deficiency. In: Schrier SL, Mahoney DH, eds. *UpToDate*. http://www.uptodate.com/online/content/topic.do?topicKey=red_cell/21725&selectedTitle=1~150&source=search_result. Accessed 11 December 2009
- Jordan K, Kellner O, Kegel T, Schmoll HJ, Grothey A (2004) Phase II trial of capecitabine/irinotecan and capecitabine/oxaliplatin in advanced gastrointestinal cancers. *Clin Colorectal Cancer* 4:46–50
- Beutler E (1994) G6PD deficiency. *Blood* 84:3613–3636
- Herman J, Ben-Meir S (1975) Overt hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency: a survey in general practice. *Isr J Med Sci* 11:340–346
- Reinke CM, Thomas JK, Graves AH (1996) Apparent hemolysis in an AIDS patient receiving trimethoprim/sulfamethoxazole: case report and literature review. *J Pharm Technol* 11:256–262, quiz 293–295
- Beutler E, Duparc S, G6PD Deficiency Working Group (2007) Glucose-6-phosphate dehydrogenase deficiency and antimalarial drug development. *Am J Trop Med Hyg* 77:779–789
- Gaetani GF, Gallano S, Miglino M, Canepa L, Ferrarie AM (1991) Absence of hemolytic potential of ofloxacin toward dehydrogenase deficient erythrocytes. *Curr Ther Res* 42:329–334
- Norfloxacin: Drug information. Copyright 1978–2009 Lexi-Comp, Inc. (2009) <http://www.uptodate.com/online/content/topic.do?jsessionid=63A4FDC99FB1FD4EC3284871C6C67EFE.1003?>

- [topicKey=drug_1_z/183660&drug=true](#). Accessed 11 December 2009
12. Andrews PA, Robinson GT (1999) Intravascular haemolysis and interstitial nephritis in association with ciprofloxacin. *Nephron* 83:359–360
 13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ (1981) A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30:239–245
 14. Lim F, Wulliamy T, Abdalla SH (2005) An Ashkenazi Jewish woman presenting with favism. *J Clin Pathol* 58:317–319
 15. Italian Ciprofloxacin Package Insert (2009) <http://www.paginesanitarie.com/skfarmaci/monografia%20di%20CIPROXIN%206CPR%20RIV%20500MG.htm>. Accessed 28 December 2009
 16. US Ciprofloxacin Package Insert (2009) http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019537s073,020780s030lbl.pdf. Accessed 28 December 2009