Drug Saf 2012; 35 (1): 85-86
0114-5916/12/0001-0085/$49.95/0

Glucose-6-Phosphate Dehydrogenase Deficiency and Safety of Methylene Blue

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In the recent review article published in *Drug Safety* by Youngster and colleagues,[1] methylthioninium chloride (methylene blue) was identified as one of seven drugs that should be avoided in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to evidence of an association with haemolysis. However, this conclusion was based on case reports from the literature of only five patients, which were not well described. Of these, three were neonates and only four were G6PD deficient.[1] In their review, the authors acknowledge conflicting evidence by stating that our published data showed methylthioninium chloride to be safe in a large study on 74 adult men with G6PD deficiency.[2] Moreover, the authors have briefly referred to our first study on the safety and efficacy of methylthioninium chloride in young children of sub-Saharan Africa with malaria but forgot to document the findings in children with G6PD deficiency. There was no haemolysis amongst the 24 children with G6PD deficiency who were treated with methylthioninium chloride.[3] Finally, two further published studies on children treated with methylthioninium chloride for uncomplicated falciparum malaria were not considered in the review. These large studies included another 132 children with G6PD deficiency, and no clinically relevant association between methylthioninium chloride treatment and haemolysis was shown.[4,5] However, the predominant type of G6PD deficiency in sub-Saharan Africa (the region with the highest malaria burden) is G6PD A-, and the degree of safety of methylthioninium chloride in populations outside Africa with more severe types of G6PD deficiency still needs to be investigated.

References

1. Youngster I, Arcavi L, Schechmaster R, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. Drug Saf 2010; 33 (9): 713-26
2. Mandi G, Witte S, Meissner P, et al. Safety of the combination of chloroquine and methylene blue in healthy adult men with G6PD deficiency from rural Burkina Faso. Trop Med Int Health 2005; 10: 32-8
3. Meissner P, Mandi G, Witte S, et al. Safety of the methylene blue plus chloroquine combination in the treatment of uncomplicated falciparum malaria in young children of Burkina Faso. Malar J 2005; 4: 45
4. Meissner P, Mandi G, Coulibaly B, et al. Methylene blue for malaria in Africa: results from a dose-finding study in combination with chloroquine. Malar J 2006; 5: 84
5. Zoungrana A, Coulibaly B, Sié A, et al. Safety and efficacy of methylene blue combined with artesunate or amodiaquine for uncomplicated falciparum malaria: a randomized controlled trial from Burkina Faso. PLoS One 2008; 3 (2): e1630

The Authors' Reply

We would like to thank Müller et al.[1] for their comment on our recent review examining the safety of drugs in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients.[2] The authors clearly have vast experience with the use of methylthioninium chloride (methylene blue) in malaria patients in sub-Saharan Africa, and they raise the concern that we have wrongly included this drug in our list of medications that should be avoided in individuals with G6PD deficiency. We agree with the authors that current data suggest that methylthioninium chloride can probably safely be administered in individuals with the G6PD A- variant, and indeed we did not include every report in our review.[3,4] However, as the authors themselves pointed out "the degree of safety of methylthioninium chloride in populations outside Africa with more severe types of G6PD deficiency still needs to be investigated."

As has just recently been exemplified by Hue et al.,[5] even in a homogeneous, closed population, a multitude of different G6PD deficiency variants can be found, resulting in various severities of enzyme defects. In most parts of the world, the diagnosis of G6PD deficiency is still based on enzymatic tests, and only a minority of patients undergoes genetic diagnosis. For that reason we did not divide the different drugs according to their safety in sub-populations. We completely agree with Müller et al.[1] that there is no clear evidence that methylthioninium chloride causes severe haemolytic reactions in G6PD-deficient patients. We feel, however, that there are enough reports of haemolytic reactions in the literature to warrant extreme caution when administering the drug in susceptible patients.[6-8]

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References

1. Müller O, Meissner P, Mansmann U. Glucose-6-phosphate dehydrogenase deficiency and safety of methylene blue [letter]. Drug Saf 2012; 35 (1): 85-6
2. Youngster I, Arcavi L, Schechmaster R, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. Drug Saf 2010; 33 (9): 713-26
3. Meissner P, Mandi G, Coulibaly B, et al. Methylene blue for malaria in Africa: results from a dose-finding study in combination with chloroquine. Malar J 2006; 5: 84
4. Zoungrana A, Coulibaly B, Sié A, et al. Safety and efficacy of methylene blue combined with artesunate or amodiaquine for uncomplicated falciparum malaria: a randomized controlled trial from Burkina Faso. PLoS One 2008; 3 (2): e1630
5. Hue NT, Charlieu JP, Chau TT, et al. Glucose-6-phosphate dehydrogenase (G6PD) mutations and haemoglobinuria syndrome in the Vietnamese population. Malar J 2009 Jul 10; 8: 152
6. Rosen PJ, Johnson C, Mcgehee WG, et al. Failure of methylene blue treatment in toxic methemoglobinemia: association with glucose-6-phosphate dehydrogenase deficiency. Ann Intern Med 1971; 75: 83-6
7. Gauthier TW. Methylene blue-induced hyperbilirubinemia in neonatal glucose-6-phosphate dehydrogenase (G6PD) deficiency. J Matern Fetal Med 2000; 9: 252-4
8. Foltz LM, Dalal BI, Wadsworth LD, et al. Recognition and management of methemoglobinemia and hemolysis in a G6PD-deficient patient on experimental anticancer drug Triapine. Am J Hematol 2006; 81: 210-1