

Case Series

The potential nephrotoxic effect of single tablet of 15 mg primaquine in G6PD deficient Hadoti region population of India

Vikash Khandelia^{1*}, Pavankumar Pyarsabadi², Umashankar Nama¹, Saurabh Chittora²,
Yogesh Swami², Hemant Richariya²

¹Department of Nephrology, ²Department of Medicine, Government Medical College, Kota, Rajasthan, India

Received: 14 February 2017

Accepted: 20 February 2017

*Correspondence:

Dr. Vikash Khandelia,

E-mail: pavankumarp145@gmail.com

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ABSTRACT

Primaquine is used in prevention of relapse of plasmodium vivax and ovale. It is known to cause haemolysis induced acute kidney injury in patients with glucose-6-phosphate dehydrogenase (G-6-PD) enzyme deficiency. Primaquine is widely used in the remote areas of Hadoti region of India by many non-registered practitioners for treatment of febrile illnesses without prior testing of G-6-PD status. Due to this practice, many patients land up with the grave consequences with significant health care burden. We report 8 such cases, which were referred to our hospital, New hospital medical college, Kota, Rajasthan, India. Our study included a series of 8 cases which were referred to our hospital with significantly deranged renal function test due to use of primaquine without prior testing of G-6-PD status. Routine blood investigations including renal function tests and G-6-PD status were measured. In our study, we found that patients with febrile illness and G-6-PD deficiency developed acute kidney injury even with a single tablet of 15 mg of primaquine. The use of even a single dose of 15 mg primaquine may not be safe in population of Hadoti region of India. Hence they should not be exposed to primaquine without prior G-6-PD testing.

Keywords: AKI, G6PD, New Hospital Medical College Kota, Primaquine

INTRODUCTION

The malaria parasite *Plasmodium vivax* causes an acute symptomatic blood-stage infection and characteristically has a liver stage of dormant parasites, called hypnozoites. Weeks to months later, these hypnozoites awaken to cause renewed blood infections, called relapses. Although considered a benign infection, acute vivax can result in severe disease and death in ~2% of hospitalised patients.^{1,2} Treatment to eliminate the hypnozoites is also challenging for several reasons. Most *P.vivax* strains relapse early and frequently, typically within 3 weeks, and cause a median of 5-6 relapses/person-year.³ Primaquine is the only licensed drug for eliminating the hypnozoites and high doses (0.5 mg/kg/day for 14 days) are needed for strains from South-East Asia.⁴⁻⁶ In patients

with the X-linked erythrocyte enzyme disorder glucose-6-phosphate dehydrogenase deficiency (G6PDd), primaquine causes dose-dependent acute haemolytic anaemia (AHA) that is greater in the more severe deficient G6PD variants, AHA can be potentially life threatening but primaquine-related deaths are very rare.⁷⁻¹³ This toxicity is a significant public health concern because G6PDd affects approximately 400 million people who live mostly in malaria-endemic countries where the median G6PDd allele prevalence is 8%. Testing for G6PDd is not performed in the majority of malaria-endemic countries. Hadoti region is one of the malaria endemic areas of Rajasthan state of India with significant burden of disease and related complications. The drug primaquine is widely used in remote areas of hadoti region by many non-registered practitioners for febrile

illnesses without prior testing of G6PD status. Due to this practice many patients landed up into life threatening acute kidney injury. We report a study of such eight cases which were referred to our hospital (NHMC, Kota) for further management. This study was done to highlight the potential nephrotoxic effect of even a low dose of primaquine (15 mg in our study) in G6PD deficient subjects.

CASE SERIES

Our study included eight patients with acute kidney injury who were referred from remote areas of hadoti region after a history of drug (primaquine) intake for febrile illness. The study included patients who were referred to our hospital with acute kidney injury from June 2016 to December 2016.

All the patients included in the study had a history of febrile illness for which they were prescribed primaquine at the remote areas of hadoti region. Over the period of course six patients among eight developed oliguria, four of them had gross hematuria and two had symptoms and signs of acute pulmonary edema and renal profile of all the patients were significantly deranged (Table 1). With such complications patients were referred to our hospital for further management and were admitted to nephrology department. At our hospital detailed history was obtained and patients were examined, vital signs were checked and monitored simultaneously and routine blood

investigations were done including G6PD status testing by standard laboratory methods.

All eight patients were found to have glucose 6 phosphate dehydrogenase enzyme deficiency with significant deranged renal profile. The blood urea was found to be as high as 265 mg/dl (ranging between 83.9 mg/dl to 265 mg/dl) and serum creatinine as high as 20.8 mg/dl (ranging between 4.1 to 20.8 mg/dl). Serum lactate dehydrogenase (LDH) levels were found to be high in all patients with values as high as 7246 U/L. Serum electrolytes were measured in all of them and hyperkalemia was found in four patients (Table 2). Arterial blood gas analysis was done and two patients were having severe metabolic acidosis.

Table 1: G-6-PD status and chief complaints of study subjects.

Age/sex	G-6-PD status	Chief complaints
27/M	Deficient	Fever, oliguria, hematuria
18/M	Deficient	Fever, vomiting, anorexia
30/M	Deficient	Fever, hematuria
56/M	Deficient	Oliguria, fever
21/M	Deficient	Hematuria, oliguria
50/M	Deficient	Dyspnea, oliguria, Fever
47/M	Deficient	Oliguria, hematuria
70/M	Deficient	Dyspnea, oliguria

G-6-PD Glucose-6-phosphate dehydrogenase.

Table 2: Biochemical parameters on day of admission.

Cases	Blood urea	Serum creatinine	Serum sodium	Serum potassium	S. LDH
1	83.9	6.9	133	4.2	7246
2	206	18.4	137	4.0	3093
3	99	4.1	138	3.2	3409
4	212	6.0	134	6.6	4300
5	136	10.6	132	5.8	2737
6	265	20.8	134	5.9	7285
7	131	7.8	136	3.9	2201
8	181	8.7	133	6.1	3320

S.LDH Serum lactate dehydrogenase.

Table 3: Duration of exposure and AKI reported and the need for hemodialysis.

Cases	Day of drug administration	AKI reported	Number of tablets consumed*	Hemodialysis requirement (yes/no)
1	Day 0	Day 6	2	No
2	Day 0	Day 5	1	No
3	Day 0	Day 3	2	No
4	Day 0	Day 4	1	Yes
5	Day 0	Day 4	3	Yes
6	Day 0	Day 5	1	Yes
7	Day 0	Day 6	4	No
8	Day 0	Day 7	3	Yes

AKI Acute kidney injury, *Primaquine (1 tablet =15 mg base).

Four patients among eight were managed with haemodialysis therapy, with one requiring multiple settings (four sessions) and other four patients were managed conservatively. Acute pulmonary edema and uraemic symptoms in the patients were the indications for haemodialysis therapy. Patients were managed under strict supervision in intensive care unit. Renal function status were monitored on regular periodic basis along with input output charting. Over the course of treatment in the hospital the general condition of patients stabilized, urine output improved and renal profile of the patients was in improving trends. patients were followed up after a brief period and renal function status monitored till complete recovery.

DISCUSSION

That primaquine can trigger acute haemolytic anaemia followed by acute kidney injury in subjects who have an inherited mutation of the glucose 6 phosphate dehydrogenase gene has been known for over a century; however, these events still occur, because when giving the drug either the G6PD status is not known, or the risk of this potentially life threatening complication is under estimated.

Here we report the potential nephrotoxic effect of primaquine in as low dose as 15 mg in population of hadoti region of India. Acute kidney injury was found in three patients with intake of a single 15 mg tablet of primaquine, which was alarming in our study as the WHO states that a single tablet of primaquine can be given in patients without prior testing of G6PD status. However, in his study ALF Alving et al showed that a weekly dose of 45 mg primaquine proved highly effective against severe vivax infections when administered for eight weeks. It cured 90% of infections, yet did not produce clinically demonstrable haemolysis in primaquine sensitive adult males with major expression of the haemolytic trait.¹⁴

The reason for such occurrence of acute kidney injury with such low dose of primaquine in population of hadoti region are obscure and may be related to G6PD variants (which could be under the influence of more drug sensitive haemolysis) or the other host factors. The degrees of G6PD deficiency varies greatly, ranging from mild in negros (African variant A-) to very high in people of eastern Mediterranean and west asian descent (Mediterranean variant B-) and in population groups scattered throughout Asia (Asian variants). In B- variant and related Asian variant individuals, even young erythrocytes are deficient in G6PD and their heamolysis results in progressive heamoglobinaemia and heamoglobinuria with serious consequences (acute kidney injury).¹⁵

However, a study by Pannacciulli et al and Reeve PA et al have reported heamolysis after administration of a single 45 mg dose in whites and in patients in Vanuata

with severe G6PD deficiency, although the occurrence of acute kidney injury was not reported.^{16,17} This is in contrast to our study where a single 15 mg dose of primaquine has caused severe acute kidney injury requiring hemodialysis therapy in four patients.

A study by Karwacki JJ et al reported severe haemolysis with renal failure requiring dialysis in a Thai soldier after three 15 mg doses of primaquine.¹⁸ Other similar study by Salvidio E et al reported severe hemolysis among G6PD deficient Sardinians with a single dose of 30 mg of primaquine.¹⁹

Similarly, in Burma, Batu AT et al reported 34-48% haemolysis of labelled G6PD deficient erythrocytes that had been injected into the normal Burmese adult males who were given a course of 15 mg daily. The degree of heamolysis in these individuals was equal to that induced by 30 mg daily in the G6PD deficient Negroes reported by Alving et al.²⁰

In Thailand, Charoenlarp et al found heamolysis of upto 18% of erythrocytes in individuals receiving single doses of 45 mg of primaquine but in both Malaysia and Thailand it has been concluded that the daily 15 mg and the weekly 45 mg course may be given without fear of haemolysis, except in a very small number of individuals.²¹

However, our study expressed concern over the indiscriminate use of primaquine even in low doses in G6PD deficient individuals of hadoti region of Rajasthan, India. Acute kidney injury was even seen in young individuals who had no prior history or evidence of kidney disease which is of utmost importance for all the treating physicians at the remote areas. With this knowledge of potential nephrotoxic effect of even single low dose of primaquine most of the untoward complications can be prevented.

CONCLUSION

Primaquine can lead to severe acute kidney injury in patients with G6PD deficiency in as low dose as 15 mg. The use of this drug without prior testing of G6PD status raise a concern to relook into the inappropriate use of primaquine in remote areas of Hadoti region, Rajasthan, India.

In present study four patients among eight required renal replacement therapy as a life saving measure which is of extreme concern in terms of both health resources and patients health burden. Therefore, primaquine should be used with extreme caution and with proper monitoring considering the serious life threatening nephrotoxicity it can cause in otherwise healthy population if not taken seriously or neglected.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Khandelia V, Pyarsabadi P, Nama U, Chittora S, Swami Y, Richariya H. The potential nephrotoxic effect of single tablet of 15 mg primaquine in G6PD deficient Hadoti region population of India. *Int J Adv Med* 2017;4:605-8.