REVIEW ARTICLE

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Medications and Glucose-6-Phosphate Dehydrogenase Deficiency

An Evidence-Based Review

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme defect and one of the most common genetic disorders worldwide, with an estimated 400 million people worldwide carrying a mutation in the G6PD gene that causes deficiency of the enzyme. Although drug-induced haemolysis is considered the most common adverse clinical consequence of G6PD deficiency, significant confusion exists regarding which drugs can cause haemolytic anaemia in patients with G6PD deficiency. In the absence of consensus among physicians, patients are subject to conflicting advice, causing uncertainty and distress. In the current review we aimed, by thorough search of the medical literature, to collect evidence on which to base decisions either to prohibit or allow the use of various medications in patients with G6PD deficiency. A literature search was conducted during May 2009 for studies and case reports on medication use and G6PD deficiency using the following sources: MEDLINE (1966–May 2009), PubMed (1950–May 2009), the Cochrane database of systematic reviews (2009), and major pharmacology, internal medicine, haematology and paediatric textbooks. After assessing the literature, we divided medications into one of three groups: medications that should be avoided in individuals with G6PD deficiency, medications that were considered unsafe by at least one source, but according to our review can probably be given safely in normal therapeutic dosages to individuals with G6PD deficiency as evidence does not contravene their use, and medications where no evidence at all was found to contravene their use in G6PD-deficient patients. It is reasonable to conclude that, over time, many compounds have been wrongly cited as causing haemolysis because they were administered to patients experiencing an infection-related haemolytic episode. We found solid evidence to prohibit only seven currently used medications: dapsone, methylthioninium chloride (methylene blue), nitrofurantoin, phenazopyridine, primaquine, rasburicase and tolonium chloride (toluidine blue). Regarding all other medications, our review found no evidence to contravene their use in normal therapeutic doses to G6PD-deficient patients.

There is a need for evidence-based global consensus regarding medication use in G6PD-deficient patients.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme defect and one of the most common genetic disorders worldwide.[1] The enzyme has an important role in preserving the integrity of the red blood cell and defending it against oxidative damage. An estimated 400 million people worldwide carry a mutation in the G6PD gene that is

associated with enzyme deficiency, with marked racial and geographic differences. Among Caucasian populations, the prevalence of G6PD deficiency ranges from <1 in 1000 among northern European populations to 50% of males among Kurdish Jews. G6PD deficiency is prevalent in Africa, China and Southeast Asia, but it is rare in Japan. In North America, the disease is mainly confined to immigrant populations.[1,2] It is an X-linked disorder and was first described in the 1950s after the development of haemolysis in patients receiving primaquine therapy.[3,4] Indeed, drug-induced haemolysis is considered the most common adverse clinical consequence of G6PD deficiency[5] (figure 1). However, infectious diseases appear to be a common precipitating factor.[6] As a result, significant confusion exists regarding which drugs can cause haemolytic anaemia in patients with G6PD deficiency. It is reasonable to conclude that many compounds have been cited as causing haemolysis because they were given to patients experiencing an infection-related haemolytic episode. Beutler[7] wrote "It is likely that in most of these anecdotes the event precipitating haemolysis was an infection or treatment with some other drug." Indeed, even today there is no consensus regarding which medications are unsuitable for patients with G6PD deficiency. Needless to say, in the absence of consensus among physicians, patients are subject to conflicting advice, causing uncertainty and distress.

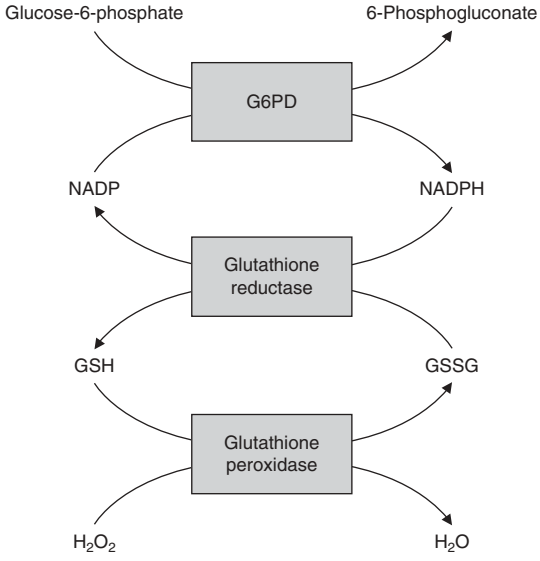

Fig. 1. Role of glucose-6-phosphate dehydrogenase (G6PD) in defense against oxidant injury. The disposal of H_2O_2, a potential oxidant, is dependent on the adequacy of reduced glutathione (GSH), which is generated by the action of the reduced form of nicotinamide adenine dinucleotide (NADPH). The synthesis of NADPH is dependent on the activity of G6PD. **GSSG** = oxidized glutathione.

As clinical pharmacologists, we are often consulted regarding treatment of G6PD-deficient patients. No single reference is generally accepted as a source of information. In an effort to compile a list of prohibited medications, we consulted three leading textbooks in the fields of internal medicine, paediatrics and haematology.[8-10] Surprisingly, of the 30 mentioned medications, only five showed concordance amongst all three texts (table I). In the current review we aimed, by a thorough search of the medical literature, to collect evidence on which it would be possible to base decisions either to support or reject the use of various medications in patients with G6PD deficiency.

1. Literature Search Methodology

A literature search was conducted during May 2009 for studies and case reports on medication use and G6PD deficiency. The following databases were searched electronically: MEDLINE (1966–May 2009), PubMed (1950–May 2009), the Cochrane database of systematic reviews (2009), and major pharmacology, internal medicine, haematology and paediatric textbooks.

Keywords were 'G6PD deficiency', 'haemolysis', 'haemolytic anaemia' and specific medications, using both generic and brand names. Textbook references, as well as the references of the bibliography of all the included studies, case reports and reviews that were identified by this search strategy, were searched manually.

After assessing the literature, medications were divided into one of three groups:

1. Medications that should be avoided in patients with G6PD deficiency. These are compounds with a well established association with haemolysis as

Table I. Drugs that should be avoided by patients with glucose-6-phosphate dehydrogenase deficiency according to three leading text books

Medication	*Williams Hematology*[8]	*Nelson Textbook of Pediatrics*[9]	*Harrison's Principles of Internal Medicine*[10]
Acetanilid	Avoid	No contraindication	Avoid
Aspirin (acetylsalicylic acid)	No contraindication	Avoid	No contraindication
Chloramphenicol	No contraindication	Avoid	No contraindication
Chloroquine	No contraindication	Avoid	No contraindication
Dapsone	No contraindication	No contraindication	Avoid
Dapsone/chlorproguanil	No contraindication	No contraindication	Avoid
Dimercaptosuccinic acid	Avoid	No contraindication	No contraindication
Furazolidone	Avoid	No contraindication	No contraindication
Glibenclamide (glyburide)	Avoid	No contraindication	No contraindication
Isobutyl nitrite	Avoid	No contraindication	No contraindication
Methylthioninium chloride (methylene blue)	Avoid	Avoid	Avoid
Nalidixic acid (NeGram)	Avoid	Avoid	Avoid
Niridazole (ambilhar)	Avoid	No contraindication	Avoid
Nitrofurantoin (furadantin)	Avoid	Avoid	Avoid
Pamaquine	No contraindication	Avoid	No contraindication
Phenacetin	No contraindication	Avoid	No contraindication
Phenazopyridine (pyridium)	Avoid	Avoid	Avoid
Phenylhydrazine	Avoid	No contraindication	No contraindication
Primaquine	Avoid	Avoid	Avoid
Probenecid	No contraindication	Avoid	No contraindication
Mepacrine	No contraindication	Avoid	No contraindication
Sulfacetamide	Avoid	No contraindication	No contraindication
Sulfamethoxazole	No contraindication	No contraindication	Avoid
Sulfanilamide	Avoid	No contraindication	No contraindication
Sulfapyridine	Avoid	No contraindication	No contraindication
Thiazolesulfone	Avoid	No contraindication	No contraindication
Tolonium chloride (toluidine blue)	Avoid	No contraindication	No contraindication
Cotrimoxazole (trimethoprim/sulfamethoxazole)	No contraindication	Avoid	Avoid
Urate oxidase	Avoid	No contraindication	No contraindication
Vitamin K analogues	No contraindication	Avoid	No contraindication

evidenced by case reports and laboratory and clinical studies.

2. Medications that can probably be given safely in therapeutic dosages to G6PD-deficient patients, including all compounds that were mentioned by any author or source as causing haemolysis in G6PD-deficient patients, but where after careful review of the literature insufficient evidence was found to implicate administration of therapeutic dosages as the cause of haemolytic anaemia.

3. Medications where no evidence at all was found to contravene their use by G6PD-deficient patients.

2. Medications that Should be Avoided in Patients with Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

See table II for overview.

2.1 Methylthioninium Chloride (Methylene Blue)

Methylthioninium chloride (methylene blue) is mainly used for the treatment of methaemoglobinaemia. Reports of haemolysis in G6PD-deficient

patients have been available since 1960.[11] In 1971, Rosen et al.[12] reported a severe case of methaemoglobinaemia in a patient who ingested aniline. Methylthioninium chloride was administered to reduce the methaemoglobinaemia, but the usual beneficial response was not obtained. Furthermore, 24 hours later, a marked haemolytic episode had occurred. The patient was found to be G6PD deficient. It was suggested that the poor response to methylthioninium chloride in this patient confirms the dependence of methylthioninium chloride on an intact hexose monophosphate shunt, which is absent in G6PD deficiency.

Gauthier[13] described three cases of premature neonates exposed to methylthioninium chloride who experienced severe haemolytic anaemia requiring transfusions. Two of them were subsequently diagnosed with G6PD deficiency.

More recently, Foltz et al.[14] reported on severe methaemoglobinaemia in a patient treated with a novel experimental anticancer drug, triapine. Treatment with methylthioninium chloride led to massive haemolysis due to concomitant G6PD deficiency. In contrast, in a study among 74 G6PD-deficient adult men, methylthioninium chloride did not cause haemolysis and haemoglobin levels remained stable in all study subjects. The authors concluded that standard dosages of methylthioninium chloride appear to be safe in G6PD-deficient African populations.[15,16]

Although conflicting data exist, most support a risk of haemolysis. Methylthioninium chloride should be avoided in G6PD-deficient patients, since no amelioration of methaemoglobinaemia can be expected and a haemolytic episode may be initiated or exacerbated.

Table II. Commonly used drugs that should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency

Dapsone
Methylthioninium chloride (methylene blue)
Nitrofurantoin
Phenazopyridine
Primaquine
Rasburicase
Tolonium chloride (toluidine blue)

2.2 Nitrofurantoin

Nitrofurantoin is an antibacterial used mainly for the treatment of urinary tract infections.

Chan et al.[17,18] performed two studies in individuals without G6PD deficiency who were transfused with ^{51}CR-labelled G6PD-deficient red cells and then received test drugs. Administration of nitrofurantoin shortened the half-life of the G6PD-deficient red blood cells by 60%. Since 1959, several groups have reported the potential for haemolysis among G6PD-deficient patients treated with nitrofurantoin.[19,20] Powell et al.[21] and Beutler[2,7] both conducted basic studies showing the haemolytic potential of nitrofurantoin in G6PD-deficient patients.

Existing data support a risk of haemolysis. Many alternative anti-infectious agents exist with a similar clinical spectrum of activity; nitrofurantoin should therefore, in our opinion, be avoided in G6PD-deficient patients.

2.3 Phenazopyridine

Phenazopyridine is a commonly prescribed analgesic used mainly for symptomatic relief of dysuria.

Several papers published in the 1980s reported cases of haemolytic anaemia in a total of seven G6PD-deficient patients prescribed phenazopyridine.[22-24] It should be noted that haemolytic anaemia has been associated with the use of phenazopyridine even in patients without G6PD deficiency.[25-28] In some of these cases, renal insufficiency may have been a contributing factor.[27,28]

Available literature suggests that phenazopyridine can cause or exacerbate haemolysis in G6PD-deficient patients, and this drug should probably be avoided in this population.

2.4 Primaquine

Primaquine is an antiparasitic agent mainly administered for the prophylaxis and treatment of malaria.

As noted in the introductory section, G6PD deficiency was discovered in the 1950s following reports of primaquine-induced haemolysis.[3,29] Investigators showed that patients exhibiting

primaquine-induced haemolysis had lower erythrocyte glutathione levels than patients without haemolysis.[30] Through the years, many reports of haemolytic anaemia following primaquine treatment have been published, including laboratory investigations,[2,19,30,31] and even today new case reports of primaquine-induced haemolysis appear in the literature.[32]

Solid evidence exists associating primaquine with haemolysis in G6PD-deficient patients: this drug should be avoided in G6PD-deficient patients.

2.5 Dapsone (Diaminodiphenylsulfone)

Dapsone (diaminodiphenylsulfone) is a sulfone antimicrobial that has mainly been administered for the treatment of leprosy. Its current uses include prophylaxis and treatment of *Pneumocystis jirovecii*.

Clinical studies by Degowin et al.[33] in 1966 showed the haemolytic activity of dapsone, albeit a lesser effect than that associated with primaquine. Beutler demonstrated the sensitivity of G6PD-deficient individuals to dapsone based on several experimental trials.[11] Using animal studies, Grossman et al.[34] showed that the haemolytic activity of dapsone lies in its *N*-hydroxy metabolites. This reaction is frequently dose related.[34,35] A recent study comparing the safety of two different regimens for the treatment of *Plasmodium falciparum* malaria showed that patients with G6PD deficiency who received dapsone had significantly lower haematocrit values as a result of a haemolytic reaction to dapsone.[36] It should be noted that several reports have shown that dapsone is also associated with haemolysis in the general population.

Available literature shows a clear association between dapsone and haemolysis in G6PD-deficient patients. This drug should probably be avoided in G6PD-deficient patients.

2.6 Rasburicase

This drug is a recombinant urate oxidase used mainly in the treatment of malignancy-associated hyperuricaemia. When administered, the resulting chemical reaction causes formation of H_2O_2 and should therefore theoretically lead to haemolysis in G6PD-deficient patients,[37,38] and indeed several reports have appeared suggesting this is the case. A recent case report described a 50-year-old African male treated with one intravenous dose of rasburicase 22.5 mg, who subsequently developed haemolytic anaemia.[38] Use of the Naranjo probability scale indicated that rasburicase probably caused the haemolytic anaemia. To err on the side of caution, patients at risk of G6DP deficiency, particularly patients of Mediterranean or African ancestry, should be screened prior to rasburicase initiation.

2.7 Tolonium Chloride (Toluidine Blue)

Tolonium chloride (toluidine blue) is a diagnostic agent used mainly for the diagnosis of oral and thyroid malignancies. The first case report connecting administration of tolonium chloride with haemolytic anaemia was published in 1959.[39] In 1970, Teunis et al.[40] reported a 62-year-old G6PD-deficient Black female who received tolonium chloride 7 mg/kg intravenously for parathyroid visualization during surgery. The following day, her urine was dark blue and later became dark red. Her Coombs test was negative and no Heinz bodies were seen. In 1971, Beutler[11] showed tolonium chloride to be haemolytic in G6PD-deficient patients based on case reports and clinical studies conducted on African-American volunteers.

Sufficient evidence exists to preclude the use of toulidine blue in G6PD-deficient patients.

2.8 Medications that Should be Avoided in G6PD Deficiency that are No Longer in Clinical Use

Solid evidence exists associating the following medications with G6PD-deficient haemolysis: acetanilide, niridazole, phenylhydrazine and sulfapyridine. As they are no longer in use, we have omitted discussion of these drugs.

3. Medications that Have Been Considered Unsafe by at Least One Source, but Overall, Evidence Does Not Contravene Use in G6PD-Deficient Patients

In this section we present medications that were named by at least one source quoted in table I, or described by other authors as prohibited for use in G6PD-deficient patients. However, our literature review indicates their use in therapeutic dosages is not contravened in G6PD-deficient patients. See table III for an overview.

Table III. Drugs that were considered unsafe by at least one source, but according to our review can probably be given safely in normal therapeutic doses to glucose-6-phosphate dehydrogenase-deficient patients

Paracetamol (acetaminophen)
Aspirin (acetylsalicylic acid)
Aminophenazone
Antipyrine
Ascorbic acid (vitamin C)
Chloramphenicol
Chloroquine
Ciprofloxacin
Dipyrone (metamizole)
Succimer (dimercaptosuccinic acid)
Furazolidone
Glibenclamide (glyburide)
Isoniazid
Isosorbide dinitrate
Norfloxacin
Nalidixic acid
Mepacrine
Quinine
Sulfacetamide
Sulfanilamide
Sulfasalazine
Sulfisoxazole
Thiazosulfone
Cotrimoxazole (trimethoprim/sulfamethoxazole)

3.1 Paracetamol (Acetaminophen)

Paracetamol (acetaminophen) is a common analgesic and antipyretic drug.

Some cases of haemolysis following paracetamol administration in patients with G6PD deficiency have been reported in the literature.[41-43] All available reports are associated with significant overdose, and there is no mention in the literature of haemolysis induced by therapeutic dosages. In a study by Chan et al.,[17,18] the drug did not alter the half-life of transfused cells lacking the G6PD enzyme. Based on available evidence, the use of therapeutic dosages of paracetamol is not contravened in G6PD-deficient patients.

3.2 Aspirin (Acetylsalicylic Acid)

Aspirin (acetylsalicylic acid) is a commonly used analgesic, antipyretic and a platelet aggregation inhibitor. According to Beutler's review from 1959,[4] administration of 3.6 g of this drug was not found to cause significant haemolysis in G6PD-deficient patients. In contrast, Chan et al.[17] described several cases of haemolysis in G6PD-deficient patients following aspirin ingestion. Later studies analysing these earlier reports concluded that the apparent haemolysis (if any) while using the usual dosage of aspirin (up to 50 mg/kg bodyweight/day) was probably caused by the underlying infectious disease and fever and not the aspirin use itself.[20,44-47] Most authors concur that for common types of G6PD deficiency, which are not related to chronic haemolytic anaemia, aspirin has no significant haemolytic effect.[46,47]

Regarding the chronic usage of a low dosage of aspirin as an anti-aggregation treatment, administration of aspirin 250 mg/day for a period of 3 months in 44 patients lacking G6PD did not induce haemolysis.[48]

Our review found no evidence to contravene the use of normal therapeutic dosages of aspirin in G6PD-deficient patients.

3.3 Aminophenazone

Aminophenazone is an analgesic, antipyretic and anti-inflammatory drug. Chan et al.[17] described a case in which this drug apparently caused haemolysis in a G6PD-deficient patient. However, in a later study, aminophenazone was administered on 171 occasions to G6PD-deficient

patients. Only two episodes of haemolysis were observed, both in febrile patients treated concomitantly with other potentially haemolytic drugs (in one case nitrofurantoin and streptomycin, while the second patient received aminophenazone in combination with aspirin and dipyrone).[20] Based on these findings, we conclude that aminophenazone can probably be given in therapeutic dosages to G6PD-deficient patients.

3.4 Antipyrine

Antipyrine is an analgesic, antipyretic and anti-inflammatory drug, currently used only in otic preparations for local pain relief. Our search of the literature showed no reports of haemolysis associated with antipyrine except in one case of severe overdose in an attempted suicide.[49]

3.5 Ascorbic Acid (Vitamin C)

Ascorbic acid (vitamin C) is used as a nutritive agent and urinary acidifier.

Ascorbic acid has an oxidative effect on haemoglobin and other proteins, and can cause a decrease in glutathione levels in G6PD-deficient red blood cells.[2] Sporadic reports of haemolysis following very large doses of ascorbic acid have appeared in the literature.[50,51] Udomratn et al.[52] used an animal model to examine the influence of large doses of ascorbic acid on G6PD-deficient human red blood cells. At the dosages used, ascorbic acid caused premature loss of G6PD-deficient human erythrocytes, but the dosage employed was equivalent to a 70 kg human ingesting ascorbic acid 40 g in a single dose.

At therapeutic dosages, there is no evidence to contravene the use of ascorbic acid in patients with G6PD deficiency.[2]

3.6 Chloramphenicol

Chloramphenicol is an antimicrobial drug. There have been several reports of anaemia in patients lacking the G6PD enzyme who were treated with therapeutic dosages of chloramphenicol, especially in those patients with the Mediterranean type of G6PD deficiency. However, it is worth noting that most of the reports were of patients treated with the drug due to typhoid fever, which itself has been shown to cause haemolysis in patients lacking G6PD.[20,53-56] In two studies by Beutler[4] and Chang et al.,[17] patients receiving tagged red blood cells lacking G6PD were unaffected by this drug.

Chloramphenicol, in therapeutic dosages, is not contravened in patients lacking the G6PD enzyme.

3.7 Chloroquine

Chloroquine is an antimalarial agent from the 4-aminoquinoline group of drugs.

In a report of 20 children lacking the G6PD enzyme and treated with chloroquine, two developed haemolysis, both of whom received the drug in tandem with other agents. One child had chloroquine co-administered with chloramphenicol and the second received chloroquine with chloramphenicol and aspirin.[57]

No reports have shown an association between haemolysis and monotherapy with chloroquine. Furthermore, in several basic studies with tagged red blood cells lacking G6PD, no effect was shown on erythrocyte lifespan in patients lacking G6PD.[4,7,17,58] It would appear, therefore, that there is no evidence to contravene chloroquine monotherapy in G6PD-deficient patients, but caution should be exercised when combining the drug with other agents with possible haemolytic effects.

3.8 Dipyrone (Metamizole)

Dipyrone (metamizole) is a pyrazolone NSAID. This medication is not available in North America and some European countries, but is widely used in South American, East European and Mediterranean countries. The drug monograph includes a warning regarding the use of this drug in G6PD-deficient patients.[2] However, only a single report from Israel in 1969 describes haemolytic anaemia following dipyrone treatment.[20] As in many other cases, this patient had an infectious disease with high fever. Our literature search did not reveal any other reports or studies establishing an association between dipyrone use and haemolysis in patients with G6PD deficiency,

thus no evidence precludes its use in therapeutic dosages in patients lacking the G6PD enzyme.

3.9 Succimer (Dimercaptosuccinic Acid)

Succimer (dimercaptosuccinic acid) is an organosulfur compound used as a chelating agent, mainly for treatment of heavy metal poisoning.

Data regarding this compound are sparse. Gerr et al.[59] reported a case of haemolysis in a G6PD-deficient patient, a 45-year-old Black male, who received succimer for symptomatic lead poisoning. On day 7, his haemoglobin and haematocrit decreased, while bilirubin increased and the treatment was discontinued. The haemolysis in this case could have been caused by the succimer, but it also could have been a result of the lead toxicity.[59]

In contrast, Graziano et al.[60] administered succimer to two G6PD-deficient children and found no signs of haemolysis.

Succimer can probably safely be given to G6PD-deficient patients.

3.10 Furazolidone

Furazolidone is an antibacterial and antiprotozoal agent mainly used to treat diarrhoea and enteritis.

One case report describes a 12-year-old patient with G6PD deficiency treated with furazolidone and chloramphenicol who developed cyanosis and jaundice.[55]

In another report, this drug was given on 23 occasions to G6PD-deficient patients. No episodes of haemolysis were observed, and current evidence supports its use in G6PD-deficient patients.[20]

3.11 Glibenclamide (Glyburide)

Glibenclamide (glyburide) is a second-generation sulphonylurea used for the treatment of type 2 diabetes mellitus. Among its adverse effects is autoimmune haemolytic anaemia.[61]

Meloni and Meloni[62] first described glibenclamide inducing G6PD-related haemolysis in a 61-year-old man of Sardinian origin with G6PD deficiency. The patient commenced glibenclamide for his newly diagnosed diabetes; 10 days later he developed haemolytic anaemia with Heinz bodies and a negative Coombs test. Glibenclamide was discontinued and these laboratory results resolved.

Another report described a 51-year-old woman with a G6PD variant who developed haemolytic anaemia without Heinz bodies and a negative Coombs test following glibenclamide treatment. These laboratory findings resolved when glibenclamide was discontinued.[63] No other reports of haemolysis with this drug among G6PD-deficient patients have appeared in the literature, and there are no warnings regarding the use of this drug in G6PD-deficient patients in the drug manufacturer information.[64] Taking into account the widespread use of glibenclamide and the scarcity of reports, it appears this drug can be used in therapeutic dosages in patients with G6PD deficiency.

3.12 Isoniazid

Isoniazid is a pyridoxine antagonist used mainly for the treatment of tuberculosis.

Three reports exist involving haemolysis in G6PD-deficient patients following isoniazid administration.[20,65] According to a study by Chan et al.,[17] the drug did not alter the half-life of transfused cells lacking G6PD.

There have been reports of anaemia responsive to pyridoxine during treatment with isoniazid in patients with G6PD deficiency.[65] In concurrence with Beutler's review from 1991,[7] and based on current literature, we found no evidence to preclude the use of this drug in therapeutic dosages in people with G6PD deficiency.

3.13 Isosorbide Dinitrate

Isosorbide dinitrate is a nitrate used for its antianginal effect. Aderka et al.[66] described two cases of G6PD-deficient patients of Iraqi origin who developed haemolytic anaemia following isosorbide dinitrate administration. Rechallenge with isosorbide dinitrate a few weeks later caused only a slight decrease in haemoglobin of no clinical importance. There are no other reports of isosorbide dinitrate-induced haemolysis. There appears

to be no contraindication to the use of isosorbide dinitrate in G6PD-deficient patients.

3.14 Nalidixic Acid

Nalidixic acid is a non-fluorinated quinolone antibacterial.

Haemolytic anaemia is a possible adverse effect of nalidixic acid in the general population. Three cases of haemolysis in G6PD-deficient individuals receiving nalidixic acid have been reported,[67-69] and accordingly there is a warning regarding the use of this drug in G6PD-deficient patients in the drug monograph. As with the reports of other anti-infective agents, all the patients described had a suspected bacterial infection at the time of administration. In light of the scarcity of reports in such a commonly prescribed medication, it appears that available data do not support avoiding use in patients with G6PD deficiency, and that therapeutic dosages of nalidixic acid are not precluded in G6PD-deficient patients.

3.15 Ciprofloxacin, Levofloxacin, Norfloxacin and Ofloxacin

Ciprofloxacin, levofloxacin, norfloxacin and ofloxacin are all fluoroquinolones, derivatives of nalidixic acid. Our literature search did not reveal reports of haemolysis in G6PD-deficient patients receiving the new-generation quinolones. There are scattered reports of haemolysis in patients receiving quinolones, without relation to G6PD deficiency. Some of these events were associated with hypersensitivity, while others were categorized as events of unknown aetiology, and generally occurred after multiple doses.[69-71]

There is a warning regarding the use of these drugs in G6PD-deficient patients in the drug manufacturers' leaflets;[72] however, this warning was formulated on the basis of the existing warning regarding nalidixic acid. No published data support this recommendation; and we found no evidence to preclude the administration of fluoroquinolones in therapeutic dosages to G6PD-deficient patients.

3.16 Mepacrine

Mepacrine is a seldom used antimalarial agent. Krudsood et al.[32] reported no cases of haemolysis when this medication was administered on ten occasions to G6PD-deficient patients. Similarly, Chan et al.[17] reported no cases of haemolysis in G6PD-deficient patients in control studies of this drug. There is no evidence to contravene administering mepacrine at therapeutic dosages to G6PD-deficient patients.

3.17 Quinine

Quinine is a commonly used antimalarial drug. Haemolysis has not been observed in published studies.[4,17]

According to Beutler's review from 1991,[7] this drug can be safely administered in therapeutic dosages to G6PD-deficient patients, and our review found no evidence to contradict this statement.

3.18 Sulfacetamide

Sulfacetamide is a sulfonamide anti-infectious agent. At present it is mainly used in topical formulations. Sulfacetamide has the theoretical potential to induce haemolysis in G6PD-deficient patients but our literature search revealed no reported cases. It appears that, in topical formulations, sulfacetamide can safely be administered to G6PD-deficient patients.

3.19 Sulfanilamide

Sulfanilamide is a short-acting sulfonamide with properties similar to those of sulfamethoxazole. In a study by Dern et al.,[73] volunteers who received transfusions of G6PD-deficient erythrocytes were highly sensitive to sulfanilamide. In the same article they also report on two G6PD-deficient men who developed acute haemolysis following administration of sulfanilamide.

Early reports showed rates of haemolysis following sulfanilamide administration ranging from 1.3% to 12% in various populations.[73-75] However, the reported dosage of sulfanilamide in all these papers was 3.6 g/day, more than four times the recommended dosage.[7,17] A thorough literature search found no cases of haemolysis induced

by therapeutic dosages. We found no evidence associating therapeutic dosages of sulfanilamide with G6PD-associated haemolysis.

3.20 Sulfasalazine

Sulfasalazine combines two active components: 5-aminosalicylic acid and sulfapyridine; it is used as an antirheumatic and gastrointestinal agent. Several haemolytic episodes after its administration in G6PD-deficient patients have been reported.[17,76-78] However, there are numerous reports of anaemia with the appearance of Heinz bodies in patients receiving this drug who were not lacking G6PD. Significant haemolytic effect on red blood cells lacking G6PD was noted when the administered dosage was close to the toxic dose of the drug. At therapeutic dosages, no haemolysis developed.[20] There are warnings regarding the use of this drug in G6PD-deficient patients in the drug monograph, but the evidence seems to indicate that there is no haemolytic effect at therapeutic dosages.

3.21 Sulfafurazole

Sulfafurazole is a sulfonamide antibacterial. As with other sulfonamides, reports of G6PD-related haemolysis exist, again all when supra-therapeutic doses were administered. In concurrence with Beutler,[7] we found no evidence to preclude the administration of therapeutic dosages of sulfisoxazole to G6PD-deficient patients.

3.22 Cotrimoxazole (Trimethoprim/Sulfamethoxazole)

Cotrimoxazole (trimethoprim/sulfamethoxazole) is a commonly used sulfonamide antibacterial. Reports on the effect of cotrimoxazole in G6PD-deficient individuals are inconclusive.[79] Chan et al.[17] conducted a study in individuals without G6PD deficiency who were transfused with ^{51}Cr-labelled G6PD-deficient red cells and then received test drugs. The haemolytic effect of sulfamethoxazole varied even for individuals with the same G6PD variant, and only at dosages of 90 mg/kg/day was the ^{51}Cr half-life altered. In another study, Chan and McFadzean[80] reported that the incidence of haemolytic episodes in G6PD-deficient patients receiving the therapeutic dosage of cotrimoxazole was the same as in the general population. Available evidence indicates that cotrimoxazole can be administrated in therapeutic dosages to G6PD-deficient patients without causing haemolytic anaemia.

4. Medications where no Evidence was found that Contravened their Use in G6PD-Deficient Patients

Table IV lists all medications that were mentioned in the literature in the context of haemolysis, but regarding which consensus exists today as to their safety for use in G6PD-deficient patients. References are shown in the table.

Table IV. Drugs for which no evidence is available that contravenes their use in glucose-6-phosphate dehydrogenase-deficient patients

Drug	References
Antazoline	4
Benzhexol	17
Chlorguanidine	17
Colchicine	7,37
Diphenylhydramine	4,7
Doxorubicin	81
Levodopa	17,82
p-Aminosalicylic acid	4,11
p-Aminobenzoic acid (PABA)	4
Phenacetin	7,20
Phenylbutazone	7,18,83
Phenytoin	7,17
Probenecid	11,17
Procainamide hydrochloride	4,7
Pyrimethamine	4,17,84
Streptomycin	20
Sulfacytine	85
Sulfadiazine	4,17,76,86
Sulfaguanidine	76
Sulfamerazine	76
Sulfamethoxypyridazine	7,87,88
Tiaprofenic acid	89
Tripelennamine	4,7
Vitamin K and derivatives	18,90-92

5. Conclusions

G6PD deficiency results from a diverse group of mutations with many geographic variants. Almost 350 different mutations have been described to date, and individual differences in susceptibility to the haemolytic effect of the same drug in different G6PD-deficient patients are therefore not unexpected. However, solid evidence supporting a clear association with drug-induced haemolysis exists for only a small number of agents (table II). Many medications that have traditionally been prohibited can probably be safely administered in therapeutic dosages to individuals with G6PD deficiency, as evidence is not available that contravenes their use.

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