Drugs causing haemolysis in G6PD deficiency subjects

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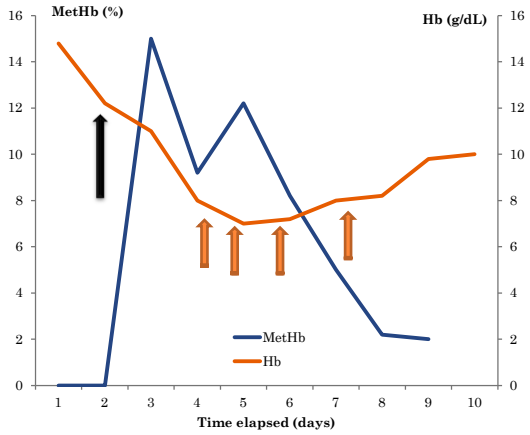
Content

- A case of acute haemolytic anaemia and methaemoglobinaemia
- G6PD and its metabolic function
- Genetics of G6PD
- Classification of G6PD and its variants
- Epidemiology of G6PD deficiency in Hong Kong
- Risk Assessment :
  - high risk patient - male, homozygote female, heterozygote old female
  - high risk drugs
- FDA recommendation on genetic biomarker regarding G6PD deficiency

Haemolysis and MetHb secondary to Rasburicase administration



- 50-yr-old African American was admitted for convulsion
- Suspected to have tumor lysis syndrome, ARF
- wcc 31x103/mm^3, serum uric acid 14.6 mg/dL (3.4 – 7.2)
- Uric acid crystals in urine microscopy
- Rasburicase 22.5 mg IV on day 2

Browning LA. Ann Pharmacother 2005

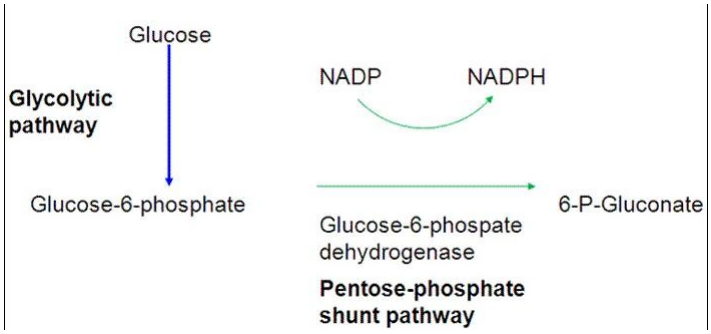
Package Insert. Elitek (Rasburicase).

- An overall incidence of haemolysis, methaemoglobinemia, or both in <1% of the 703 patients assessed for serious ADR.
- Gender (63% male)
- Age (median 10 y, range 10 d to 88 y)
- Ethnic background (73% white, 9% black, 4% Asian, 14% other or unknown)

New York: Sanofi-Synthelabo, March 2004

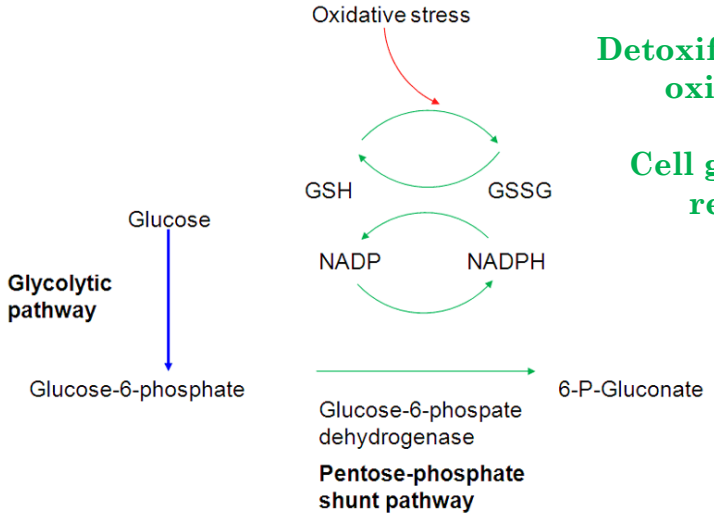
GLUCOSE 6-PHOSPHATE DEHYDROGENASE (G6PD) AND ITS METABOLIC FUNCTION

- Catalyzes the first step in the pentose phosphate pathway
- Only source of NADPH for glutathione metabolism in RBC



http://bestpractice.bmj.com/best-practice/monograph/704/basics/pathophysiology.html

GLUCOSE 6-PHOSPHATE DEHYDROGENASE (G6PD) AND ITS METABOLIC FUNCTION



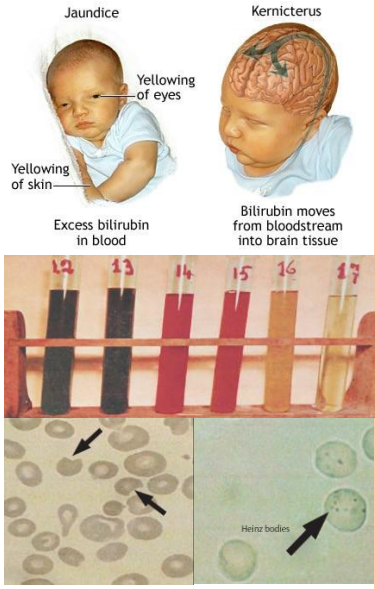
Detoxification of oxidants

Cell growth - redox

http://bestpractice.bmj.com/best-practice/monograph/704/basics/pathophysiology.html

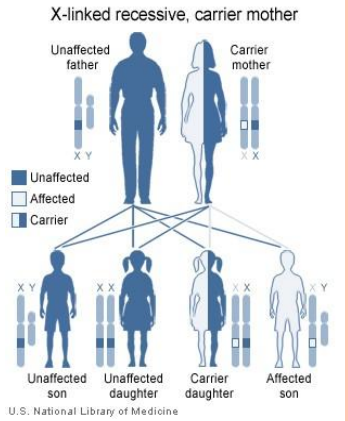
CLINICAL MANIFESTATIONS OF G6PD DEF

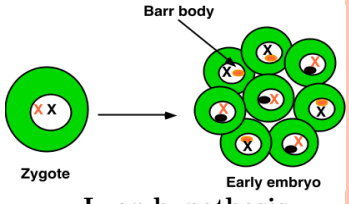
- Severe neonatal jaundice causing kernicterus
- Chronic non-spherocytic haemolytic anaemia (CHSHA)
- Massive intravasuclar haemlysis as an idiosyncratic reaction to multiple drugs and chemicals
- Severe haemolysis as an unusual complication of illnesses
- Haemolysis after ingestion of fava bean (Favism)



GENETICS OF G6PD

- The gene for G6PD is located on the X chromosome band X q28
- G6PD def is expressed in:
  - males carrying a variant gene
  - heterozygous females have variable G6PD activity
    - degree of lyonization
    - degree to which the G6PD variant is expressed





Lyon hypothesis

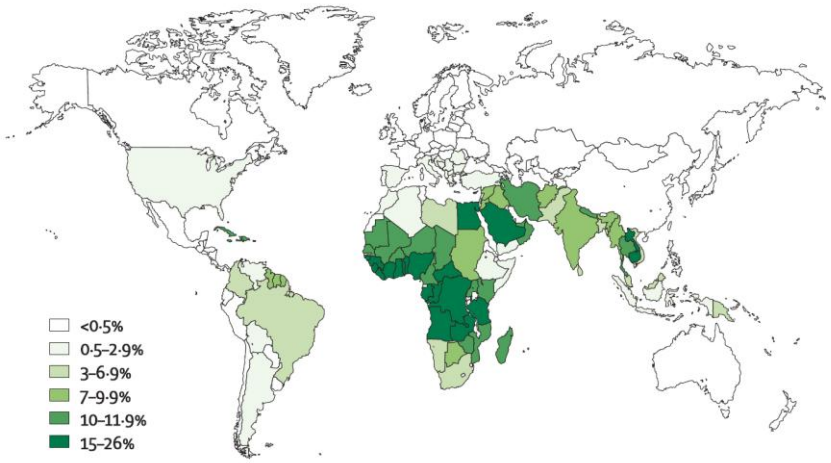
CLASSIFICATION OF G6PD AND ITS VARIANTS

- 442 allelic variants, and 160 mutations of G6PD deficiency have been reported

Type	Enzyme activity	Clinical Symptoms	Abundance and geographic distribution	Mutations
1	Less than 1% or undetectable	Chronic hemolytic anemia	Very rare with no precise geographic distribution	G6PD-Buenos Aires G6PD-Durham
2	Less than 10%	Acute hemolytic Anemia mediated drugs and fava beans	Abundant in all parts of the world	G6PD-Mediterranean G6PD-Cassano G6PD-Santamaria
3	10-60%	Acute or chronic hemolytic anemia	Abundant in malarious area	G6PD-A- G6PD-Seattle G6PD-Canton G6PD-Rignano
4	60-90% with normal activity	Asymptomatic	Not specified	G6PD-Mantalbano G6PD-Orissa
5	More than 110% with increasing of activity	Asymptomatic	Not specified	Not reported

World health Organization Group. Glucose-6-phosphate dehydrogenase deficiency. Bull World Health Organ 1989; 67(6): 601-611.

WORLD MAP DISTRIBUTION OF G6PD DEFICIENCY



WHO working group. Glucose-6-phosphate dehydrogenase deficiency. *Bull World Health Organ 1989;* ***67: 601–11.***

Prevalence of G6PD deficiency

Population Groups	No. tested	G6PD def %	Reference
(HK) Newborn Chinese Male	1379	4.4 (male)	Chan TK 1983
(HK) All Newborn Chinese 1984-2000	~920000	4.5 (male) 0.3 (female)	Lam STS 2003
Asia			
China		2-5	WHO 1972
India		4-19	
Japan		<1	
Filipinos		7.1	Chan TK 1983
Malaya		2.6 (Malays) -17 (Aborigines)	
Africa			
West – Ghana		24	WHO 1972
Nigeria		2-25	
Central – Angola		11-27	
Congo		6-23	
East – Kenya		2-25	
Tanzania		2-28	
Europe			
Greece		1-32	WHO 1972
Italy		<1	

Estimation of incident of G6PD deficiency in Hong Kong

- Hardy-Weinberg formula ($p^2 + 2pq + q^2 = 1$)
- p = frequency of mutant gene of male, q = frequency of normal gene of male in a population
- $p + q = 1$.
- Heterozygote female = 2pq
- Homogygote normal female = q^2

4.5% male
8.6% female

- Take p = 4.5%, q = 95.5%
- Proportion of females
  - homozygous normal (q^2) = 91.2%
  - heterozygous (2pq) = 8.6%
  - homozygous mutant (p^2) = 0.2%

(Prevalence in female = 0.27% on neonatal screening)

Spectrum of G6PD mutations in 179 HK Chinese

G6PD variant	No. (%)	Clinical Class
G6PD Canton (nt 1376 G->T)	56 (31%)	II-III
G6PD Kaiping (nt 1388 G->A)	53 (30%)	II-III
G6PD Gaohe (nt 95 A->G)	19 (11%)	II-III
G6PD Viangchan (nt 871 G->A)	14 (8%)	
G6PD Chinese-4 (nt 392 G->T)	7 (4%)	

G6PD Canton has biochemical properties similar to those of G6PD Mediterranean

Ma ES. 2007

Factors that affect individual susceptibility to, and severity of, drug-induced oxidative haemolysis

Inherited

- Metabolic integrity of the erythrocyte
- Precise nature of enzyme defect
- Genetic differences in pharmacokinetics

Acquired

- Age
- Dose, absorption, metabolism, and excretion of drug
- Presence of additional oxidative stress (infection)
- Effect of drug or metabolite on enzyme activity
- Pre-existing haemoglobin concentration
- Age distribution of red blood cell population

DRUGS TO BE AVOIDED IN G6PD DEFICIENCY

WHO Working Group 1989

Drug Group	Example	Comment
Antimalarials	Primaquine Pamaquine	African A- variant may take it at reduced dosage under close monitoring Chloroquine may be used for prophylaxis or treatment
Sulphonamides / suphones	Sulphailamide Sulphapyridine Sulphadimidine Sulphacetamide Salazopyrin Dapson	
Anti-bacterials	Co-trimoxazole Nalidixic acid Nitrofurantoin Chloramphenical	African A- variant should avoid it
Analgesics	Aspirin Phenacetin	Moderate doses can be used
Others	Vitamin K analogues Probenecid Dimercaprol (BAL) Methylene Blue	1 mg can be given to babies

DRUGS WHICH CAN CAUSE HAEMOLYSIS IN G6PD-DEF INDIVIDUALS

Harrison's Internal Medicine 17th ed

	Definite Risk	Possible Risk	Doubtful Risk
Antimalarials	Primaquine Chlorproguanil	Chloroquine	Quinine
Sulphonamides / Sulphones	Sulphametoxazole Dapsone	Sulfasalazine Sulfadimidine	Sulfisoxazole Sulfadiazine
Antibacterial/ Antibiotics	Cotrimoxazole Nalidixic acid Nitrofurantoin Niridazole	Ciprofloxacin Norfloxacin	Chloramphenicol P-Aminosaclicylic acid
Antipyretic/ Analgesics	Acetanilide Phenazopyridine	Acetylsalicylic acid (>3 g/d)	Acetylsalicylic acid (<3 g/d) Acetaminophen Phenacetin
Other	Naphthalene Methylene blue	Vitamin K analogues Ascorbic acid > 1 g Rasburicase	Doxorubicin Probenecid

DRUGS WHICH CAN CAUSE HAEMOLYSIS IN G6PD-DEF INDIVIDUALS

British National Formulary Sept 2010

	Definite Risk	Possible Risk
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Sulphonamides / Sulphones	Sulphametoxazole Dapsone	Sulfasalazine Sulfadimidine
Antibacterial/ Antibiotics	Cotrimoxazole Nalidixic acid Nitrofurantoin Niridazole	Ciprofloxacin Norfloxacin
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DRUGS WHICH CAN CAUSE HAEMOLYSIS IN G6PD-DEF INDIVIDUALS

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	Definite Risk	Possible Risk
Antimalarials	Primaquine Chlorproguanil Pamaquin	Chloroquine Quinine, Qinidine
Sulphonamides / Sulphones	Sulphametoxazole Dapsone	Sulfasalazine Sulfadimidine
Antibacterial/ Antibiotics	Cotrimoxazole Nalidixic acid Nitrofurantoin Niridazole	Ciprofloxacin Norfloxacin
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Other	Naphthalene Methylene blue	Vitamin K analogues

Drugs which can cause haemolysis in G6PD-def individuals

British National Formulary Sept 2010

	Definite Risk	Possible Risk
Antimalarials	Primaquine Chlorproguanil Pamaquine	Chloroquine Quinine, Qinidine
Sulphonamides / Sulphones	Sulphametoxazole Dapsone	Sulfasalazine Sulfadimidine
Antibacterial/ Antibiotics	Cotrimoxazole Nitrofurantoin Niridazole Nalidixic acid Ofloxacin Ciprofloxacin Moxifloxacin Norfloxacin	
Antipyretic/ Analgesics		Acetylsalicylic acid (>1 g/d)
Other	Naphthalene Methylene blue	Probenecid Rasburicase

Recommendations are different

- No pre-marketing drug-testing requirements
- Controlled studies
  - No standardised methods of testing
    - In vitro tests
    - In vivo tests
- Case reports
  - Concurrent infections, diabetic ketosis
  - Concomitant use of drugs
  - Different drug dosage
  - Different drug response in different G6PD variants
  - Different drug response in same patient
    - False negative results

REVIEW ARTICLE

Drug Saf 2010; 33 (9): 713-726
0114-5916/10/0009-0713/$49.95/0

Medications and Glucose-6-Phosphate Dehydrogenase Deficiency

An Evidence-Based Review

Ilan Youngster,[1] *Lidia Arcavi,*[2] *Renata Schechmaster,*[2] *Yulia Akayzen,*[3] *Hen Popliski,*[3] *Janna Shimonov,*[3] *Svetlana Beig*[3] and *Matitiahu Berkovitch*[1]

Avoid — Evidenced by case reports and laboratory and clinical studies

Probably Safe — Insufficient evidence was found after careful review

Safe — No evidence at all was found to contravene their use

Avoid	Probably Safe	Safe
Primaquine	Chloroquine	Antazoline
Dapsone	Quinie	Chlorguanidine
Nitrofurantoin	Aminophenazone	*P*-Aminosalicylic acid
Phenazopyridine	Sulfacetamide	*P*-Aminobenzoic acid (PABA)
Methylene blue	Sulfanilamide	Phenylbutazone
Tolonium chloride (Toluidine blue)	Sulfasalazine	Sulfacytine
Rasburicase	Sulfisoxazole	Sulfadiazine
	Thiozosulfone	Sulfaguanidine
	Aminophenazone	Sulfamerazine
	Cotrimoxazole	Sulfamethoxypyridazine
	Glibenclamide	Pyrimethamine
	Chloramphenicol	Streptomycin
	Mepacrine	Tiaprofenic acid
	Isoniazid	Tripelennamine
	Nalidixic acid	Vitamin K and derivatives
	Ciprofloxacin	Doxorubicin
	Norfloxacin	Colchicine
	Antipyrine	Diphenylhydramine
	Paracetamol	Levodopa
	Metamizole	Benzhexol
	Aspirin	Probenecid
	Ascorbic acid	Phenytoin
	Succimer	Procainamide
	Isosorbide dinitrate	

Youngster I. Drug safety 2010; 33(9): 713-26

Determining the potential drug-induced haemolysis in G6PD deficiency

- The WHO recommends testing of drugs to predict the risk of haemolysis in G6PD-deficient individuals if the drugs are to be prescribed in areas of high prevalence of G6PD deficiency
- Preclinical *In vitro* tests (fall in glutathione in G6PD def red cells and/or hexoae-monophosphoate pathway in G6PD-normal RBC):
  - Acorbic acid, cysteine
  - L-dopa
- Clinical *In vivo* tests (aim at determining risk/benefit ratio)

FDA categorized genomic biomarkers required for use with the drug therapy

Biomarker	**Label context (1=Required; 2=Recommended; 3=Information only)**			**Other example**
	Representative label	Test	Drug	
G6PD def	**G6PD deficiency and risk** "Rasburicase administered to patients with G6PD def can cause severe hemolysis. ELITK administration should be immediately and permanently discontinued in any patient developing hemolysis. It is recommended that patients at higher risk for G6PD def (patients of African or Mediterranean ancestry) be screened prior to starting ELITEK therapy	2	Rasburicase	Dapsone
G6DP def with alternate context	**G6PD deficiency and tolerance** "Hemolytic reactions (moderate to severe) may occur in G6PD def. If primaquine phosphate is prescribed for an individual with erythrocytic G6PD def or NADH methemoglobin reductase def, the person should be observed closely for tolerance."	3	Primaquine	Chloroquine

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm (2007)

TABLE OF PHARMACOGENOMIC BIOMARKERS IN DRUG LABELS

Drug	Therapeutic Area	Biomarker	Label Sections
Rasburicase	Oncology	G6PD	Boxed warning, contraindications
Chloroquine	Antiinfectives	G6PD	Precautions
Dapsone	Antiinfectives / Dermatology	G6PD	Warnings and precautions, Adverse reactions, Use in specific populations, Patient counseling information, Overdose

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm (Assessed 28 Aug 2013)

CDC GUIDELINES ON CHOOSING A DRUG TO PREVENT MALARIA

- Cannot be used in patients with G6PD deficiency
- Cannot be used in patients who have not been tested for G6PD deficiency
- There are costs and delays associated with getting a G6PD test done; however, it only has to be done once. Once a normal G6PD level is verified and documented, the test does not have to be repeated the next time primaquine is considered
- Cannot be used by pregnant women
- Cannot be used by women who are breastfeeding unless the infant has also been tested for G6PD deficiency

http://www.cdc.gov/malaria/travelers/drugs.html (Assessed 28 Aug 2013)

Conclusion

- G6PD deficiency results from a diverse group of mutations with many geographical variants
- Individual susceptibility to haemolytic effect of the drug is variable, thus a drug found to be safe in some G6PD-def individuals may not be equally safe in others.
- G6PD deficient-individual is prohibited to use a lot of medications
- Solid evidence supporting a clear association with drug-induced haemolysis is lacking
- Clearance of G6PD status in drug label is often lacking
- Clearance of G6PD status during drug development is lacking

Thank You