

Zopiclone: An Under-Recognised Cause of Oxidative Haemolysis and Implications for Public Health

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Disclosures

- ▶ No disclosure

Background

- ▶ Drug-induced oxidative haemolysis is commonly linked to glucose-6-phosphate dehydrogenase (G6PD) deficiency
- ▶ However, the epidemiological pattern remains poorly characterised
- ▶ Zopiclone is **not considered a causative agent** in common educational materials (e.g. UpToDate)
- ▶ We identified that zopiclone may be potentially under-recognised as a potential cause
- ▶ Lead to review of our oxidative haemolysis cases

Medicines and other substances likely to be UNSAFE in moderate to severe G6PD deficiency*	
Medications	
Chlorpropamide	
Dabrafenib	
Dapsone (diaminodiphenyl sulfone)	
Fluoroquinolones (ciprofloxacin, moxifloxacin, norfloxacin, ofloxacin) [†]	
Methylene blue (methylthionium chloride) ^Δ	
Nalidixic acid [◇]	
Nitrofurantoin, nifuratel, and nitrofurazone (nitrofur) [◇]	
Phenazopyridine (pyridium)	
Primaquine and tafenoquine	
Rasburicase and pegloticase	
Sulfonylureas (eg, glipizide, glyburide [glibenclamide])	
Chemical exposures and foods	
Fava beans	
Henna compounds (black and red Egyptian)	
Naphthalene (mothballs, lavatory deodorant, garden pesticide)	
Phenylhydrazine	
"RUSH" (isobutyl nitrite, amyl nitrite)	

From UpToDate “drug-induced hemolytic anemia”

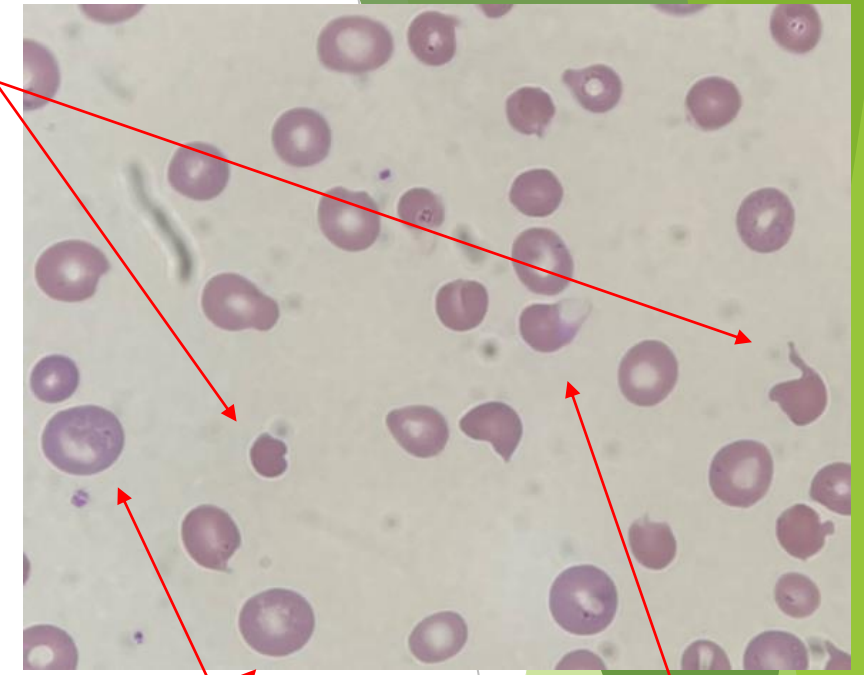
Objective

- ▶ To characterise the clinicopathological features of drug-induced oxidative haemolysis at Tuen Mun Hospital

Method

- ▶ Retrieved Heinz body test requests at Tuen Mun Hospital from Laboratory Information System (LIS) during the period 1st January 2012 to 31st December 2022
- ▶ Heinz body test requests were routinely ordered by pathologists for new cases of oxidative haemolysis and by clinicians for investigation of haemolytic anaemia
- ▶ Case definition:
 - ▶ Morphological evidence (bite/blister cells and polychromasia) plus ≥ 1 biochemical marker:
 - ▶ Elevated indirect bilirubin $>12 \mu\text{mol/L}$
 - ▶ Elevated lactate dehydrogenase (LDH) $>220 \text{ U/L}$
 - ▶ Reduced haptoglobin $<0.30 \text{ g/L}$
- ▶ Clinical history, medication records, and laboratory data were reviewed
- ▶ Patient progress was tracked through 31st December 2023

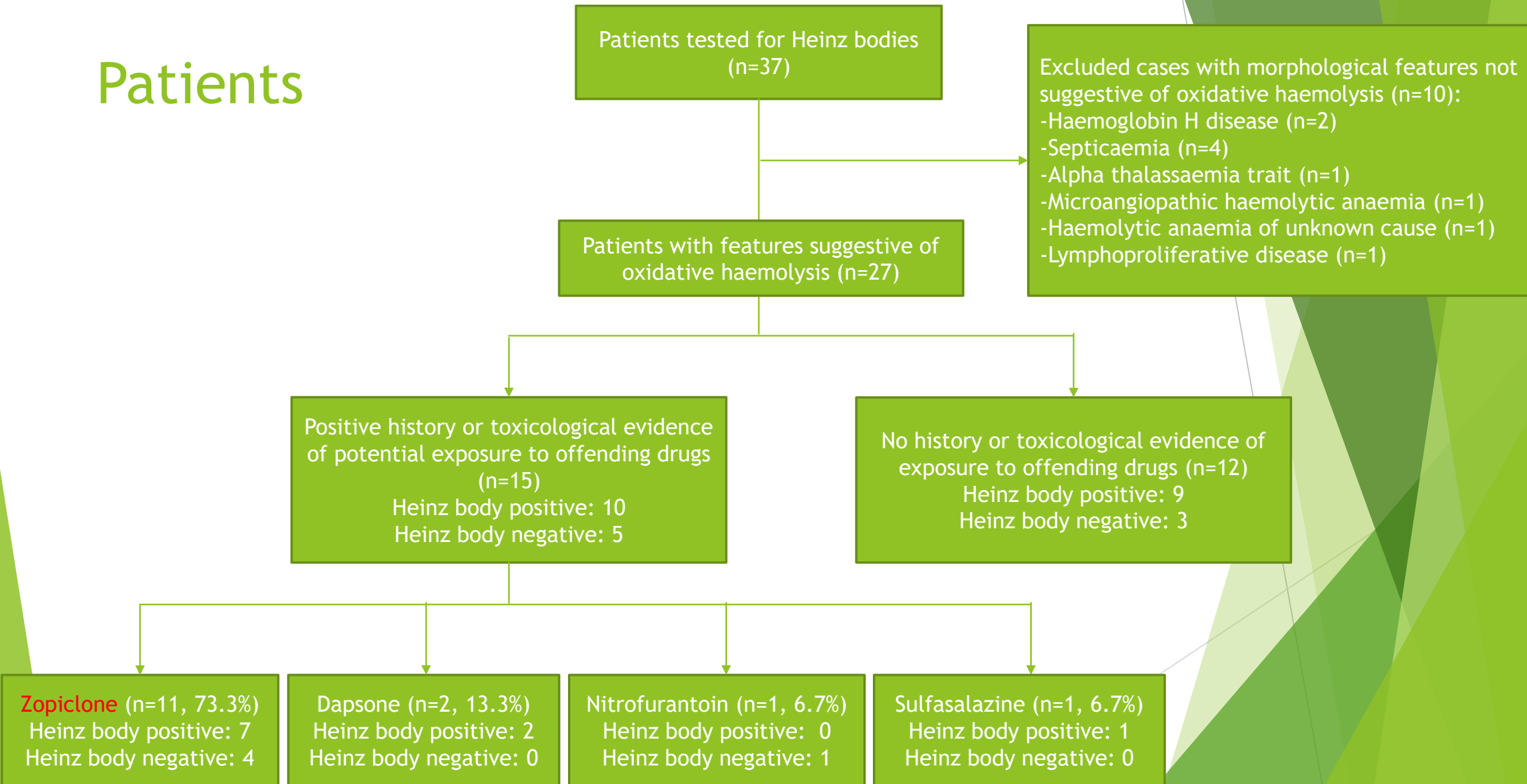
Bite cells



Polychromasia

Blister cells

Patients



Zopiclone-induced oxidative haemolysis

- ▶ Emerged as the most frequent cause (11/15, 73.3%) of oxidative haemolysis
- ▶ Prevalent in **females** (81.8%) and associated with **depression and/or substance use disorders** (81.8%)
- ▶ Only one male had confirmed G6PD deficiency
 - ▶ In contrast to the traditional teaching of **G6PD deficiency (X-linked recessive disorder) plus triggers** being the major cause

Two distinct presentations of zopiclone-induced oxidative haemolysis

- ▶ Acute zopiclone overdose (4/11 patients, 36.3%)
 - ▶ Reported as case reports in the literature
 - ▶ Single episode of intentional ingestion of a large amount of zopiclone
 - ▶ 50-500 times the daily dose of 7.5 mg
 - ▶ Present with psychomotor symptoms
 - ▶ 3/4 (75%) patients presented with methaemoglobinaemia
 - ▶ Mild oxidative haemolysis



Two distinct presentations of zopiclone-induced oxidative haemolysis (Con't)

- ▶ Chronic zopiclone overdose (7/11 patients, 63.6%)
 - ▶ **Not described before** in the literature
 - ▶ Involves daily or intermittent consumption of **~3-30 times** the daily dose of 7.5 mg
 - ▶ **Lack of psychomotor symptoms**
 - ▶ **Methaemoglobinaemia absent** in these cases
 - ▶ Oxidative haemolysis could be a **prominent feature**
 - ▶ **As low as 4.4 g/dL** at presentation requiring transfusion



Delayed or Missed Diagnoses in Chronic zopiclone overdose

- ▶ All these cases had missed or delayed (7-61 months) diagnosis
- ▶ Cases identified through the urine toxicology results in this study
 - ▶ But the clinicians often failed to identify zopiclone as the culprit
- ▶ Could have recurrent anaemia requiring multiple transfusions (up to 56 units over 26 admissions!)
- ▶ Other complications
 - ▶ Iron overload
 - ▶ Renal impairment due to haemolysis



Source of zopiclone

- ▶ Zopiclone is **prescription-only medicine**
- ▶ Most patients (90.9%) in this study had **unknown or illegitimate sources** of zopiclone
 - ▶ Notably, two reported acquiring hundreds of zopiclone tablets from local pharmacies **WITHOUT prescriptions**
 - ▶ A concerning issue of **lax zopiclone dispensing by local pharmacies**



Diagnostic Challenges in Chronic Zopiclone Overdose

- ▶ **Lack psychomotor symptoms and methaemoglobinaemia** typically seen in acute zopiclone overdose
 - ▶ Present predominantly with oxidative haemolysis, and the haemolytic anaemia can be more profound
- ▶ **Not including zopiclone** as a potential cause in **most educational materials** about oxidative haemolysis → under-recognition
- ▶ Most patients in this study obtained zopiclone outside public hospitals
 - ▶ Providing **inaccurate medication histories or even denying drug use**
 - ▶ Lax zopiclone dispensing by local pharmacies

A significant threat to patient safety
and public health!


Publication of our findings

- ▶ New England Journal of Medicine
- ▶ International Journal of Laboratory Hematology



The NEW ENGLAND
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Drug-Induced Oxidative Hemolysis

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Zopiclone Overdose Is an Important and Under-Recognized Cause of Drug-Induced Oxidative Hemolysis: A Case Series Identified by Heinz Body Test Request

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**Medline ® Abstracts for References 27,28 of 'Drug-induced hemolytic anemia'****27**[PubMed LinkOut](#) | [PubMed](#)

TI Zopiclone Overdose Is an Important and Under-Recognized Cause of Drug-Induced Oxidative Hemolysis: A Case Series Identified by Heinz Body Test Request.

AU Lam WK, Law WYF, Yip SF

SO Int J Lab Hematol. 2024;

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PMID

28[PubMed LinkOut](#) | [PubMed](#)

TI Drug-Induced Oxidative Hemolysis.

AU Lam WK, Yip SF

SO N Engl J Med. 2024;390(16):1513.

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PMID

Thrombotic microangiopathy

Purine analogs

Other mechanisms

EVALUATION

Typical presentation/when to suspect drug-induced hemolysis

Peripheral blood smear review

Laboratory testing based on initial findings

Commonly used tests

Oxidant injury may be exacerbated by glucose-6-phosphate dehydrogenase (G6PD) deficiency but can occur in individuals without G6PD deficiency as well [26]. Zopiclone, a sleep aid that some individuals obtain without a prescription, has also been reported to cause severe oxidant hemolysis, especially in female patients, most of whom had a normal G6PD screen [27,28].

Details of hemolysis and specific medications in G6PD deficiency are discussed separately. (See "Glucose-6-phosphate dehydrogenase (G6PD) deficiency", section on 'Avoidance of unsafe drugs and chemicals'.)

Partial list of medicines and other substances thought to be unsafe or safe in individuals with G6PD deficiency

Other Actions and Future Perspectives

- ▶ Raised discussion in NTWC Drug and Therapeutics Committee and HAHO Chief Pharmacist's Office
- ▶ Enhanced education to the public (potential users)
- ▶ Multidisciplinary collaborations to enhance patient safety involving different parties
 - ▶ Pharmacy
 - ▶ Quality and Safety
 - ▶ Department of Health
 - ▶ Internal medicine
 - ▶ Psychiatry
 - ▶ Hong Kong Academy of Medicine

Summary

- ▶ Zopiclone is an important but under-recognised cause of oxidative haemolysis
- ▶ Novel clinical pattern of oxidative haemolysis due to chronic zopiclone overdose
- ▶ A significant concern for patient safety and public health
 - ▶ Lack of psychomotor symptoms seen in acute overdose
 - ▶ Missed or delayed diagnoses due to a lack of awareness
 - ▶ Lax dispensation practices of zopiclone
- ▶ Ongoing efforts to tackle the problem

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