

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

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Disclosures

- ▶ No disclosure

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 (methylthioninium chloride) [△]	
Nalidixic acid [◊]	
Nitrofurantoin, nifuratel, and nitrofurazone (nitrofural) [◊]	
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”

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

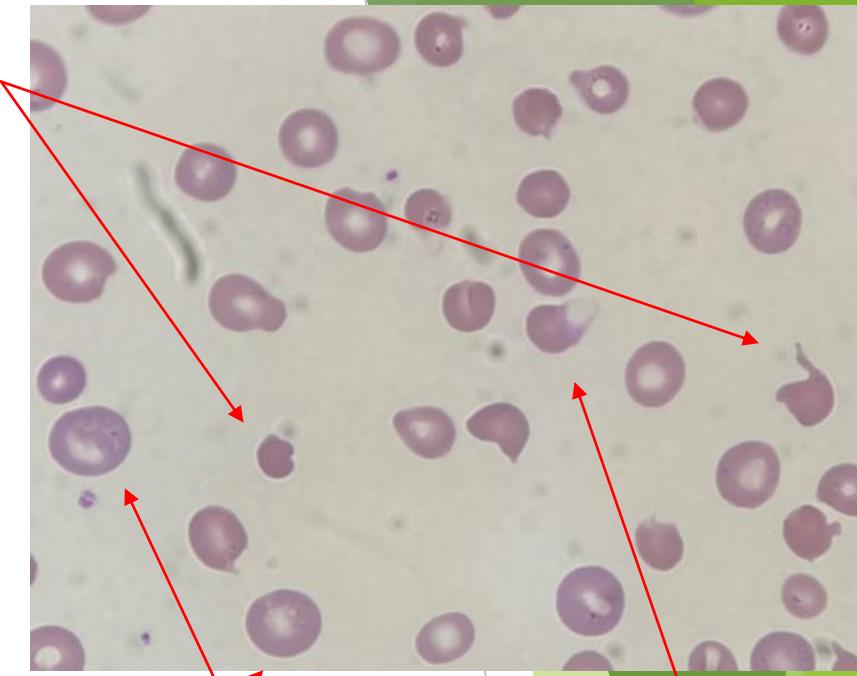
Objective

- ▶ 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

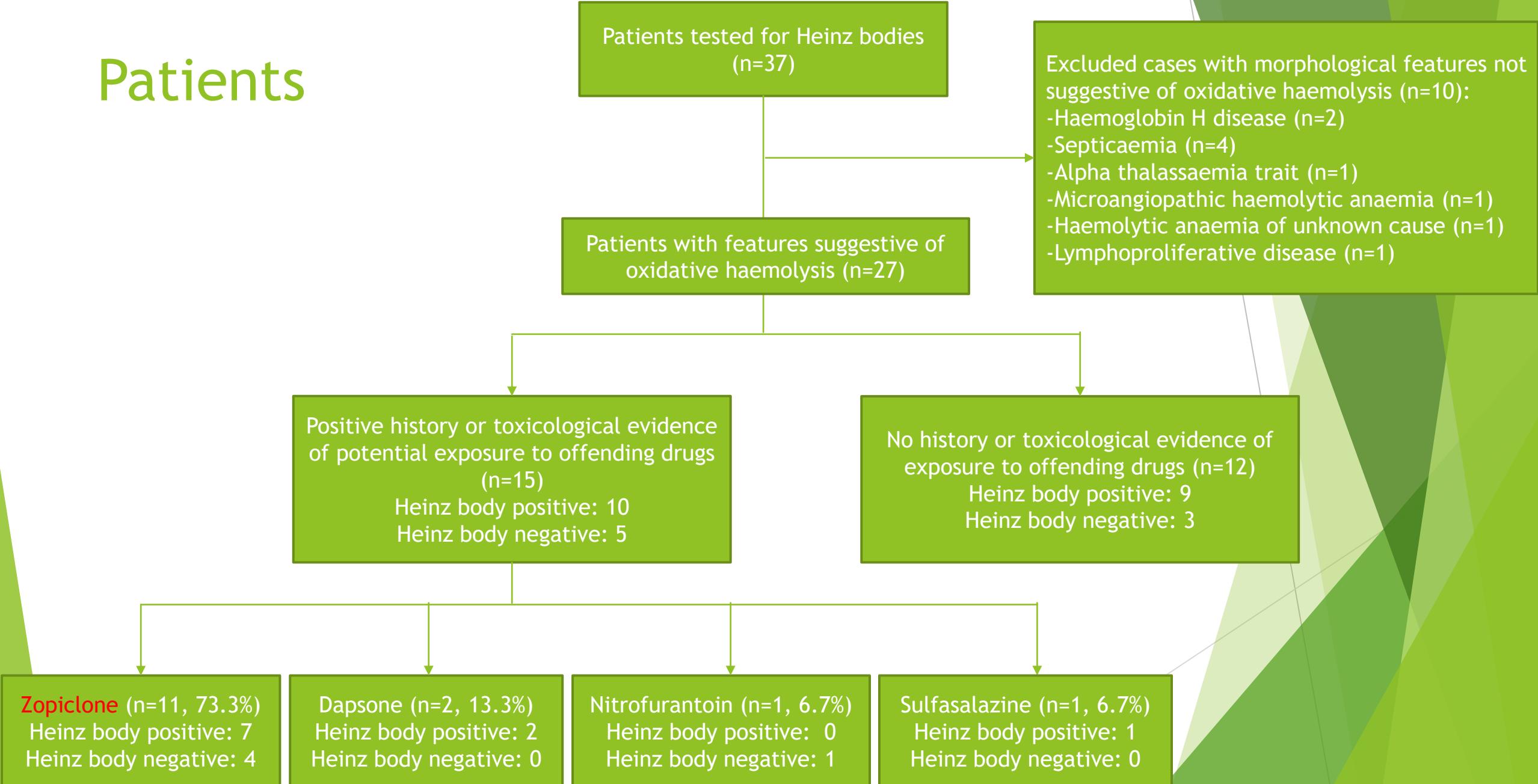
Bite cells



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 **methaemoglobinemia**
 - ▶ Mild oxidative haemolysis



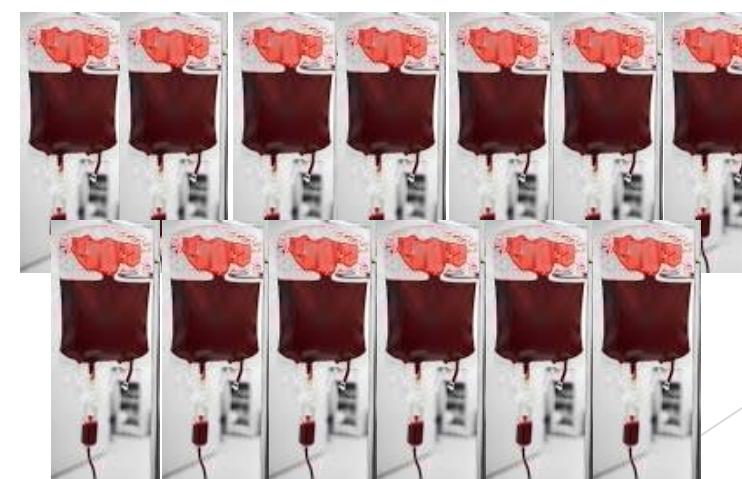
Two distinct presentations of zopiclone-induced oxidative haemolysis (Con't)

- ▶ 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
 - ▶ Methaemoglobinemia 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 methaemoglobinemia 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

The background of the slide features a large, abstract graphic on the right side. It consists of several overlapping, thin, light-green triangles of varying sizes and orientations. Some triangles point upwards and to the left, while others point downwards and to the right, creating a dynamic, layered effect. The overall color palette is a soft, muted green.

A significant threat to patient safety
and public health!

Publication of our findings

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



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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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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 dispensing practices of zopiclone
- ▶ Ongoing efforts to tackle the problem

Acknowledgement

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