Understanding Porphyrogenicity: A Pharmacological Approach to Drug Safety

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Background

Porphyrias are a group of disorders caused by inherited defects in the enzymes of the heme biosynthetic pathway. Individuals with these conditions are susceptible to potentially fatal acute attacks, often triggered by drugs.[1]

Predicting the porphyrogenicity of drugs - whether a drug can induce an acute attack - is crucial for the safe management of patients with acute porphyrias.

Drug Classification

Drugs are classified using the Norwegian Porphyria Centre (NAPOS) database categories.[2]

NP	**Not porphyrinogenic** Used as a first-line choice. No precautions needed.
PNP	**Probably not porphyrinogenic** Used as a first-line choice. No precautions needed.
PSP	**Possibly porphyrinogenic** Only use when no safer alternatives are available. Precautions motivated in vulnerable patients.
PRP	**Probably porphyrinogenic** Prescribe only on **strong** or **urgent** indications. Precautions motivated in all patients.
P	**Porphyrinogenic** Prescribe only on **urgent** indications. Precautions should be taken in all patients.

Current Practice

WMAS provides the UK Porphyria Medicines Information Service (UKPMIS), which publishes an annual list of medicines considered safe for use in acute porphyrias.[3]

UKPMIS, in collaboration with the International Porphyria Network, is refining a global classification for drug porphyrogenicity to enhance consistency and reliability in safety recommendations for porphyria patients worldwide.

Pharmacological Analysis

Experimental data on drug porphyrogenicity is limited, making predictions complex.

Assessing porphyrogenicity involves understanding a drug's interaction with the heme biosynthetic pathway, particularly its effect on delta-aminolevulinic acid synthase 1 (ALAS1).

Focus on predicting porphyrogenicity based on drug metabolism.

The algorithm developed by Thunell et al. evaluates various drug properties which are linked to this system.[1]

Key Drug Properties

- Is there evidence of clinical porphyro-genicity?
- Does the drug cause endocrine effects?
- Does the drug have significant hepatocyte load?
- Does the drug cause CYP enzyme induction?
- Does the drug cause CYP irreversible inhibition?
- Does the drug cause ALAS1 induction?

Discussion

- Porphyrogenicity assessment requires individual clinical decisions.
- Accuracy relies on the quality of pharmacological data, with assessor expertise introducing subjectivity.
- Limited data may result in over-classification.
- Evaluation methods are regularly reviewed to improve predictive robustness.
- *MI practitioners should seek advice from UKPMIS for medicines not on the safe list or classified as anything other than NP/PNP on the NAPOS database, or in complex cases.*

References

1. Hift R, Thunell S, Brun A. Drugs in porphyria: From observation to a modern algorithm-based system for the prediction of Porphyrogenicity. Pharmathera 2011; 132: 158-69.
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4. Thunell S, Pomp E, Brun A. Guide to drug porphyrogenicity prediction and drug prescription in the acute porphyrias. Br J Clin Pharmacol 2007; 64: 668–679.