What to Expect from a Phenytoin Drug-Drug Interaction Study: Adverse Event Profiling and Safety Assessment

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BACKGROUND

Nitrosamine impurities in rifampin forced drug developers to pivot to alternative CYP3A inducers for drug-drug interaction (DDI) studies like phenytoin or carbamazepine.

Advantages of phenytoin > carbamazepine

- No dose titration
- No black box warning
- Shorter or similar time to induction

However, drug developers seem to hesitate to administer phenytoin in a DDI study due to:

- Lack of (personal) experience
- Few published results
- Not commonly prescribed as anti-epileptic drug
- Safety profile concerns

STUDY AIM

To summarize adverse event (AE) type and incidence related to phenytoin administration in healthy volunteer (HV) DDI studies.

METHODS

Pooled AE analysis from 5 DDI studies conducted at Celerion, but not otherwise published, where phenytoin was administered (100 mg TID) as a CYP3A inducer for 14 days, followed by 2-7 days in combination with investigation drug (IP). CYP2C9 and CYP2C19 poor metabolizers were excluded.

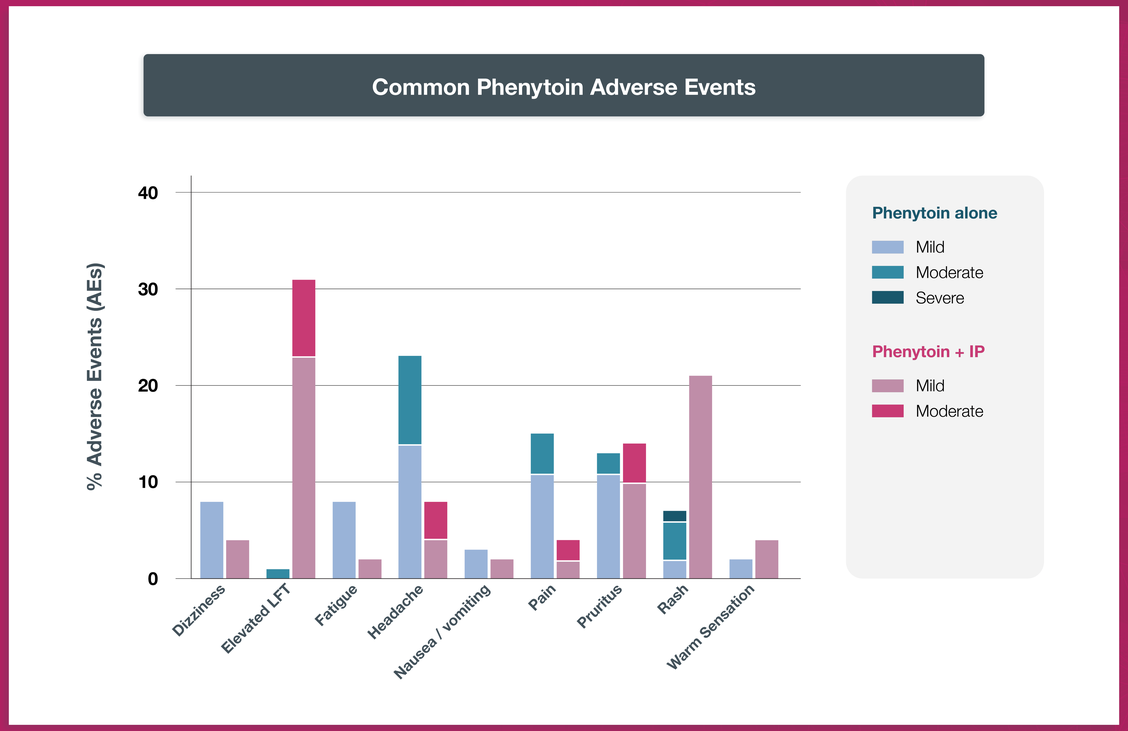
RESULTS

Majority (79%) of phenytoin-related AEs were mild and transient in nature. No serious AEs were observed. Most common AEs were ***elevated liver function tests (LFT), headache, and rash.***

CONCLUSION

Phenytoin had reasonable safety & AE profile was in line with published findings. Elevated labs may result from greater exposure to (hepatotoxic) drug metabolites as a result of a DDI.

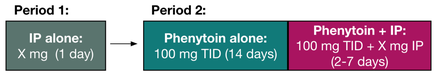
Phenytoin has a reasonable safety profile and is a favorable alternative to rifampin for use in healthy volunteer DDI studies



SCAN HERE

Learn more about rifampin alternatives for DDI studies in response to current nitrosamine impurity issues

Figure 1. Fixed Sequence Study Design



Each study enrolled 14 - 28 HV participants

Figure 2. Proportion of Phenytoin-Related AEs in 5 DDI Studies

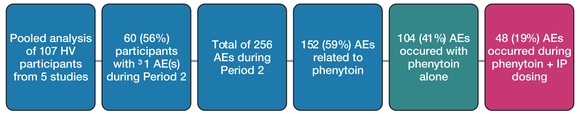
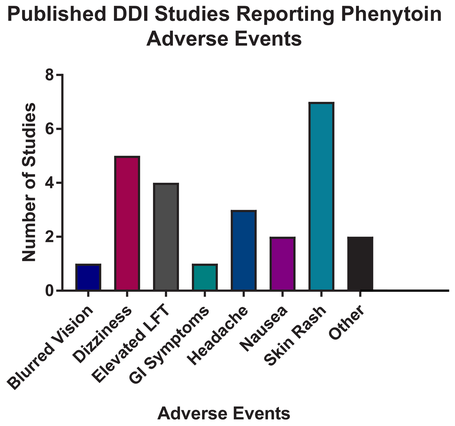


Figure 3. Literature Summary of AEs Associated with Phenytoin DDI Studies*



*Review of 16 published DDI studies administering phenytoin as a perpetrator drug. Adapted from: Overcoming Rifampin Impurity Challenges for DDI Studies: Phenytoin as an Alternative, presented at ACCP 2022 Annual Meeting , Bethesda, MD.

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