# Overcoming Rifampin Impurity Challenges for DDI Studies: Phenytoin as an Alternative

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## BACKGROUND

- Rifampin, an antibacterial drug used to treat tuberculosis, is a strong CYP3A inducer and therefore often administered in drug-drug interaction (DDI) studies.
- Due to recent N-nitrosamine impurity findings in marketed rifampin formulations, its application in healthy volunteer DDI studies was halted in 2020.
- While there are a number of potential rifampin alternatives (Table 1), phenytoin remains the most viable option for healthy volunteer DDI studies.
- We reviewed published DDI studies to provide a comprehensive characterization of phenytoin-induced changes in drug exposure as well as its safety profile.

Box 1
**Rifampin Impurity Issue**

- N-nitrosamines are common and present in low levels in food, beverages, cosmetics, water, and tobacco products
- However, above acceptable intake limits, they are regarded as a "cohort of concern" in ICH M7 due to their high mutagenic and carcinogenic potential
- 1-methyl-4-nitrosopiperazine (MNP) levels in rifampin capsules were found above the acceptable intake limits of 0.16 parts per million (ppm)
- To avoid drug shortages and allow patients to continue with lifesaving rifampin treatment the FDA indicated that they would not object to MNP levels up to 5 ppm. However, will not accept the use of rifampin for healthy volunteer DDI studies

Table 1
**Alternative CYP3A4 Inducers**

| Inducers | Drug Type and Indication | Effects on other CYPs | Comments | Suitable Rifampin Replacement |
|---|---|---|---|---|
| **Apalutamide** | Nonsteroidal antiandrogen non-metastatic, castration-resistant prostate cancer | Strong inducer of CYP2C19; weak inducer of CYP2C9* | Increased risk of seizure; increased incidence of fall and fractures* | ✗ |
| **Carbamazepine** | Sodium channel blocker, anticonvulsant | Strong inducer of CYP2B6; weak inducer of CYP2C9 | Dose titration recommended to mitigate side effects. Black box warning for serious (potentially fatal) dermatologic reactions | ✗ |
| **Enzalutamide** | Nonsteroidal antiandrogen, prostate cancer | Moderate inducer of CYP2C9 and CYP2C19 | Increased risk of seizure; increased incidence of fall and fractures** | ✗ |
| **Mitotane** | Adrenal cytotoxic agent, Cushing's syndrome and adrenal cortical carcinoma | | Common adverse reactions (>15%) include: anorexia, nausea, vomiting and diarrhea; depression, dizziness or vertigo; and rash *** | ✗ |
| **Phenytoin** | Sodium channel blocker, anticonvulsant | Strong inducer of CYP2C19; moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9 | Preferred perpetrator | ✓ |
| **Rifabutin** | Antimicrobial, turbercolosis and chronic staphylococcal infections | Weak inducer of CYP34A | MHRA recommendation; not an option listed | ✗ |
| **St. John's wort** | Herbal supplement derived from Hypericum perforatum plant | | Effect varies widely and is preparation-dependent | ✗ |

Adapted from FDA https://www.fda.gov/drugs/drug-interactions-labeling/drug-developmentand-drug-interactions-table-substrates-inhibitors-and-inducers Table 3-3. *per Erleada (Apalutamide) label; **per Xtandi (Enzalutamide) label; *** per Lysodren (Mitotane)

## METHODS

- A literature review of clinical trials revealed 16 studies evaluated the effect of phenytoin as a perpetrator on drug substrates. Four studies included patients, the remainder enrolled healthy volunteers.
- For each substrate, Area-Under the Curve (AUC) fold change and 95% confidence intervals (CI) were calculated if not reported.
- Phenytoin results were compared to published rifampin DDI findings, if available.
- Available safety findings for phenytoin were summarized.

Table 2
**Summary of Phenytoin DDI Studies**

| Substrate Drugs | Predominant Metabolizing CYP* | Substrate Dose | Substrate Dose | Phenytoin Dose |
|---|---|---|---|---|
| **Celecoxib [1]** | CYP2C9 | 22 Glioblastoma patients | 400 mg BID | Chronic anti-seizure medication (including Phenytoin) |
| **Clinafloxacin [2]** | Hepatic metabolism | 16 HV | 200 or 400 mg BID; 5 & 21 days | 100 mg TID; 21 days |
| **Digoxin [3]** | P-gp | 6 Male HV | 1 mg IV & 0.4 mg b-acetyldigoxin PO for 7 days | 200 mg BID; 7 days |
| **Lopinavir (LPV) / Ritonavir (RTV) [4]** | CYP3A | 12 HV | LPV/RTV 400/100 mg BID; 11 days | 300 mg QD; 11 & 23 days |
| **Tirilazad mesylate [5]** | CYP3A | 12 Male HV | 1.5 mg/kg IV; every 6h for 5 days (21 doses) | 200 mg TID; 16 doses |
| **Bromfenac [6]** | CYP2C9 | 12 Male HV | 50 mg TID; 4 days | 300 mg QD; 7 & 14 days |
| **Mirtazapine [7]** | CYP3A | 19 Male HV | 15-30 mg QD; 15 days | 200 mg QD; 10 days |
| **Gefitinib [8]** | CYP3A4 | 18 Male HV | 250 mg SD | 2.5 mg/kg BID; 7 days |
| **Posaconazole [9]** | P-gp | 36 HV | 200 mg QD; 10 days | 200 mg QD; 10 days |
| **Atorvastatin [10]** | CYP3A4 and transporters (OATP1B1/1B3, P-gp, or BCRP) | 44 HV | 40 mg QD; 7 days & 3 weeks | 4 mg/kg QD; 3 weeks |
| **Losartan [11]** | CYP2C9 and CYP3A4 | 16 HV | 50 mg QD; 9 days | 4 mg/kg (max 400 mg/d); 9 days |
| **Ivabradine [12]** | CYP3A4 | 18 Male HV | 10 mg SD | 150 mg BID; 5 days |
| **Voriconazole [13]** | CYP2C19 | 21 Male HV | 200 mg BID; 7 & 21 days | 300 mg QD; 7 days |
| **Quetiapine [14]** | CYP3A4 | 17 Schizophrenic patients | Dose escalation to 250 mg TID; 10 days | 100 mg TID; 10 days |
| **Nisoldipine [15]** | CYP3A4 | 12 Epilepsy patients vs 12 HV | 40 and 20 mg SD | Chronic administration |
| **Midazolam [16]** | CYP3A4 | 6 Epilepsy patients vsn7 HV | 15 mg SD | Chronic anti-seizure medication (including Phenytoin) |

*Per drug label.
BID = twice daily
HV = healthy volunteer
IV = intravenous
PO = by mouth
QD = once daily
SD = single dose
TID = three time per day

Table 3
**Summary of Rifampin DDI Studies**

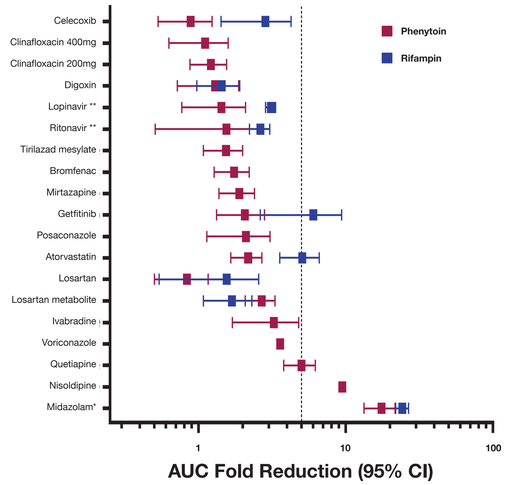
| Substrate Drug* | Study Population | Substrate Dose | Rifampin Dose |
|---|---|---|---|
| **Celecoxib [17]** | 12 Male HV | 200 mg QD; SD & 5 days | 600 mg QD; 5 days |
| **Digoxin [18]** | 8 Male HV | 1 mg SD PO or IV | 600 mg QD; 15 days |
| **Losartan [19]** | 10 HV | 50 mg QD; 7 days | 300 mg BID; 7 days |
| **Lopinavir (LPV) – Ritonavir (RTV) [20]** | 19 HIV patients | LPV/RTV 400mg/100 mg BID; 1 & 8 days | 600 mg QD; 8 days |
| **Gefitinib [21]** | 18 Male HV | 500 mg QD; 10 days | 600 mg QD; 16 days |
| **Midazolam [23]** | 10 HV | 15 mg SD | 600 mg QD; 5 days |

*List of studies in which a phenytoin DDI was also conducted.

SD = single dose
BID = twice daily
HV = healthy volunteer
IV = intravenous
PO = by mouth
QD = once daily
HIV = human immunodeficiency virus
TID = three time per day

## RESULTS

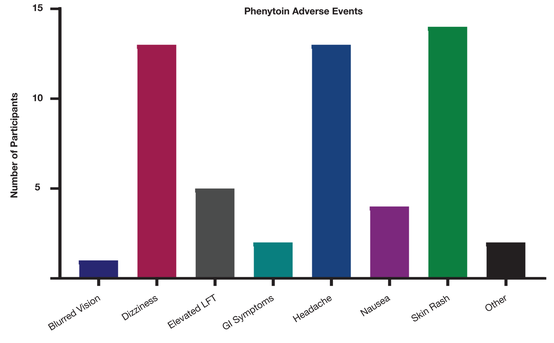
Figure 1
**Phenytoin and Rifampin Induced AUC-Fold Change**




*Phenytoin and/or anti-seizure medication co-administration in patients. **Combination ritonavir and lopinavir therapy. Dashed line represents 5-fold reduction

- Substrates cover a wide range of CYP3A4 sensitivity; with midazolam, nisoldipine, quetiapine being most sensitive.
- Digoxin and celecoxib represent P-gp and CYP2C9 induction, respectively.
- Overall, phenytoin resulted in an average (95% CI) AUC-fold reduction of 3.2 (1.3, 5.2).

Figure 2
**Dizziness, Headache and Skin Rash Are the Most Common Phenytoin Related Adverse Events**




- Phenytoin-related adverse events were mild to moderate, and transient in nature.
- Skin rash and dizziness AEs were reported in 7 and 5 studies, respectively.

## SIGNIFICANCE

- Rifampin will need to be replaced by alternative perpetrators for application in DDI studies until sufficient and uncontaminated batches become available.
- In the meantime, the use of phenytoin as an inducer of CYP3A4 has been shown to be effective.
- A recommended dose regimen of 100 mg TID (total daily dose 300 mg/day) for at least 21 days was found to be generally safe and well tolerated in healthy subjects.

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Box 2

Read the full Mini-Review:
**Rifampin Drug-Drug-Interaction Studies; Reflections on the Nitrosamine Impurities Issue**

## CONTACT INFORMATION

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