Nitrosamines and Rifamycins

LTBI ECHO

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Project ECHO®

UMass Memorial Health Care

Nitrosamines

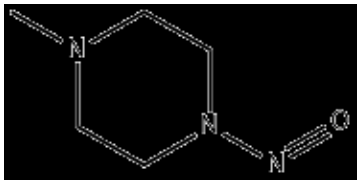
- Class of compounds commonly found in water and foods and some medications
  - *e.g.*, cured and grilled meats, dairy products and vegetables, ranitidine (Zantac)
  - For drugs, may be introduced during the manufacturing process, storage, or by gut flora
  - Everyone is exposed to some level of nitrosamines
- FDA and other global regulatory agencies have set internationally-recognized *acceptable daily intake limits* for nitrosamines
- Nitrosamine impurities may increase the risk of cancer
  - If exposed to above acceptable levels and over long periods of time
    - Estimated a person taking a drug that contains nitrosamines at-or-below the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer >1/100,000

https://www.fda.gov/media/85885/download

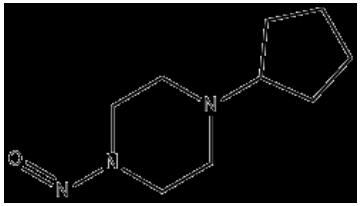
FDA 9/01/2020

Nitrosamines and Rifamycins

- Rifampin: 1-methyl-4-nitrosopiperazine (C5H11N3O; MNP)



- Rifapentine: 1-cyclopentyl-4-nitrosopiperazine (C9H17N3O; CPNP)



Nitrosamines and Rifamycins

- In order to *maintain supply of these drugs*, FDA has raised the maximum acceptable limits of contamination with these impurities for rifampin and rifapentine

Acceptable Limits of Nitrosamine (FDA), 8/26/20

Medication	Normal Intake daily Limit	Temporary Intake daily Limit
Rifampin	0.16 ppm of MNP	5 ppm of MNP
Rifapentine	0.1 ppm of CPNP	14 ppm of CPNP*

* Increased 10/29/20 to 20ppm

Health Canada

- Update on Rifampin Drug Shortage*
  - Issue:
    - Identified slightly higher than acceptable levels of a nitrosamine impurity in lots of rifampin (2.2ppm; limit 2.1ppm)
    - risks of not being treated immediately are greater than would result from short term use of the drug
  - What to do:
    - Do not stop taking your rifampin without first discussing treatment options with your health care provider

* 3/15/2020

CDC/FDA

- 6/15/20: Suspension of Sanofi rifampin-based products Rifadin, Rifamate, and Rifater announced (FDA)
  - Advised to seek other sources of rifampin
- 6/18/2020: Notification of rifapentine (Priftin®, Sanofi) nitrosamine impurity
  - Temporary suspension of production
  - Continue treatment in persons receiving the drug, if available
    - If acceptable to provider and patient
      - Consider alternative regimens for treatment of LTBI (rifampin or INH-based restart)
      - Consider increased risk of drug-induced liver injury and lower completion rates with INH regimens
  - Do not start new rifapentine-based regimen until shipments resume and local supplies are reestablished
- 8/26/20: Impurities identified in rifampin
  - Manufacturers should notify FDA when testing shows levels that exceed the acceptable intake limits of 0.16 ppm for MNP and 0.10 ppm for CPNP.
  - FDA will determine on a case-by-case basis whether those drugs should be released for distribution
- 9/11/20: DTBE recommends that providers continue prescribing rifampin and rifapentine for all TB and latent TB infection (LTBI) treatment per existing guidelines.

Carcinognesis and Rifamycins

- DTBE is not aware of any data showing an association between cancer and use of rifamycins in humans.
- However, DTBE is also not aware of any rigorous studies that have looked for this association.

Carcinogenesis and Nitrosamines in Rifamycins

Strong nasal carcinogenicity and genotoxicity of 1-nitroso-4-methylpiperazine* after low dose inhalation in rats

Klein, RG, Schmezer, P, Hermann, R., *et al*

Carcinogenesis, 20:8, 1629–1632, 1999.
https://doi.org/10.1093/carcin/20.8.1629

*** MNP; contaminant in rifampin**

Recommendations

- Review rifamycin-based regimens and nitrosamine impurities, risks *vs* benefits, with your patient
  - Consider also risks of alternate regimens (*e.g.,* hepatotoxicity of 9 mos INH); deferral of treatment
  - *Treatment must be acceptable to the patient*

- TB Disease:
  - Continue use of rifampin, if acceptable to the patient, as the risk of not taking rifampin likely outweighs any potential risk from nitrosamine impurities

- LTBI:
  - If already taking rifampin or rifapentine-containing regimens for LTBI, continue this treatment, if acceptable to the patient.
  - If clinician or patient prefers to stop rifamycin, a complete regimen of 6 or 9 months of isoniazid can be started, or the original regimen can be completed with a *proportionate duration (sic)* of one of the isoniazid-only regimens (consider INH toxicities).

- Pregnancy and children
  - ?

Current Status

- NTCA and NSTC have had several conversations with FDA, CDC, and manufacturers of Rifampin
  - Source(s) of impurities have been identified as an Active Pharmaceutical Ingredient(s) (api) introduced during manufacture
  - Various manufacturers of rifampin for US distribution have provided encouraging information about their ability to reduce this contamination but are uncertain about their ability to return to the original FDA acceptable maximum limit (0.16ppm MNP for rifampin)

Courtesy D. Wegener

Current Status

- Rifapentine
  - FDA in October, 2020, increased the maximum acceptable limit for CPNP contamination further from 14 to 20ppm (orig. 0.10ppm)
  - Unclear *re* resumption of supply
- Rifabutin
  - NOT subject to nitrosamine contamination (FDA, January, 2021)
  - Availability and use as a rifampin replacement are unclear and are under discussion

Rifampin Shortage, 2022

- As of April 1, 2022, the national shortage of rifampin announced in December continues
  - No clear end date identified
- MDPH requested rifampin from CDC's Drug Stockpile
  - Has been shipped to hospital pharmacies
  - May need to submit another request
  - Expiration date for CDC's stockpiled rifampin: 4/30/22
- Some pharmacies (Walgreens) report no supply issues
- Providers should continue to use rifampin
  - Assure that patients *currently receiving* rifampin successfully re-fill their prescription each month
    - Have pharmacist contact MDPH (617-983-6970) if they encounter a supply issue and cannot fill a prescription
  - For *new therapy* consider alternatives when acceptable (*e.g.,* treatment of LTBI).

Additional information: https://www.accessdata.fda.gov/scripts/drugshortages/ (search word: rifampin)

Next?

- Dorman, S.E., *et al.* Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. NEJM 384:1705-1718, 2021
  - Used ***daily*** rifapentine (7/7 d) at 1,200mg/d
    - (*re,* current dosing 900mg/wk max 3HP)
  - Formal recommendations published by CDC 3/2022.

Nitrosamines (cont'd)

- Health care professionals should continue to prescribe medications when clinically appropriate even though they may have low levels of nitrosamine impurities
- Health care professionals can educate patients about alternative treatment options to medications with potential nitrosamine impurities if available and clinically appropriate
- For information *re* recalls: FDA recalls webpage

FDA 9/01/2020