Interim advice on the use of rifampicin for post-exposure prophylaxis (PEP), in light of recent information on nitrosamine impurities in rifampicin

A number of different problems have affected the supply of rifampicin and MDT to countries this year. The most recent of these has been the discovery of impurities (nitrosamines) in rifampicin that are assumed to pose a health risk if high cumulative doses are consumed. Certain nitrosamines were found to increase the risk of cancer in long-term animal studies, although direct evidence of harm is still lacking. Nitrosamines are found in many products, e.g., various types of food, especially in baked or fried food, drinking water, tobacco smoke and rubber products. The particular impurity in rifampicin concerns a nitrosamine called MNP (1-methyl-4-nitrosopiperazine). This is most likely a by-product in the production of rifampicin. This compound would need to be washed out of the final drug product. Although this issue was only discovered recently due to new screening of drugs for nitrosamine recommended by WHO and other authorities, it is considered likely that nitrosamines have been present in rifampicin for years. Because this compound appears to be common to all manufacturers, they must all come up with ways to improve their processes to reduce or eliminate the impurities.

With regard to nitrosamine, it is the cumulative dose that is important, suggesting that it is not a serious issue for treatment with MDT or its use as PEP, in which the total 'lifetime dose' of rifampicin is low, when compared with treatment for TB (except in countries such as the US, where MDT with daily rifampicin is given for 2 years). The European Medicines Agency (EMA) has indicated that treatment for both TB and leprosy should continue, while the manufacturing process is revised to minimize these impurities.[1] The US Food & Drug Administration (FDA) has recently added 'prevention of serious infections' to this.[2]

The FDA currently recommends a daily limit of 5 ppm, which is has been temporarily raised from the original very conservative threshold of 0.16 ppm. Both these limits have longer-term rifampicin use in view, such as in treatment of TB where a 600mg dose of rifampicin is given daily for 6 months (in adults). We therefore consider the potential health risk posed by a single dose of rifampicin to be negligible. However, since SDR-PEP is given to healthy individuals, ethics would demand that all known risks to health be minimised.

Similar issues are being addressed in the TB field, where combination preventive treatment is used for children (age 2-5) and persons living with HIV, comprising either a 3-month regimen of daily rifampicin and isoniazid, or a 3-week, 12-dose combination of isoniazid and rifapentine (3-HP). A different nitrosamine has been found in rifapentine (1-cyclopentyl-4-nitrosopiperazine (CPNP)). Similar to rifampicin, an FDA statement recommends that TB treatment containing rifapentine (mostly second line treatment) be continued. A cut-off level of nitrosamine impurities has been specified below which rifapentine can be used, as for MNP in rifampicin. A large TB consortium conducting the implementation studies of the 3-HP regimen has decided to continue with the distribution using the same cut-off level as specified for treatment, considering the cumulative dose of CPNP ingested in 12 doses to pose a negligible risk.

The WHO Global TB Programme has taken up the issue of nitrosamine impurities in rifampicin and rifapentine with the WHO Pre-qualification (PQ) Team - Medicines (a global quality assurance programme for medicines). WHO PQT/MED is pursuing this with all producers of API and finished product. This is still ongoing and further guidance will be provided when this is completed. They

[1] https://www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities#rifampicin-medicines-section

[2] https://www.fda.gov/drugs/drug-safety-and-availability/fda-works-mitigate-shortages-rifampin-and-rifapentine-after-manufacturers-find-nitrosamine

have been very helpful and have stated their position with regard to SDR-PEP as follows, "… we understand that the rifampicin products may be used "off label" based on the fact that the WHO 2018 Guidelines for the Diagnosis, Treatment and Prevention of Leprosy recommend single dose rifampicin for leprosy contacts. For this use, the nitrosamine issue is considered to be of no clinical concern."

The Global Leprosy Programme has advised that any actions or recommendations from our side should be aligned with those of the WHO Global TB Programme (GTB) to avoid undermining their position in the implementation of the 3-HP prophylactic regimen. We are now in conversation with the WHO GTB and WHO PQT/MED and they indicated they would be happy to tackle the rifampicin issue for TB and leprosy jointly. WHO PQT/MED is pursuing the issue of nitrosamine contamination of rifampicin with all producers of 'active pharmaceutical ingredient' and finished product. This is still ongoing and further guidance will be provided when this is completed. The GTB advised that "it will be prudent to wait until the PQ analyses are completed before having a firm position on this."

The EMA is currently conducting further investigations and a risk assessment of the nitrosamine impurities and will give updated advice from time to time. The EMA has a deadline of March 31st, 2021, for providing this risk analysis for chemical medicines. Regarding the issue of SDR-PEP they have said, "We would also like to highlight that no market actions have been taken so far in the EU and no restrictions to any treatments with rifampicin were envisaged."

In view of the above, we will wait with any recommendations regarding SDR-PEP distribution until the various ongoing investigations and the conversation with the Global TB and PQ programmes have concluded and their position has become clear.

Where ILEP is involved in the distribution of MDT or rifampicin, we **recommend** that only batches be purchased and/or used that have maximum nitrosamine levels below 5ppm per day as recommended by the US FDA. Recent samples from currently available batches of MDT were tested and found to have levels of nitrosamine under this limit, so if testing is not possible at present, current stocks of MDT are deemed to be safe.

Given the challenges in MDT supply, MDT availability and supply should be taken into account when planning or implementing PEP programmes. There are two main considerations:

1. When there is a shortage of MDT, any available rifampicin may need to be used for treatment of leprosy patients, rather than for chemoprophylaxis among contacts.
2. Whenever active case-finding efforts are undertaken, including contact examinations, the availability of treatment for any new cases identified must be ensured (preferably MDT). MDT is essential and safe for treatment of leprosy patients. Novartis/Sandoz has resumed producing and releasing MDT batches that have been tested for nitrosamines and found to be below the safety level currently recommended by the US FDA.

Since screening for nitrosamine has not been standard in the quality control process of rifampicin, we **recommend** that this be included as part of all future quality control testing of rifampicin.

WHO PQT/MED requested all manufacturers/suppliers of rifampicin or its active ingredient to undertake a risk evaluation for nitrosamine impurities by end of 2020.[3] Therefore, such testing should be done by each company producing rifampicin and/or by the national drug authority in

[3] https://extranet.who.int/pqweb/sites/default/files/documents/FAQ_Nitrosamine_18Dec2020.pdf

charge of monitoring the quality of drugs. Experiences to date suggest that this is not the case in several countries.

The latest news is that purified rifampicin is likely to become available in July/August 2021.

ILEP Technical Commission

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