Nifurtimox Is Ineffective against Drug-Resistant Mycobacteria

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Multidrug- and extensively drug-resistant tuberculosis (TB) and diseases caused by the naturally drug-resistant nontuberculous mycobacteria (NTM) are emerging health threats. For both, new effective treatment regimens are direly needed; strategies include the repurposing of existing antibiotics (1, 2).

Nitrofurantoin is a nitrofuran-class antimicrobial agent used as first-line therapy in uncomplicated urinary tract infections (3). Nitrofurantoin has *in vitro* activity against *Mycobacterium tuberculosis* (4) and, to a lesser extent, *Mycobacterium avium* (5). Nitrofurantoin is rapidly excreted by the kidney, achieving low peak concentrations in plasma (427 ± 227 ng/ml) (6). This inhibits it from achieving effective drug concentrations outside the bladder and thus precludes a role for it in the treatment of mycobacterial diseases. Nifurtimox, which is effective in the treatment of Chagas disease (7), is the only commercialized nitrofuran that achieves high tissue concentrations, evidenced by its low peak concentrations in plasma ($1,361$ ng/ml after a dose of 15 mg/kg of body weight) (7) but its high distribution volume of 755.3 ± 283.8 l (8). Thus, nifurtimox might also be active *in vivo* against mycobacterial infections.

To assess the activity of nifurtimox against mycobacteria, we performed broth microdilution as recommended by CLSI guidelines (9) in both cation-adjusted Mueller-Hinton (CAMH; Becton, Dickinson and Company; Drachten, The Netherlands) and Middlebrook 7H9 (M7H9; Becton, Dickinson and Company; Drachten, The Netherlands) broth. Nifurtimox was ordered from Sigma-Aldrich (lot 043M4717V; Sigma-Aldrich, Zwijndrecht, The Netherlands) and reconstituted in dimethyl sulfoxide. We tested 2-fold serial dilutions ranging from 500 μ g/ml to 0.49 μ g/ml against *Mycobacterium tuberculosis* H37Rv, *M. abscessus* CIP 104536, *M. peregrinum* ATCC 700686, *M. intracellulare* DSM 43223, *M. chimaera* DSM 44623, and *M. avium* ATCC 700898. We defined the MIC as the first concentration at which there was no visible growth.

The MICs of nifurtimox against these mycobacteria are presented in Table 1. Only *M. tuberculosis* showed some susceptibility to nifurtimox; MICs against the NTM were at least 2- to 8-fold higher. This reflects the lower susceptibility of NTM to nitrofurantoin

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TABLE 1 MICs of nifurtimox against mycobacterial reference strains in M7H9 and CAMH broth

<i>Mycobacterium</i> strain	MIC (μ g/ml) in CAMH	MIC (μ g/ml) in M7H9
<i>M. abscessus</i> CIP 104536	>500	500
<i>M. peregrinum</i> ATCC 700686	>500	500
<i>M. intracellulare</i> DSM 43223	250	125
<i>M. chimaera</i> DSM 44623	250	125
<i>M. avium</i> ATCC 700898	>500	>500
<i>M. tuberculosis</i> H37Rv	NA ^a	62.5

^aNA, not applicable.

than that of *M. tuberculosis* (4, 5). Even for *M. tuberculosis*, it is questionable whether these MICs can be overcome by safe and tolerable doses of nifurtimox.

Nifurtimox seems not to be a viable option for mycobacterial chemotherapy. Other nitrofurans are still being investigated as new compounds against mycobacteria (10). We encourage these researchers to continue their work, as effective compounds against multidrug- and extensively drug-resistant TB and NTM disease remain direly needed.

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