State of the Globe: Doxycycline - An Old Wine in a New Bottle for Gram-Negative Sepsis

The modern medicine era is undergoing a pandemic of "antibiotic resistance." The multidrug-resistant (MDR) Gram-negative organisms are hitting the most harm. While gasping in this sinking scenario, our best bet is either to search for new promising powerful antibiotics or to resharpen the old ones. As the development promise of newer antibiotics is not vibrant, the restoration of previously invented but abandoned "old" antibiotics is routine.[1] Moreover, the new uses of old antibiotics are also in game.

Doxycycline is one such "old" broad-spectrum antibiotic discovered in the early 1960s and is still in use.[2] It is synthetically derived from *Streptomyces* sp. bacteria.[3] The best part of it is its activity against Gram-positive, Gram-negative bacteria, spirochetes, and *Mycoplasma*. Such a wide spectrum of coverage makes it lucrative to use in different and difficult scenarios too. Being highly lipophilic, it crosses cytoplasmic membranes (by lipophilicity or by energy-dependent manner) to reach target tissues and into Gram-positive bacteria. Vis-a-vis, it makes a cationic coordination complex to penetrate the porin channels in Gram-negative bacteria.[3] It has an exclusive mechanism of action for bacteria. After entering into prokaryotic cells, it binds to the 30S ribosomal unit. By binding, the growing polypeptide chain is prevented by the nonassociation of amino acid with the ribosomal A-site during the elongation phase. Thus, doxycycline forces to yield a futile cycle of translation. The bacteria cannot construct essential proteins of their choice, and bacterial growth alters leading to the eventual death of the bacteria.[4,5]

The pharmacokinetic profile of doxycycline is unique. The volume of distribution is 0.7 L/kg, and the half-life is 18–24 h.[5] Doxycycline is prescribed as 100 mg twice daily or 200 mg once daily dose. Doxycycline peak serum concentrations are dose dependent. The serum concentration achieves 1.7–2 mg/L (dose of 100 mg), whereas 200 mg reaches 5–6 mg/L. It is bacteriostatic in 2–4 times of minimal inhibitory concentration (MIC), whereas it can be bactericidal in 8–16 times of MIC.[6] It was noted that a single 200 mg dose of doxycycline administered either orally or IV achieved sufficient serum concentration to be effective against most GNB, especially in tissue infections.

de Macedo *et al.* did a review (published in this issue of the journal) to know if doxycycline may be a therapeutic option for the treatment of MDR Gram-negative bacteria as the focus.[7] As discussed, doxycycline has been active against notorious MDR Gram-negative bacteria such as *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Escherichia coli*, against whom all are desperately seeking new antibiotic options. With an extensive search, they quoted eight studies of a total of 59 patients. A specific methodology was not described, and articles were selected by independent reviewers based on title and abstracts. The lower respiratory tract and the urinary tract are the two main infection sites where favorable outcomes were noted with using doxycycline mostly with other antibiotics. Clinical improvement was the highest in urinary tract infection (UTI) at 93.4%. The most common bacterium found in these studies was *A. baumannii.* Doxycycline was not used alone in most cases of pneumonia; vis-à-vis, it was used alone in most UTI cases.

In another similar type of review, the reviewer targeted only a single MDR organism, i.e., *Acinetobacter* and tetracycline group of antibiotics and got good low death rate in Doxycycline group.[3] However, the importance of the drug cannot be concluded strongly from both of these reviews as they have included retrospective studies with a small number of patients.

Hence, to conclude, "old" antibiotics like doxycycline may be used in MDR Gram-negative bacterial infection as a kind of "last-resort" option for urinary tract and to some extent respiratory infections, especially with *A. baumannii* along with other antibiotics.

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