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How active are antibiotics when directed towards bacteria hiding intracellularly? Do accumulation and sub-cellular disposition matter?

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Many bacteria survive and even thrive in eukaryotic cells (macrophages, endothelial cells, osteoblasts and keratinocytes) where they escape immune defenses, explaining the relapsing and/or recurrent character of many infections. Using human THP-1 monocytes, we undertook a systematic examination of the intracellular accumulation and disposition of antibiotics; their activity in a pharmacodynamic model measuring their extracellular concentration needed to obtain a static effect ($C_{s;}$ equivalent to an intracellular MIC) and their maximal efficacy (Emax; decrease of CFU for an infinitely large extracellular concentration). Most antibiotics show Cs values similar to MIC in broth, disregarding their levels of cellular accumulation; E_{max} systematically lower (less decrease in CFU) than in broth. Antibiotics restricted to phagolysosomes and poorly diffusible are inactive against bacteria thriving in the cytosol (e.g., *Listeria monocytogenes*), but those primarily located in the cytosol but highly diffusible can act in all sub-cellular compartments. We conclude that the most important and predictive property for intracellular activity is the sub-cellular bioavailability of antibiotics and not their accumulation per se; part of the intracellular inoculum cannot be eradicated by antibiotics, suggesting the need to develop new approaches to tackle with persistent infections.

Biography

Paul M Tulkens has completed his MD from the Université Catholique de Louvain and also completed his PhD. He did his Postdoctoral studies at the Rockefeller University, New York. He has created the Unit of Cellular and Molecular Pharmacology and has also launched the activities of clinical pharmacy at the Université Catholique de Louvain. He has published more than 280 papers in reputed journals and has been serving as an Editorial Board Member of several journals dealing with antibiotics.

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