Influence of Inhibitors of P-glycoprotein (P-gp) and Multidrug Resistance-Associated Protein (MRP) on the Accumulation and Intracellular Activity of CEM-101, a Novel Macrolide/Ketolide, in Human THP-1 Macrophages: Comparison with Azithromycin

S Lemaire, F Van Bambeke, PM Tulkens

Background:

Macrolides accumulate in macrophages thanks to their weak basic character. However, this can be partly defeated by active efflux, as observed for azithromycin, a substrate of P-gp in macrophages (AAC 2003;47:1047-51). Using AZM as a comparator, we have examined CEM-101, a novel macrolide/ketolide antibiotic, for intracellular accumulation and activity, and for modulation of these properties by P-gp.

Methods:

Human THP-1 macrophages were used throughout. Accumulation was measured by microbiological assay. Intracellular activity was determined against phagocytized *S. aureus* (ATCC 25923; MICs: CEM-101, 0.125 mg/L; AZM, 0.5 mg/L) using dose-response approach (AAC 2006;50:841-51). Verapamil (100 µM) was used as inhibitor of P-gp, and gemfibrozil (250 µM) as inhibitor of MRP (a family of unrelated multidrug transporters).

Results:

Accumulations and activities after 24 h incubation, with and without efflux transporters inhibitors are shown in Table.

Condition	AZM			CEM-101		
	Cc/Ce[1] (24h)	Intracellular activity (D log cfu at 24 h)		Cc/Ce[1] (24h)	Intracellular activity (D log cfu at 24 h)	
		Static dose (mg/L)	E_{max} [2]		Static dose (mg/L)	E_{max} [2]
control	127.7 ± 23.5	~7.0	0.10 ± 0.09	268.1 ± 7.1	~0.02	-0.85 ± 0.23
Verapamil	216.37 ± 46.6	~0.2	-0.37 ± 0.15	290.2 ± 12.9	~0.03	-0.59 ± 0.22
Gemfibrozil	129.12 ± 2.69	~3.8	-0.12 ± 0.20	308.2 ± 47.8	~0.03	-0.73 ± 0.20

[1] apparent cellular to extracellular concentration ratio
[2] maximal decrease of intracellular cfu compared to post-phagocytosis inoculum (calculated from non-linear regression [sigmoidal] of dose-effect response experiments)

Conclusions:

Compared to AZM, CEM-101 (i) shows a larger cellular accumulation and intracellular activity, and (ii) is not a substrate of P-gp.