Contrasting effects of ertapenem (ETP) against intracellular \textit{L. monocytogenes} (L.m.) and \textit{S. aureus} (S.a.) in a model of THP-1 macrophages

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RESULTS

\textbf{Background.} ETP is a penem with an unusually long half-life, yielding efficacy against extracellular infections with a once-daily schedule. We have studied its activity in two types of intracellular infections (L.m., [cytosol]; S.a., [phagolysosomes]).

\textbf{Methods.} MIC and MBC were measured in TSB. Intracellular activity in THP-1 macrophages was determined as previously described by Caryny et al. for L.m. (AAC, 2002; 46:2095-2103), and by Sendel et al. for S.a. (AAC, 2003; 47:2283-2292) with minor adaptations. Meropenem (MEM) was used for comparison.

\textbf{Results.}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Drug & MIC (\mu g/L) & MBC (\mu g/L) & MIC (\mu g/L) & MBC (\mu g/L) \\
\hline
ETP & 0.35 & > 64 & 0.05 & 0.15 \\
MEM & 0.35 & > 64 & 0.05 & 0.25 \\
\hline
\end{tabular}
\caption{MIC and MBC of ETP and MEM against L.m. and S.a.}
\end{table}

ETP and MEM display similar activity against S.a. but MEM is more active than ETP against L.m. MBC values suggest that both drugs are bacteriostatic against L.m. and bactericidal against S.a.

\textbf{Methods.} Extracellular and intraphagocytic activities against \textit{L. monocytogenes} and \textit{S. aureus} in a 24 h model

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure}
\caption{Change in the number of extracellular or intracellular L. m. or S. a. after 24 h incubation in control conditions or with ETP (155 mg/L) or MEM (50 mg/L). Data are mean ± SEM of 3 independent experiments.}
\end{figure}

AIM OF THE STUDY

To compare the extracellular (broth) and intracellular (THP-1 infected cells) activity of ETP (long half-life penem) and MEM (short half-life penem):

- against \textit{L. monocytogenes} and \textit{S. aureus},
- using a concentration corresponding to the peak observed in human receiving conventional doses of these antibiotics.

\textbf{INTRODUCTION}

Intracellular infections remain a medical challenge due to (i) their recurrent character and (ii) the difficulty for antibiotics to gain access to the infected compartment (\textit{L. monocytogenes}, cytosol; \textit{S. aureus}, phagolysosomes).

\textit{Beta-lactams} often constitute a first choice in our therapeutic armamentarium because of their diverse spectrum of activity and high therapeutic index. We recently showed that they also display bac
teridial activity against the intracellular forms of infections localized either in the cytosol (L.m.) or in the phagolysosomes (S.a., post-A48H). Because of their short half-life and time-dependent activity, they need, however, repeated administrations. In this respect, molecules with prolonged half-life like ertapenem may potentially offer a therapeutic advantage.

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\textbf{INTRODUCTION}

\textbf{EXTRACELLULAR ACTIVITY}

\textbf{METHODS}

\begin{itemize}
\item Minimal Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC) were determined in Tryptic Soy Broth (TSB) by arithmetic and geometric dilutions respectively.
\item Extracellular activity were determined by CFUs counting after a 24 h incubation with the antibiotic in TSB.
\end{itemize}

\textbf{RESULTS}

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\textbf{Conclusions}

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\item ETP fails to control the intracellular growth of \textit{L. monocytogenes}, in sharp contrast with meropenem, which causes a 2 log decrease as compared to the initial inoculum.
\item Intracellular infections remain a medical challenge due to (i) their recurrent character and (ii) the difficulty for antibiotics to gain access to the infected compartment (\textit{L. monocytogenes}, cytosol; \textit{S. aureus}, phagolysosomes).
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teridial activity against the intracellular forms of infections localized either in the cytosol (L.m.) or in the phagolysosomes (S.a., post-A48H).
\item Because of their short half-life and time-dependent activity, they need, however, repeated administrations. In this respect, molecules with prolonged half-life like ertapenem may potentially offer a therapeutic advantage.
\item The data suggests that ETP would be an appropriate alternative for MEM for intracellular \textit{S. aureus} infections but not for \textit{L. monocytogenes} infections.
\item The reasons for these discrepancies need to be further explored but could be related to the higher intrinsic activity of MEM against L.m. (MIC values), an insufficient intracellular bioavailability of ETP (binding to cytosolic constituents?), and an insufficient intracellular bioavailability of ETP (binding to cytosolic constituents?).
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\textbf{CONCLUSIONS}

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\item Both penems show a similar behavior against extracellular bacteria but are far more active against S.a. than against L.m., which can be related to their static effect against the latter organisms.
\item ETP fails to control the intracellular growth of \textit{L. monocytogenes} in sharp contrast with meropenem, which causes a 2 log decrease as compared to the initial inoculum.
\item Intracellular infections remain a medical challenge due to (i) their recurrent character and (ii) the difficulty for antibiotics to gain access to the infected compartment (\textit{L. monocytogenes}, cytosol; \textit{S. aureus}, phagolysosomes).
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