1-O-hexadecyloxypropyl cidofovir (CMX001) effectively inhibits polyomavirus BK replication in primary human renal tubular epithelial cells

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 1194063
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Year 2010
Title 1-O-hexadecyloxypropyl cidofovir (CMX001) effectively inhibits polyomavirus BK replication in primary human renal tubular epithelial cells
Journal Antimicrobial agents and chemotherapy
Volume 54
Number 11
Pages / **Article-Number** 4714-22

Antiviral drugs for treating polyomavirus BK (BKV) replication in polyomavirus-associated nephropathy or hemorrhagic cystitis are of considerable clinical interest. Unlike cidofovir, the lipid conjugate 1-O-hexadecyloxypropyl cidofovir (CMX001) is orally available and has not caused detectable nephrotoxicity in rodent models or human studies to date. Primary human renal proximal tubular epithelial cells were infected with BKV-Dunlop, and CMX001 was added 2 h postinfection (hpi). The intracellular and extracellular BKV DNA load was determined by quantitative PCR. Viral gene expression was examined by quantitative reverse transcription-PCR, Western blotting, and immunofluorescence microscopy. We also examined host cell viability, proliferation, metabolic activity, and DNA replication. The titration of CMX001 identified 0.31 M as the 90% effective concentration (EC(90)) for reducing the extracellular BKV load at 72 hpi. BKV large T antigen mRNA and protein expression was unaffected at 24 hpi, but the intracellular BKV genome was reduced by 90% at 48 hpi. Late gene expression was reduced by 70 and 90% at 48 and 72 hpi, respectively. Comparisons of CMX001 and cidofovir EC(90)s from 24 to 96 hpi demonstrated that CMX001 had a more rapid and enduring effect on BKV DNA and infectious progeny at 96 hpi than cidofovir. CMX001 at 0.31 M had little effect on overall cell metabolism but reduced bromodeoxyuridine incorporation and host cell proliferation by 20 to 30%, while BKV infection increased cell proliferation in both rapidly dividing and near-confluent cultures. We conclude that CMX001 inhibits BKV replication with a longer-lasting effect than cidofovir at 400Œ lower levels, with fewer side effects on relevant host cells in vitro.

Publisher American Society for Microbiology
ISSN/ISBN 0066-4804
edoc-URL http://edoc.unibas.ch/dok/A6004294
Full Text on edoc No;
Digital Object Identifier DOI 10.1128/AAC.00974-10
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/20713664
ISI-Number WOS:000284155000028
Document type (ISI) Journal Article