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SCY-078, a Novel Intravenous and Oral Antifungal Agent, Demonstrates Extensive Tissue Distribution in Rats Following Single Intravenous Infusions and Oral Doses of [^{14}C]SCY-078

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INTRODUCTION

- SCY-078 is an intravenous (IV) and orally (PO) bioavailable ß-1,3-glucan synthesis inhibitor currently in clinical development for invasive and mucocutaneous infections caused by *Candida* or *Aspergillus* species (spp).
- Oral SCY-078 recently demonstrated clinical activity in proof-of-concept studies in invasive candidiasis as well as vulvovaginal candidiasis (VVC)
- SCY-078 inhibits fungal glucan synthesis (GSI), but is structurally distinct from other currently available GSIs (echinocandins), and demonstrates *in vitro* activity against both azole-resistant and the majority of echinocandin-resistant strains of *Candida* spp.

The objectives of this study were to characterize, following single PO or IV infused doses of [^{14}C]SCY-078, to pigmented and non-pigmented rats, the:

1) Pharmacokinetics (PK)
2) Tissue distribution profile
3) Rate and extent of excretion

METHODS

Male Han Wistar rats and male and female Long-Evans rats were administered [^{14}C]SCY-078 as either a single 1-hr IV infusion of 5 mg/kg or as a single PO dose of 15 mg/kg in order to evaluate routes of elimination, and the time/exposure relationship in blood and tissues.

RESULTS

The fraction absorbed following PO administration was ~33%. SCY-078 was extensively distributed into tissues. Tissue concentration versus time indicated a rapid distribution phase over the first 8 h followed by a 24-168 h elimination phase.

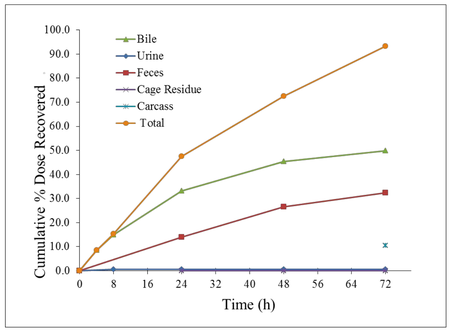
The blood:tissue ratios in the organs typically associated with invasive fungal disease were as follows: spleen (54), liver (50), lung (31), bone marrow (25), kidney (20), skin (12 non-pigmented, 18 pigmented), vaginal tissue (9) and skeletal muscle (4).

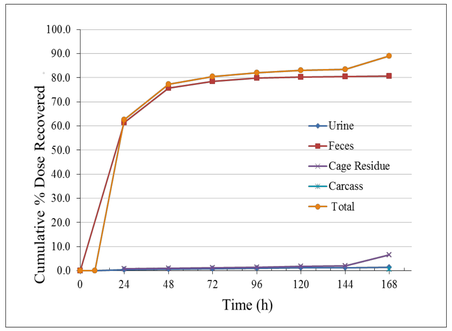
Distribution to CNS tissues was low with little, if any, radioactivity being detected in brain and spinal cord.
The distribution profile was similar between pigmented and non-pigmented animals.

Mean $t_{1/2}$ was 7.5 and 9.8 h, C_{max} was 1.8 and 0.716 µg equiv/mL, and $AUC_{0\text{-}inf}$ was 11.8 and 15.0 µg equiv•h/mL, respectively.
T_{max} was 1 h after an IV dose and 4 h after a PO dose.
C_{max} in most tissues was observed at 0.083 h (IV) and 4 h (PO) post-dose.

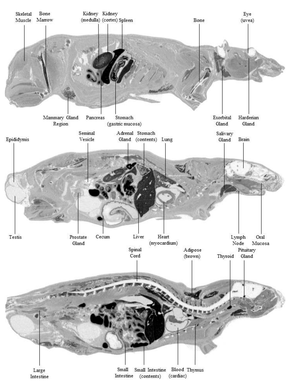
Following either an IV or PO dose, elimination was primarily in feces and bile. Approximately 91-92%% of the radioactive dose was recovered after 168 h (IV) and 72 h (PO) whereas urine recovery was ≤3.1%.

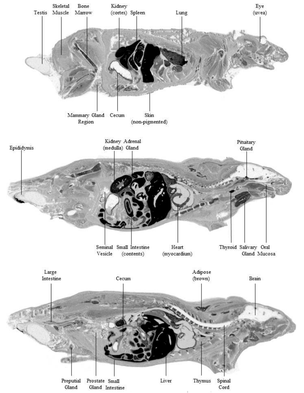
Time course of excretion of radioactivity following IV (5 mg/kg) or Oral (15 mg/kg) administration of ^{14}C-SCY-078





Whole-Body Autoradiograms in Rats following IV (5 mg/kg) or PO (15 mg/kg) of [^{14}C]SCY-078





CONCLUSION

SCY-078 is widely distributed after IV or PO dosing in rats. The concentrations in tissues, commonly affected by fungal infections (e.g., spleen, kidney, liver, lung and vagina), exceeded plasma concentrations by several fold.
These results support development of SCY-078 for treating systemic and mucocutaneous fungal infections.