Pharmacokinetics of cycloheximide in rats and evaluation of its effect as a blocker of intestinal lymph absorption

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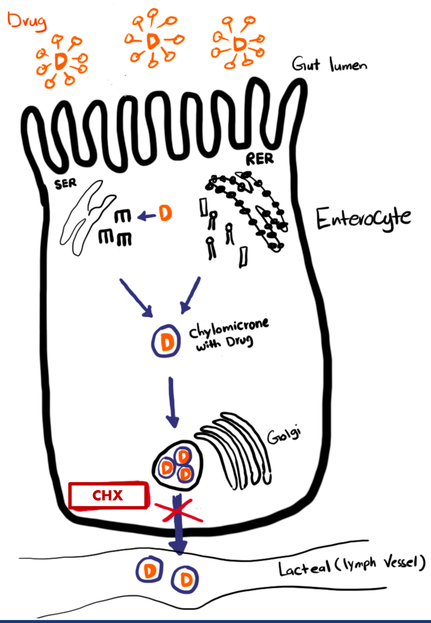
INTRODUCTION

- Cycloheximide (CHX) is a protein synthesis inhibitor that can block the formation of intestinal lymph.
- It has been used as a non-surgical tool to study the contribution of intestinal lymph in drug absorption owing to its inhibitory effect on lymph flow. However, systemic exposures were not studied after dosing with CHX. Moreover, the used doses in animal studies (≥3 mg/kg) are associated with significant toxicity, and involved intraperitoneal (ip) injection, which may bypass the enterocytes where the compound acts as inhibitor of lymph flow.
- Thus, it is crucial first to determine the systemic exposure and pharmacokinetic parameters of CHX in rats. Then, examining the efficacy of CHX as inhibitor of intestinal lymph flow using non-toxic dose.



OBJECTIVES

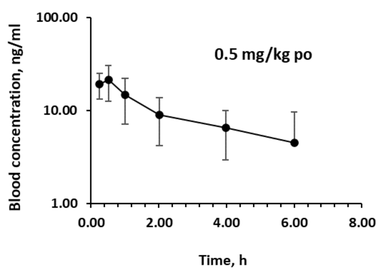
To characterize the pharmacokinetics (PK) and effect of low dose CHX on lymphatic fat absorption.

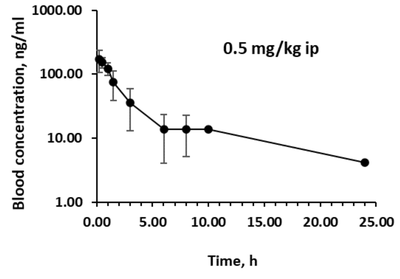
METHODS

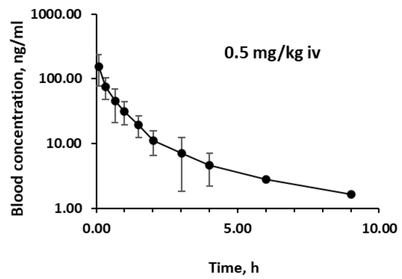
PK study: Jugular-vein cannulated male Sprague-Dawley rats were administered 0.5 mg/kg CHX orally (po), intraperitoneal (ip), or intravenously (IV). Serial post-dose blood samples were drawn for 24 h and assayed using a published LC-MS/MS assay method [(1)].

Fat absorption study: Another four cannulated rats were given, on day 1, peanut oil (2 mL/kg) and on day 2, peanut oil 30 min after 2.5 mg/kg CHX orally. Blood was measured for CHX, cholesterol and triglyceride after the gavages. Body weight was monitored.

RESULTS



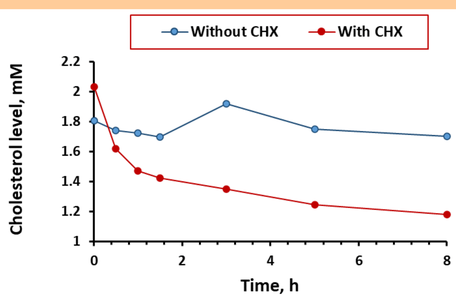




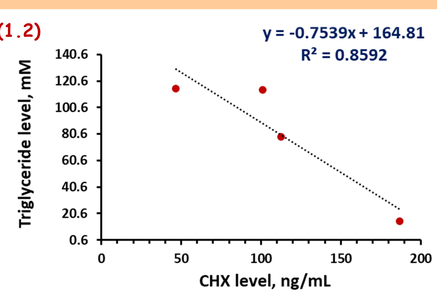
Parameters	IV, Mean±SD	PO, Mean±SD	IP, Mean±SD
Dose, mg/Kg	0.5	0.5	0.5
Cmax, ng/mL	156.1 ± 77.9	21.5 ± 8.29	181.4 ± 50.3
tmax, h	0.08 ± 0	0.25 ± 0	0.26 ± 0.01
t1/2, h	1.85 ± 0.501	10.4 ± 17.6	5.01 ± 3.88
Vdss, L/kg	7.78 ± 2.92	29.4 ± 12.8	4.63 ± 0.835
CL, mL/min/kg	78.1 ± 27.5	149.3 ± 140	23 ± 12.9
Q, mL/min/kg	55.2	55.2	55.2
Hepatic Extraction Ratio, E	> 0.7	> 0.7	0.41

- After injection, CHX follows a multicompartment model with moderately high clearance (CL), large volume of distribution (Vdss) and short half-life (t½).
- The oral absolute bioavailability (F) of CHX was 47%
- The relative bioavailability after ip doses was higher than after iv doses, suggesting a process such as enterohepatic recycling. The relative F of CHX after po doses compared to ip was 15%.
- The hepatic extraction ratio after po and iv dosing are higher than ip dosing.
- Mean urine recoveries (% dose) after iv was 9%, ~2-fold more than po dose.

(1.1)

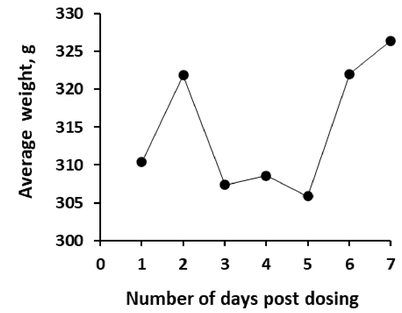


(1.2)



- After oral gavage of 2.5 mg/kg CHX, cholesterol and triglyceride levels were reduced significantly by 51% and 23%, respectively, compared to control group. This would reflect a reduction in the fat absorption from the intestinal and consequently slowing the intestinal lymph flow (n=8) (Figures 1.1 and 1.2).

RESULTS (cont.)



- About 5% reduction in the body weight after 48 h of CHX oral dosing (2.5 mg/kg) (n=4)
- However, it seems that rats recovered from the toxicity on day 6 and 7 post dosing

CONCLUSION

This study is the first to report the pharmacokinetics of cycloheximide in rats

Low dose CHX in rats showed moderately high CL and extensive distribution.

The low po F, coupled with its CL and higher ip than iv area under the blood concentration vs. time curves (AUC) suggested enterohepatic recycling, and poor oral absorption and/or significant intestinal metabolism.

Even low oral doses could reduce lipid absorption and presumably chylomicron formation.

Using oral dose of 2.5 mg/kg showed a temporarily lowering of body weight

FUTURE DIRECTIONS

Performing plasma biochemistry assay including ALT/AST, CRP, and Creatinine.

Evaluate the used dose of CHX on the lymphatic absorption of some model compounds for lymphatic absorption.

REFERENCE

(1) PMID: 35032893