

in vitro

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Title: In vitro study of interaction of some phenothiazines and purines with famciclovir metabolism catalyzed by guinea pig liver aldehyde oxidase.

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Abstract: Famciclovir is a guanosine nucleoside analogue with activity against herpes viruses and hepatitis B virus. Following oral administration, famciclovir is rapidly hydrolyzed to 6-deoxypenciclovir which undergoes extensive oxidation to penciclovir. *In vitro* studies have shown that both famciclovir and 6-deoxypenciclovir serve as substrates for hepatic aldehyde oxidase. Thus, it would be likely that those compounds that act as aldehyde oxidase inhibitors/substrates interfere with penciclovir formation. In the present *in vitro* study, the possible interaction of some phenothiazines and purins with the metabolism of famciclovir is investigated. Aldehyde oxidase was partially purified from guinea pig liver and the interaction of chlorpromazine, promethazine, phenothiazine, azathioprine, 6-mercaptopurine, theophylline, caffeine and allopurinol with famciclovir or 6-deoxypenciclovir oxidation was investigated using spectrophotometric or HPLC methods. Only phenothiazines caused marked inhibition on both oxidations with chlorpromazine giving the highest inhibition. The oxidation of famciclovir or 6-deoxypenciclovir was not significantly affected by allopurinol (the xanthine oxidase inhibitor) confirming that aldehyde oxidase, not xanthine oxidase, is the major molybdenum hydroxylase in the oxidation of both substrates in guinea pig liver fractions.

Key words: Aldehyde oxidase, famciclovir, penciclovir, drug interaction, phenothiazines, purines.

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Sciences.

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B

in vitro

HPLC

()

Harrell.()

()

()

NADPH

)

%

)

(

%

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(xanthine: O₂ oxidoreductase

()

EC 1.2.3.2)

() ()

in vitro

varicellzoster

herpes simplex

()

(aldehyde: O₂ oxidoreductase EC 1.2.3.1)

SmithKline Beecham
Pierce (BSA) Sigma
in vivo
(P450
(
()

Dunkin-Hartley

(g)
KCl °C
EDTA / mM (% / w/v,
()
()

UV-VIS

Shimadzu 2101

μM

/ mM pH= Sorenson
() EDTA

() ()

()

(mM) % μM

Sorenson

EDTA / mM pH=

HPLC

510 Waters

Vmax () Km UV- WISP 710B

() KI () 455 LC VIS

Lineweaver-Burke plot Spherisorb :

() Shimadzu ODS2 5μm (25 cm x 4.6 mm, i.d.)

μBondapack C18

(pH = / / mM)

/ ml/min (:)

Pierce BCA Protein Assay nm

() (μM)

ml

/ mM (mM pH =)

°C EDTA

μl

% μl

/ /

μl

() HPLC

μM

()

)

) (

)

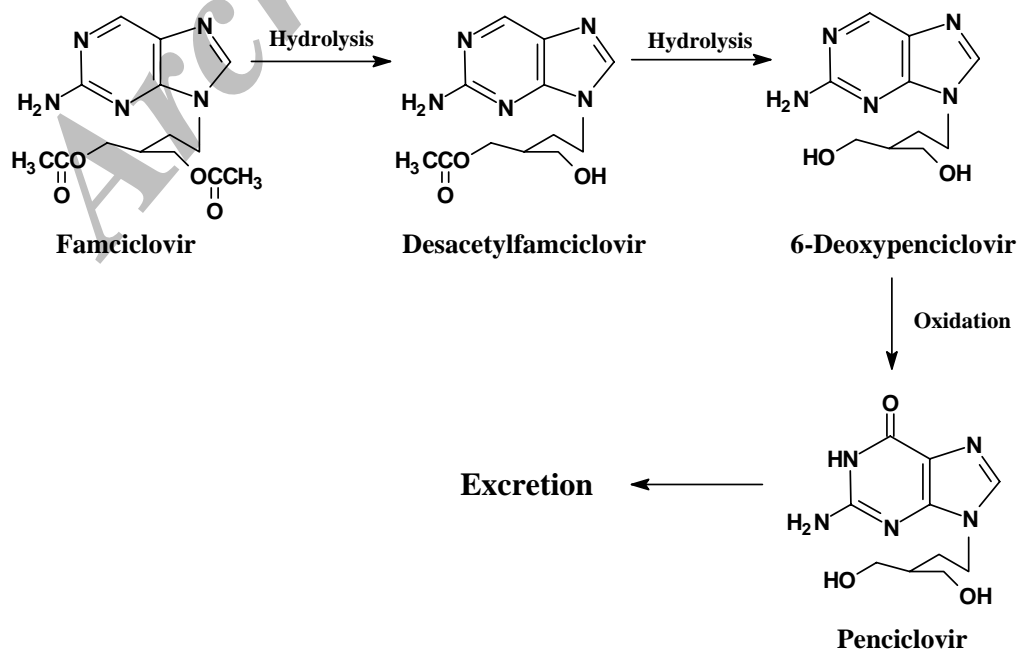
(μM)

μM

μM

*

(μM)			(μM)		
\pm	\pm	\pm	\pm	\pm	\pm
\pm	\pm	\pm	\pm	\pm	\pm
\pm	\pm	—	\pm	\pm	—
—	—	\pm	—	—	\pm
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± $\mu\text{g}/\text{min}/\text{mg}$ protein			(n=) ± $\mu\text{g}/\text{min}/\text{mg}$ protein *		





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