SUSTIVA: UNCOVERING THE MECHANISM FOR THE METABOLISM-DEPENDENT, SPECIES-SELECTIVE NEPHROTOXICITY

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SNC PARTNERS LLC

ACKNOWLEDGEMENTS

- *DRUG METABOLISM AND PHARMACOKINETICS*
  - GERALD MIWA, ABDUL MUTLIB, LAWRENCE GAN, SHARON DIAMOND, MARY GRUBB, SURESH BALANI, ROBIN WAY, GIL LAM, CHECK QUON, STEVE UNGER, BILL FISKE, BARBARA MASSELLO, AMITA JOSHI, BEN CHIEN, HAO CHEN, DONNA BILSKI, FOSTER BROWN, RUTH ANN ZECCOLA, LAUREN RICHARDS, HANK PIENIASZEK

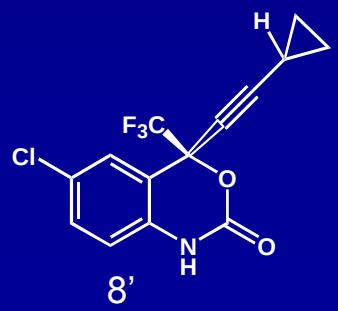
- *SAFETY ASSESSMENT*
  - RICK ROBERTSON, RON GERSON, PAUL MEUNIER, PAT HALEY, MARC DAVIES, BRIAN GEMZIK, DAVE KRAHN, BRAD BARNES

- *CHEMISTRY AND VIROLOGY*
  - STEVE SEITZ, JAY MARKWALDER, GREG NEMETH, TONY COCUZZA, PAUL ANDERSON, GEORGE TRAINOR, MIKE PIERCE, AL MICAL, PAT CONFALONE, SUE ERICKSON-VIITANEN

- *PHARMACEUTICS*
  - MIKE MAURIN, SUSAN ROWE, SHELLEY RABEL

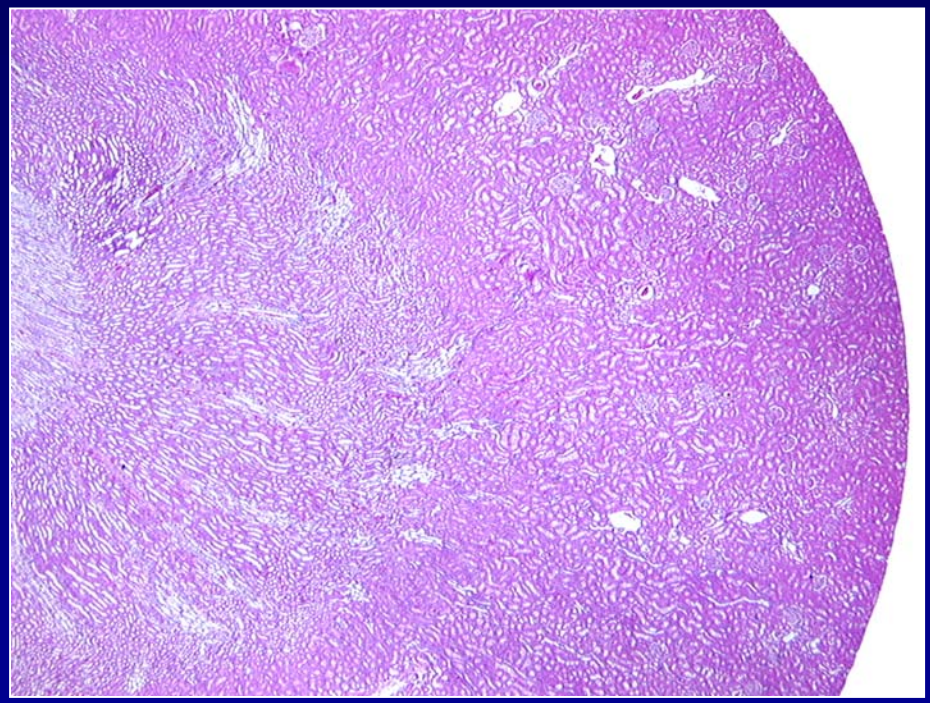
SUSTIVA®
EFAVIRENZ

- CURRENTLY THE PREFERRED NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR FOR THE COMBINATION THERAPY OF HIV-AIDS
- EFFECTIVE AT 600 MG ONCE DAILY
- INDUCES CYP 2B, 3A AND UGT ENZYMES IN RODENTS AND PRIMATES INCLUDING HUMANS
- IS A SUBSTRATE FOR CYP 2B6 (8'-HYDROXYLATION)

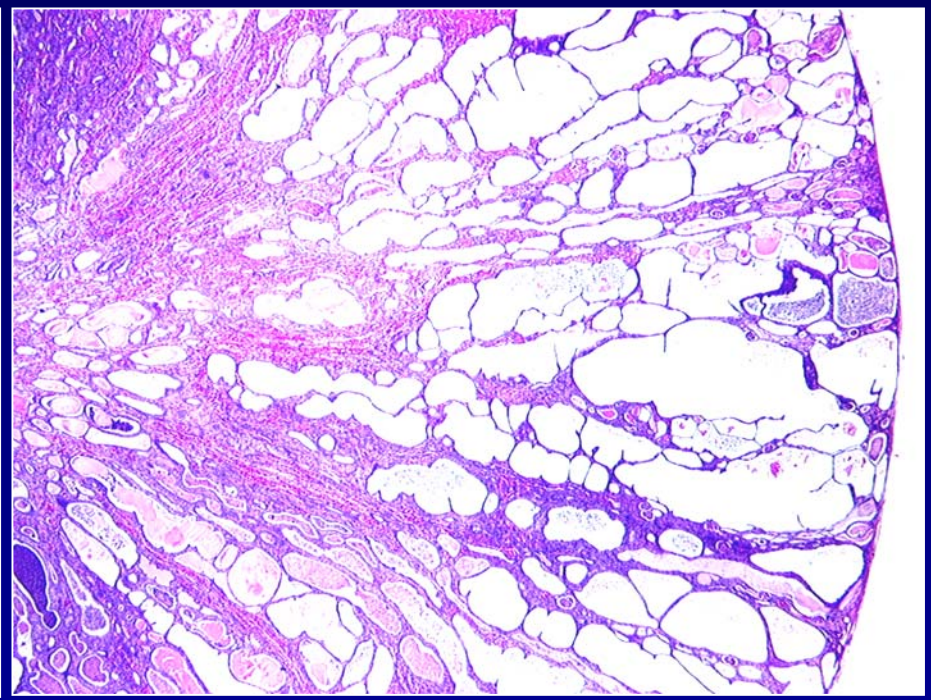


8'

YOU KNOW YOU'RE HAVING A BAD DAY WHEN...



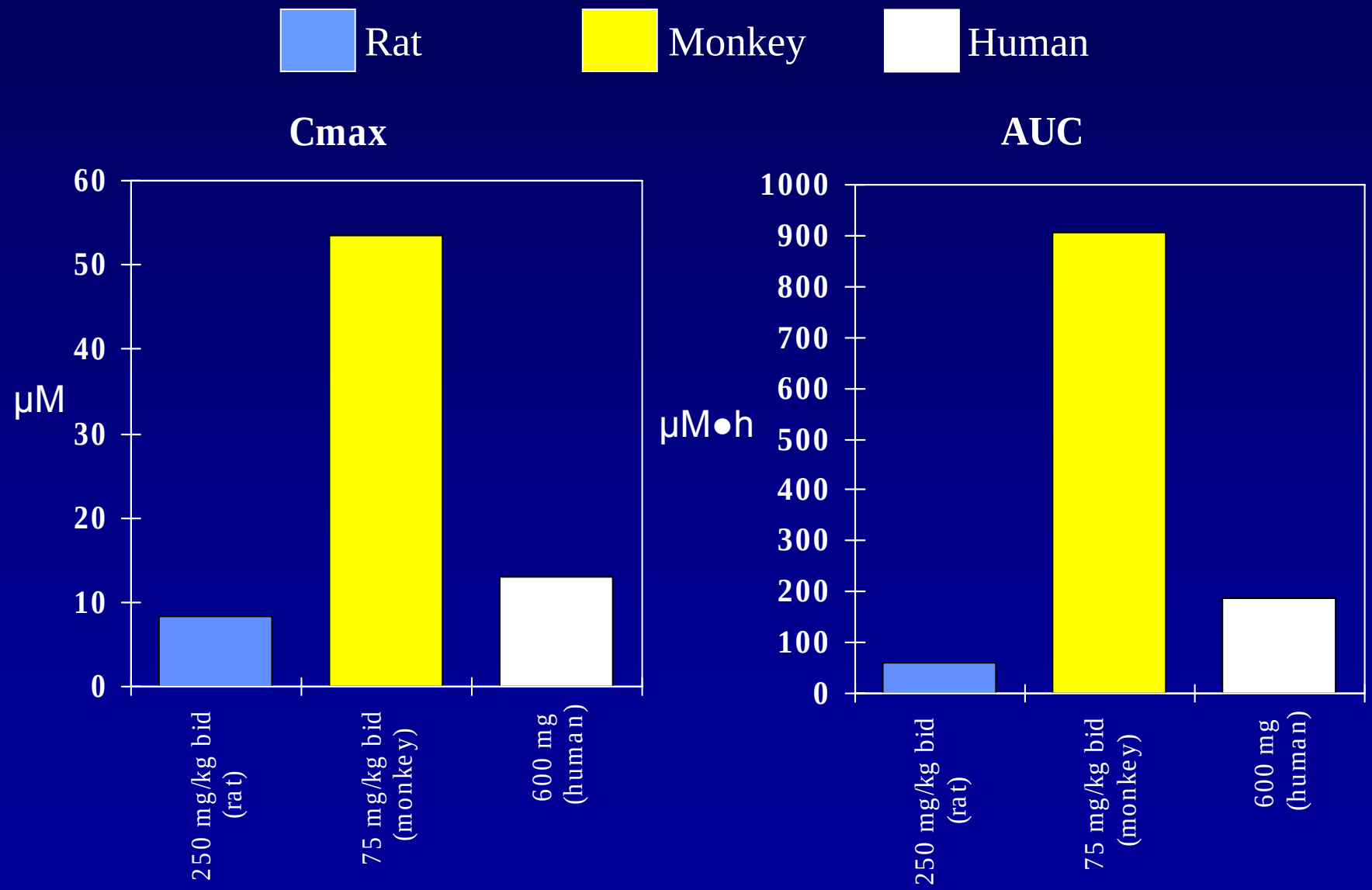
CONTROL (20X)



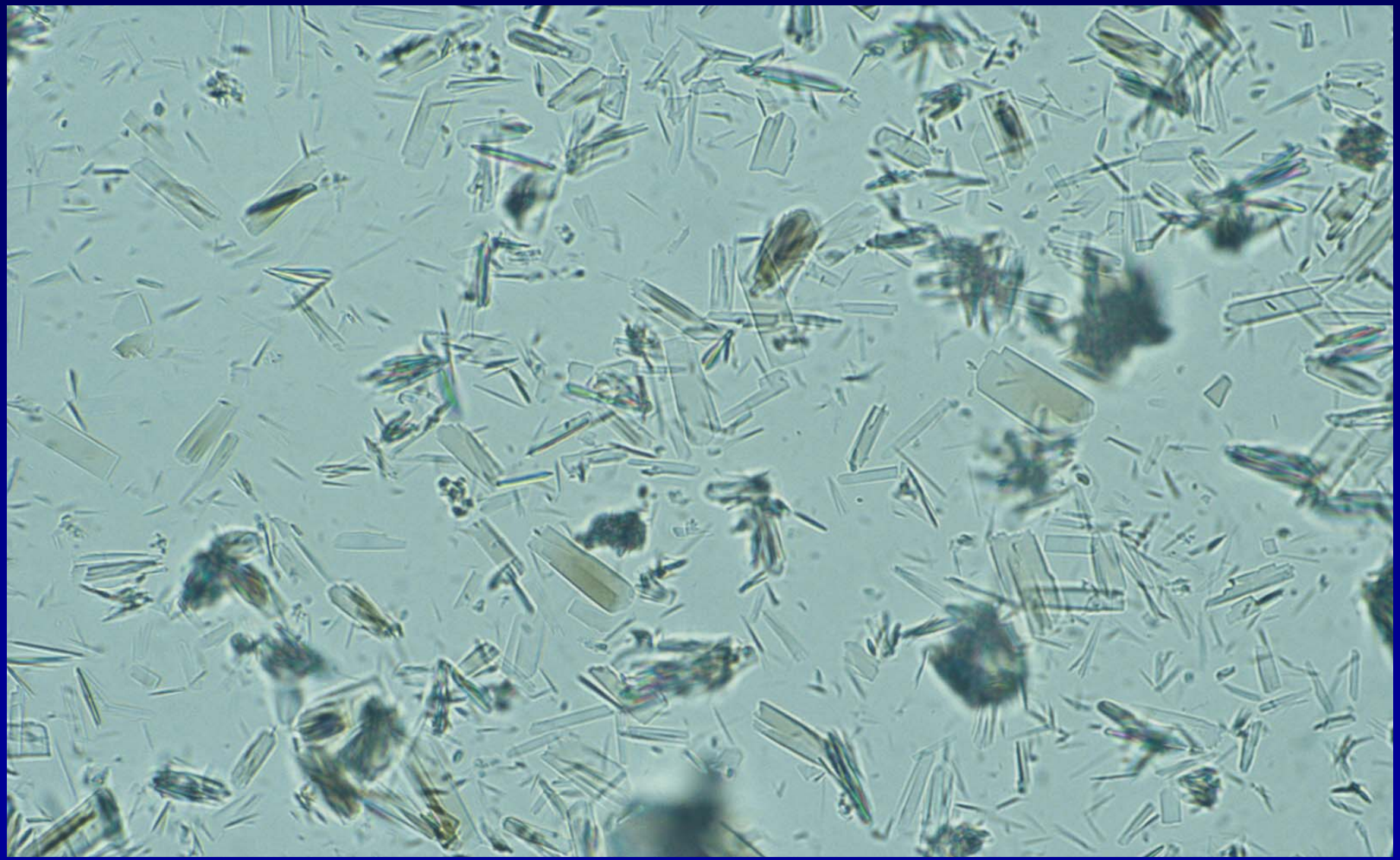
EFAVIRENZ-TREATED (20X)

EFAVIRENZ PRODUCED PROXIMAL CONVOLUTED TUBULAR EPITHELIAL CELL NECROSIS IN RATS (BUT NOT MONKEYS) IN A DOSE-DEPENDENT MANNER

THE LACK OF NEPHROTOXICITY IN MONKEYS IS NOT THE RESULT OF POOR EXPOSURE



DRUG-RELATED CRYSTALS PRESENT IN RAT URINE AFTER NEPHROTOXIC ORAL DOSES OF EFAVIRENZ



EFAVIRENZ PRODUCES PROXIMAL TUBULAR EPITHELIAL CELL NECROSIS IN RATS

- WHAT WAS KNOWN
  - NEPHROTOXICITY WAS FOUND ONLY IN RATS, NOT MONKEYS
  - METABOLITE PROFILE IN ANY SPECIES WAS UNDEFINED
  - A CRYSTALLINE SEDIMENT WAS PRESENT IN RAT URINE

HYPOTHESES

HIGH CONCENTRATIONS OF A METABOLITE WERE PRECIPITATING OUT IN THE TUBULES LEADING TO RENAL DAMAGE AND CRYSTALURIA

(CHEMICAL PATHWAY)

OR

A SPECIES-SPECIFIC REACTIVE METABOLITE WAS FORMED OR PROCESSED IN RATS

(BIOCHEMICAL PATHWAY)

ISOLATION AND IDENTIFICATION OF THE URINARY CRYSTALS AS THE 8-HYDROXYGLUCURONIDE

- CRYSTALS WERE ISOLATED FROM THE URINE OF RATS DOSED ORALLY WITH 500 MG/KG/DAY, DRIED AND DISSOLVED IN ^{2}H METHANOL

- STRUCTURE WAS DETERMINED BY MS AND NMR AND ULTIMATELY CONFIRMED BY SYNTHESIS OF AUTHENTIC METABOLITE

- pH DEPENDENT SOLUBILITY WAS DETERMINED BY PHARMACY

  pH 5.3 0.5 mg/mL pH 6.4 8.7 mg/mL

- TOXICOKINETIC STUDIES WITH ISOLATED AND SYNTHETIC 8-OH GLUCURONIDE AND 8-OH EFAVIRENZ WERE CONDUCTED WITH RATS

- CONCENTRATIONS OF BOTH METABOLITES WERE MEASURED IN PATIENT PLASMA AND URINE

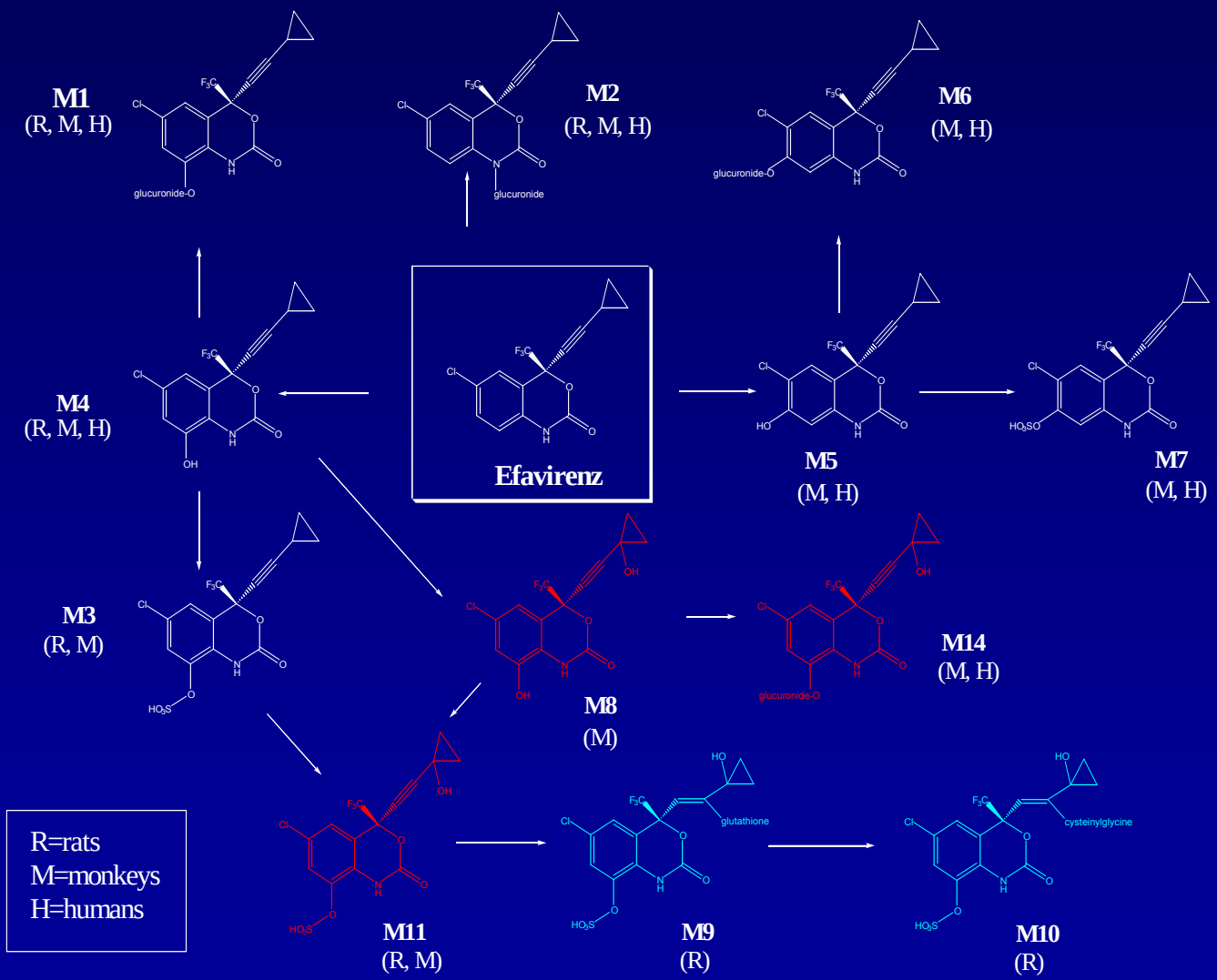
HYPOTHESIS B: RATS FORM OR PROCESS A SPECIES-SELECTIVE NEPHROTOXIC METABOLITE

KEY QUESTIONS

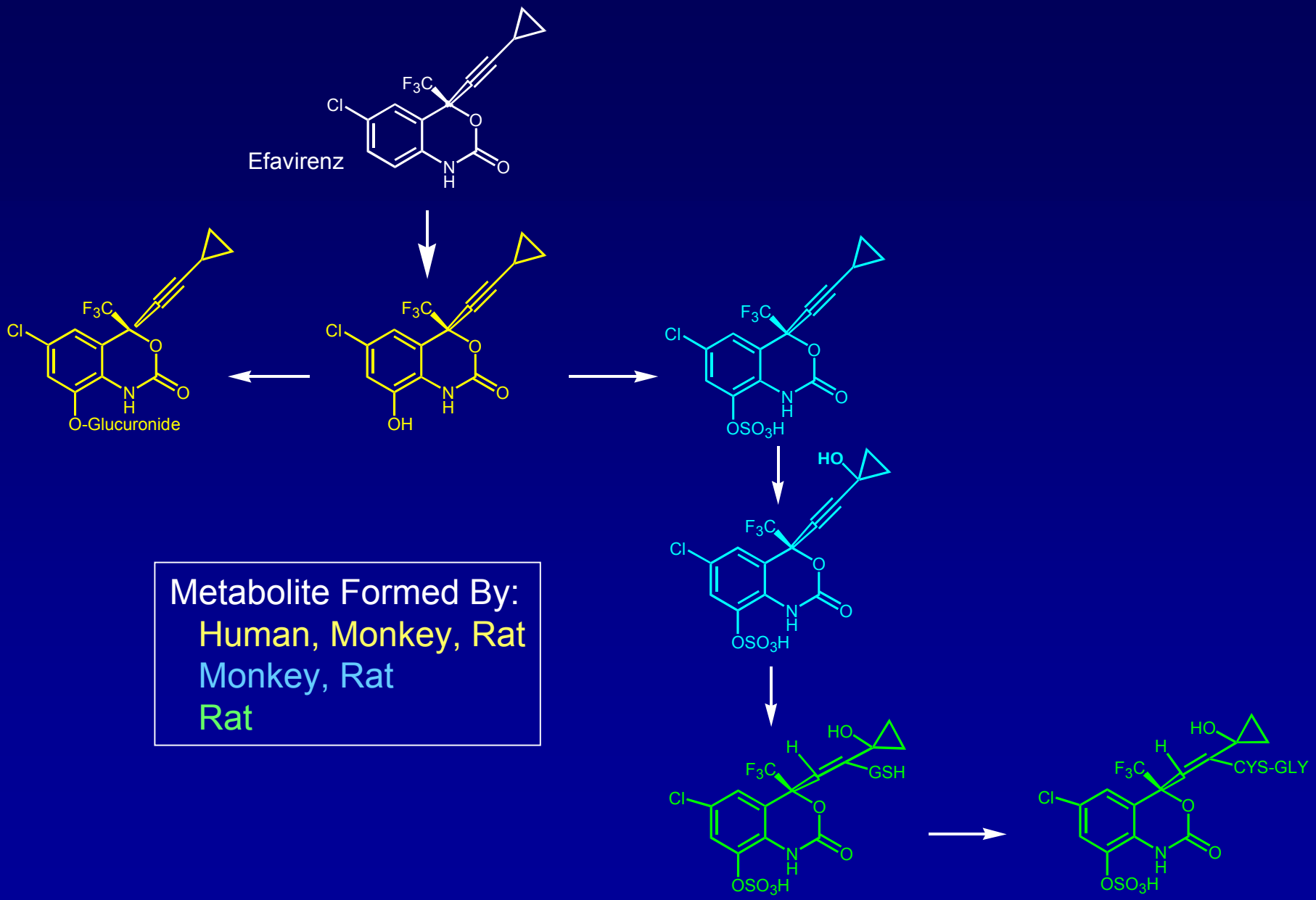
WHAT ARE THE METABOLITES FORMED AND EXCRETED BY EACH SPECIES, INCLUDING HUMANS ?

IF THERE IS A RAT-SELECTIVE METABOLITE, HOW IS IT FORMED AND HOW CAN THE FORMATION AND PROCESSING BE RELATED TO THE NEPHROTOXICITY OBSERVED ?

SPECIES-DEPENDENT METABOLISM OF EFAVIRENZ

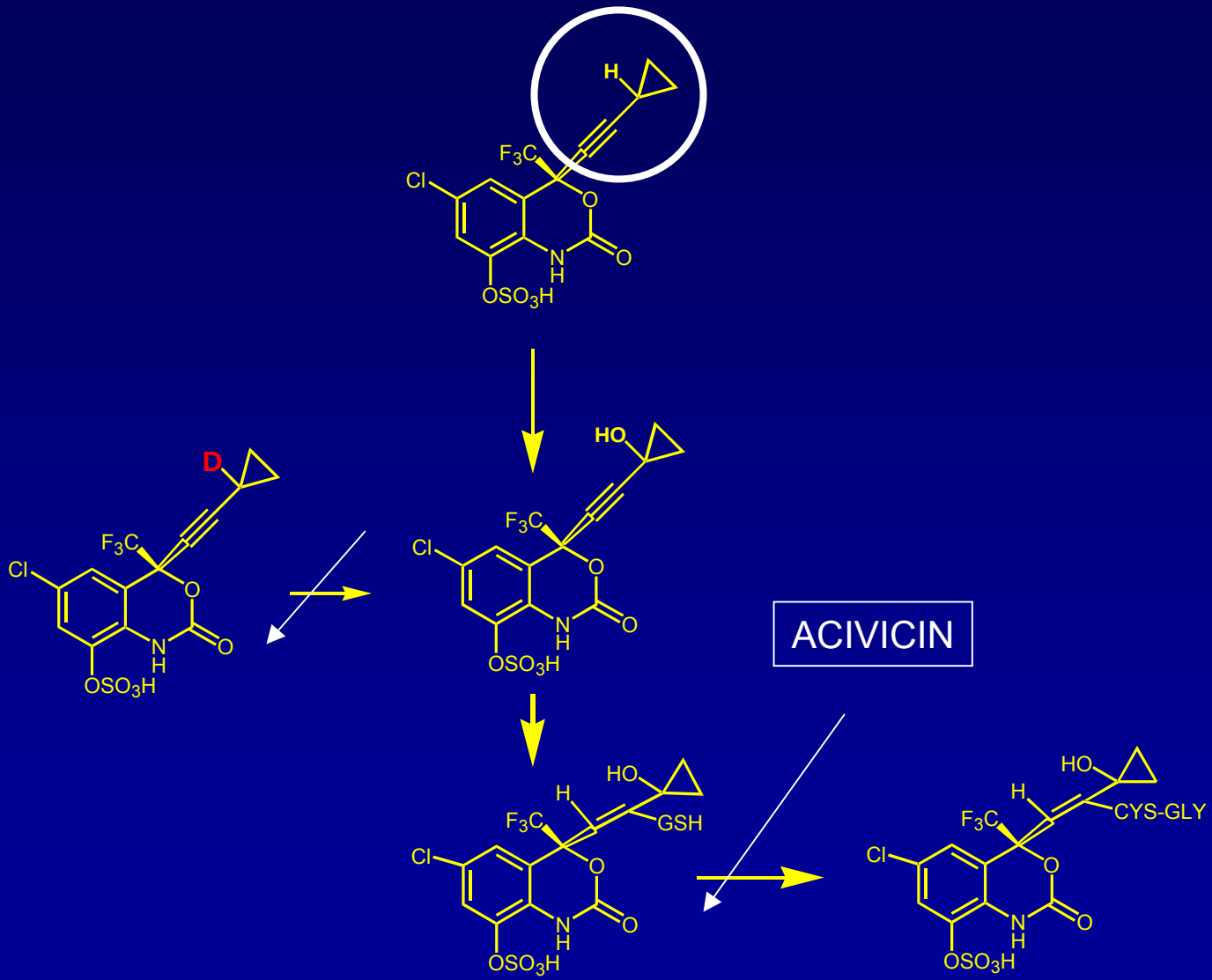


Rat-Specific Formation of Efavirenz Glutathione Conjugate

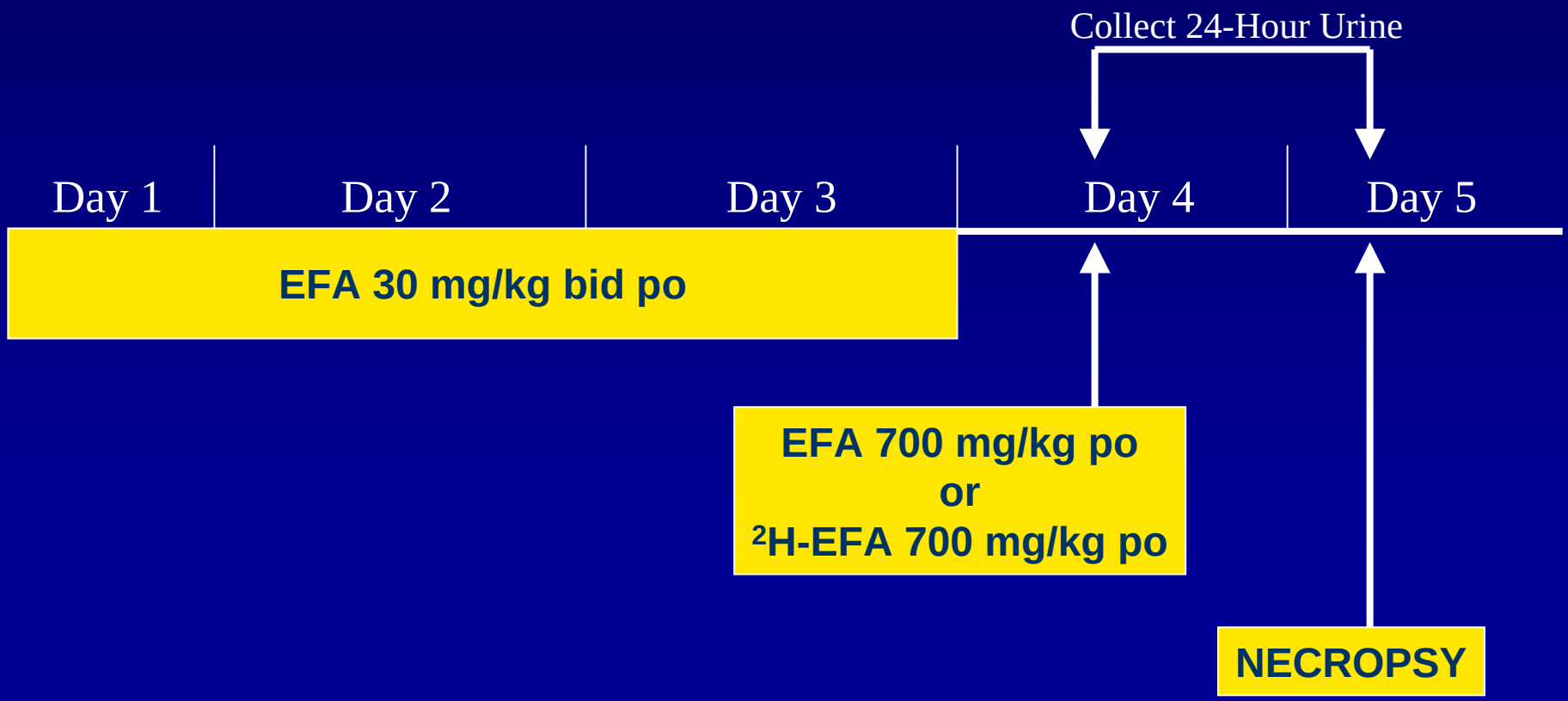


Metabolite Formed By:
- Human, Monkey, Rat
- Monkey, Rat
- Rat

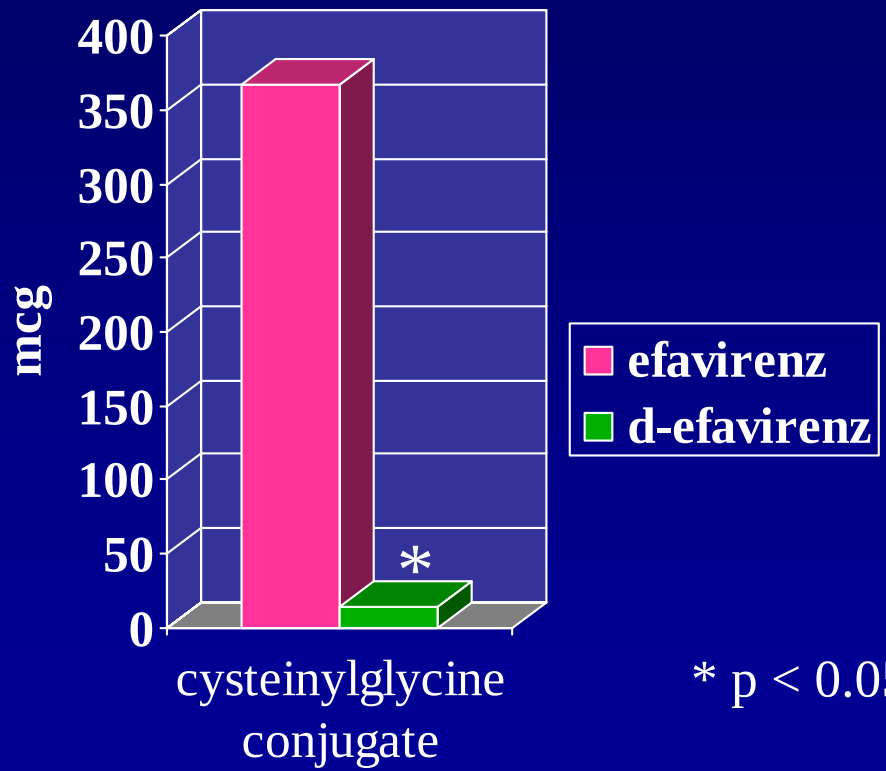
SELECTIVE DEUTERATION INHIBITS EFAVIRENZ OXIDATION AND ULTIMATE GLUTATHIONE CONJUGATION



STUDY PROTOCOL FOR DEUTERATED EFAVIRENZ ADMINISTRATION



DEUTERATED EFAVIRENZE DECREASES THE URINARY EXCRETION OF THE CYS-GLY BUT NOT THE 8-OH GLUCURONIDE METABOLITE OF EFAVIRENZ



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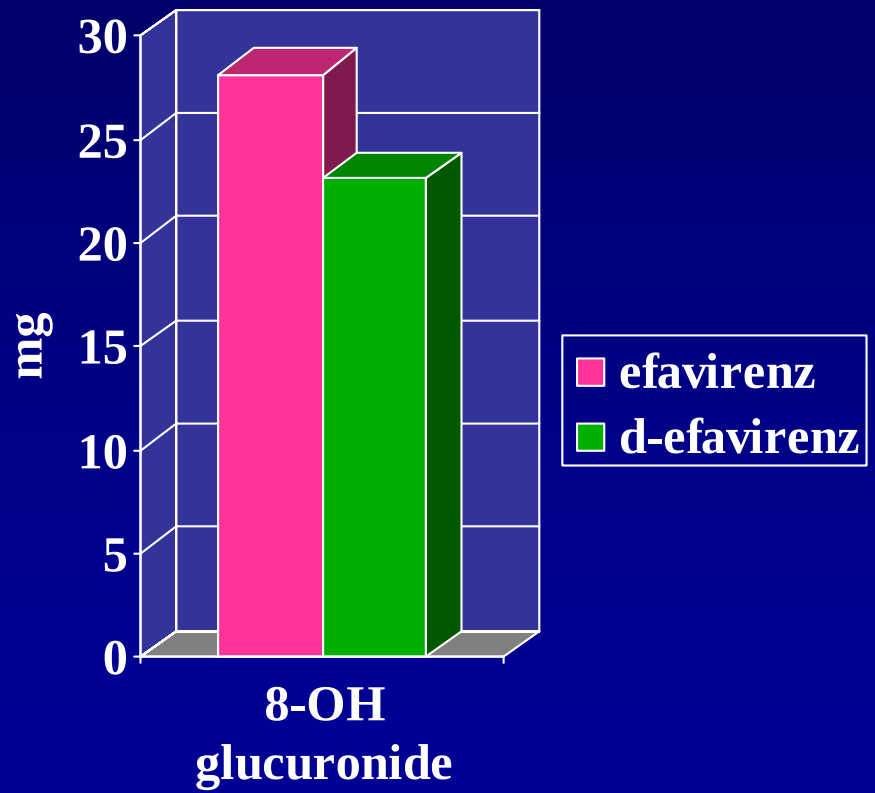
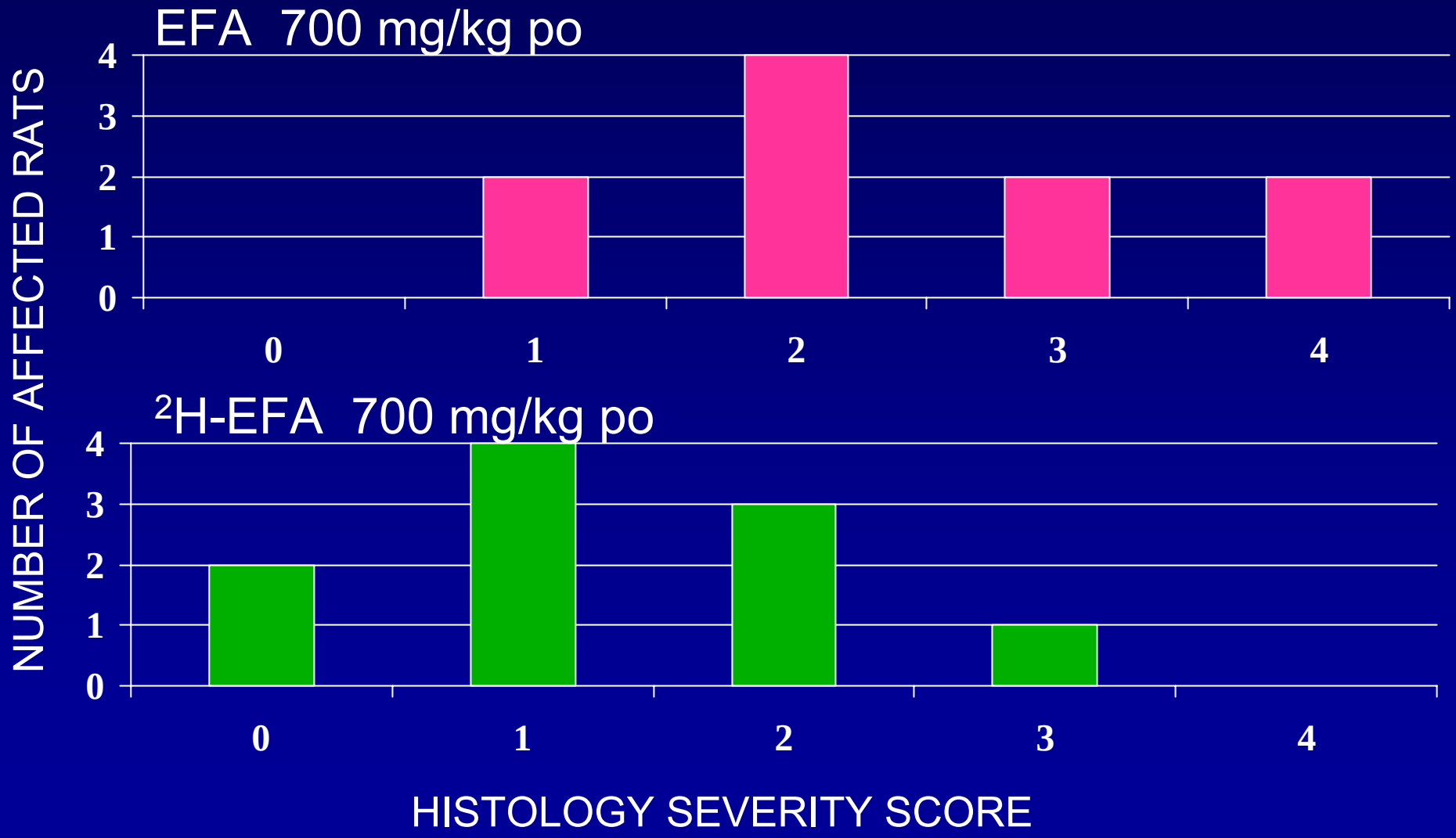
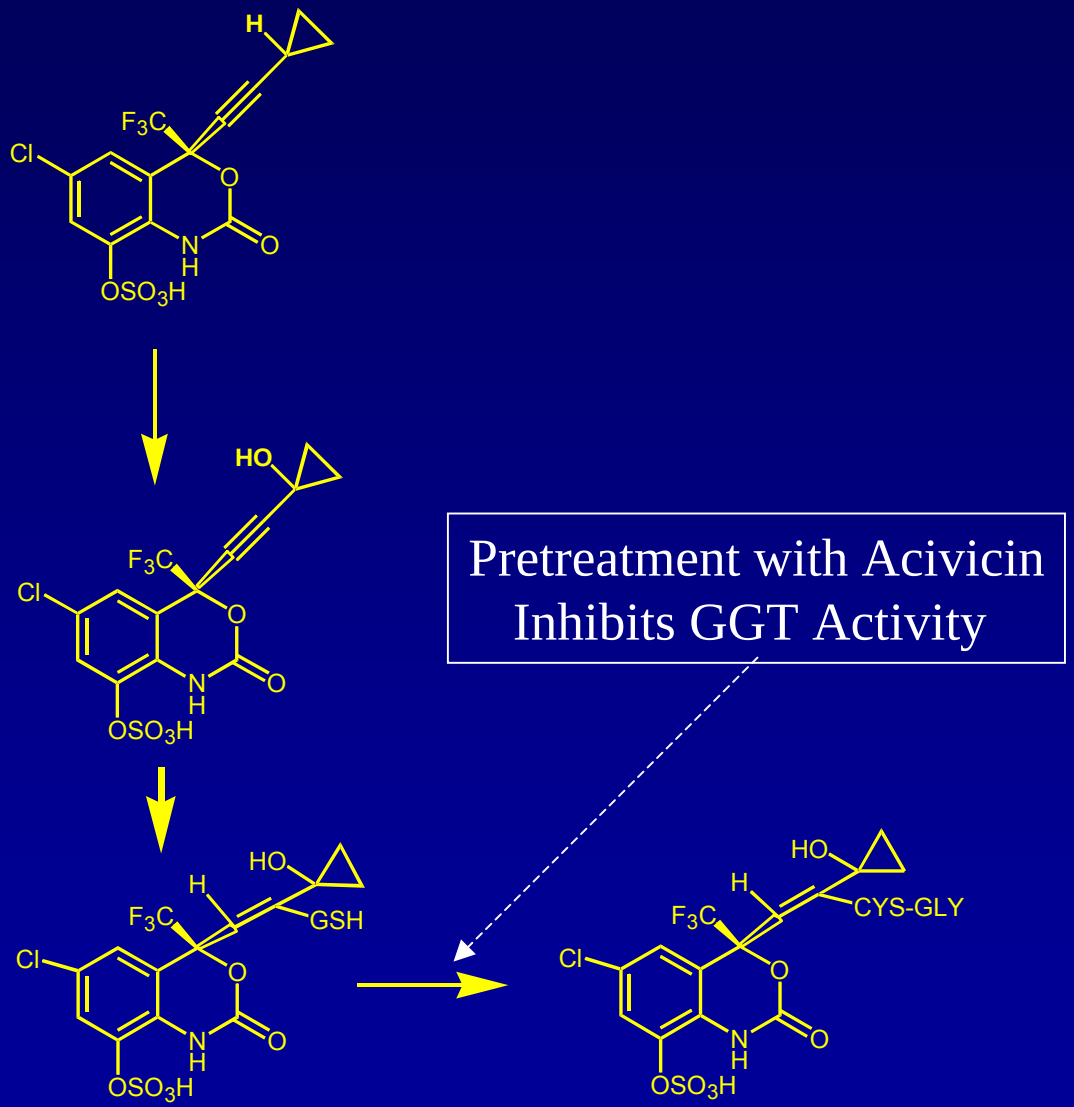


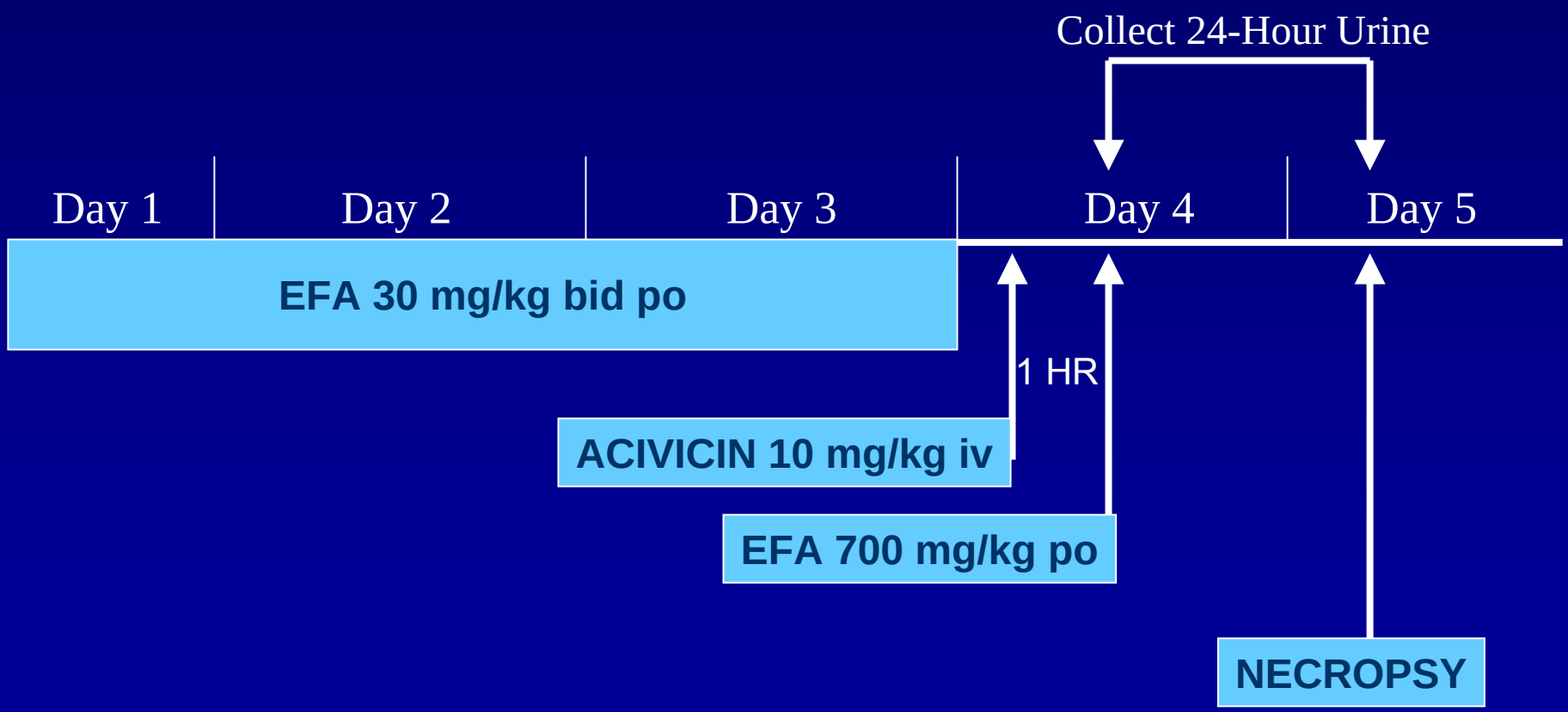
DEUTERATED EFAVIRENZ DECREASES THE SEVERITY AND INCIDENCE OF NEPHROTOXICITY



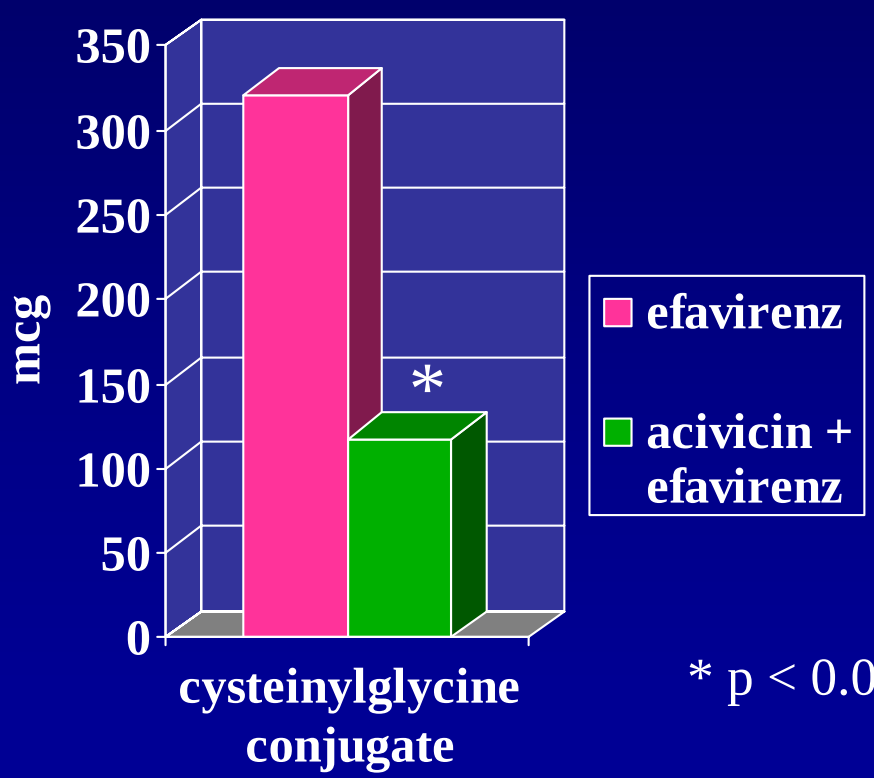
INHIBITION OF EFAVIRENZ GLUTATHIONE CONJUGATE CATABOLISM BY ACIVICIN



STUDY PROTOCOL FOR THE INHIBITION OF GGT ACTIVITY BY THE PRETREATMENT WITH THE SELECTIVE INHIBITOR ACIVICIN



ACIVICIN PRETREATMENT DECREASES THE URINARY EXCRETION OF THE CYS-GLY BUT NOT THE 8-OH GLUCURONIDE METABOLITE AFTER EFAVIRENZ



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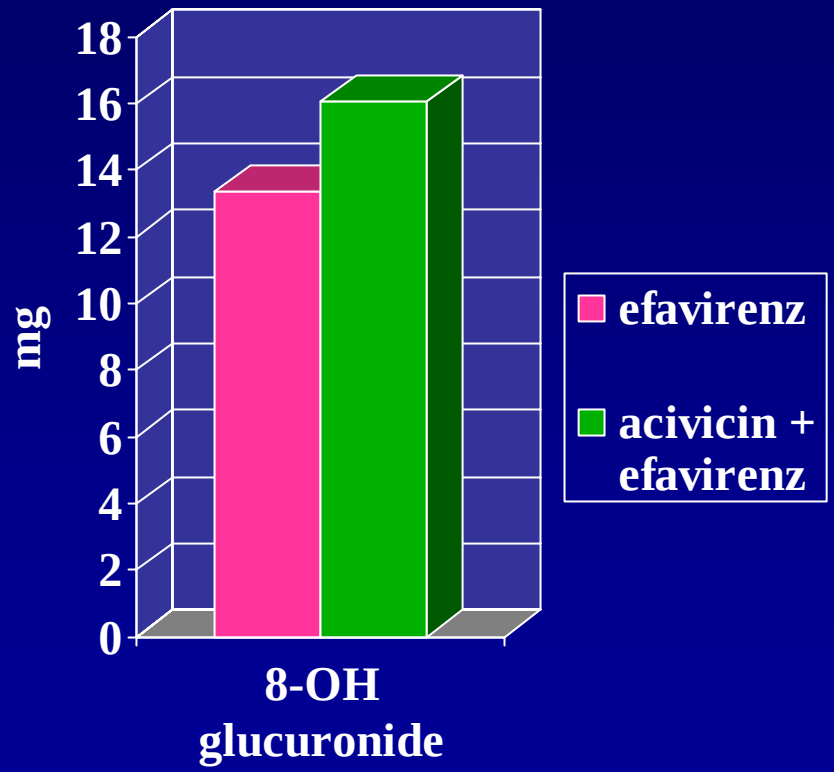
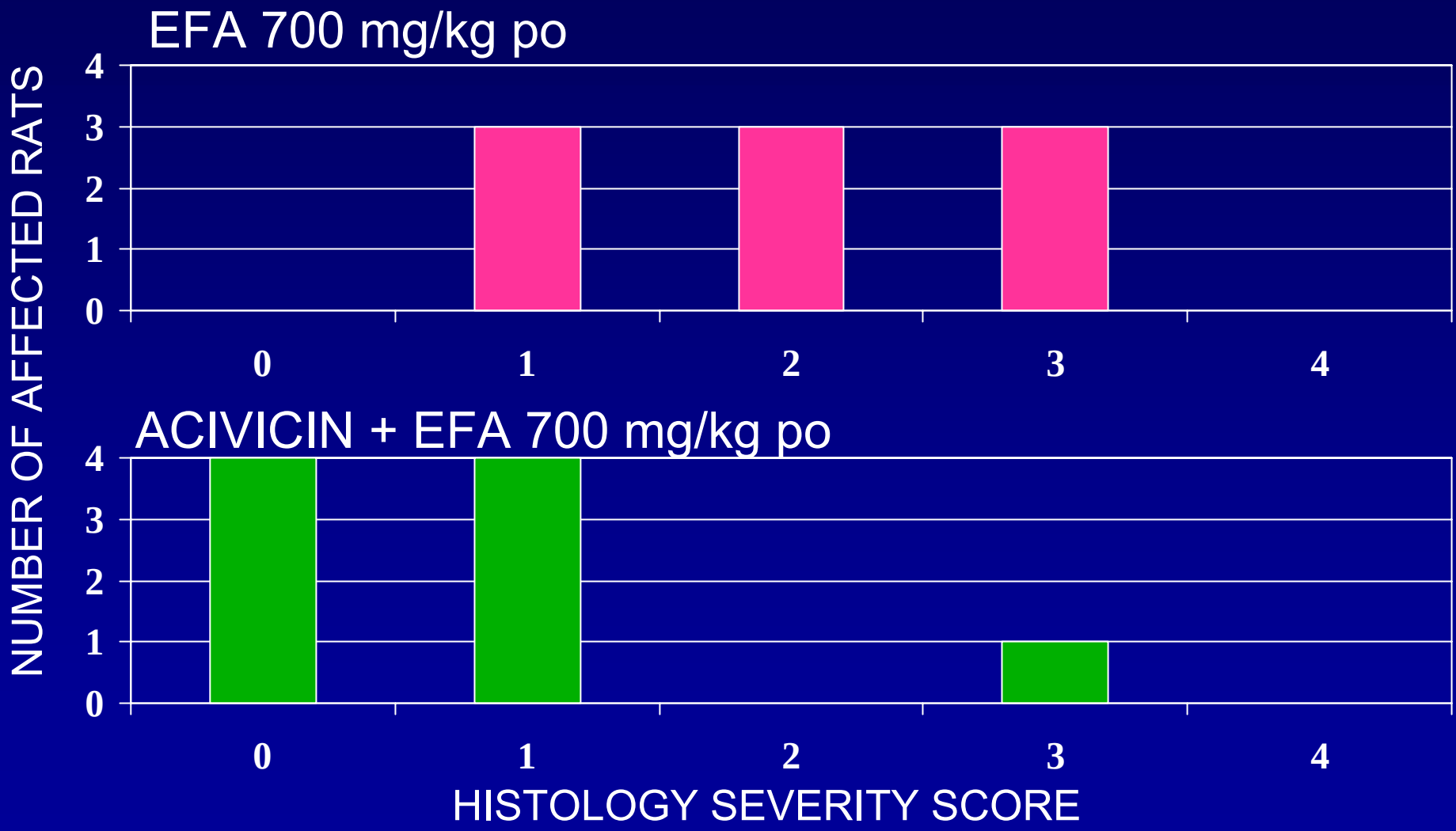
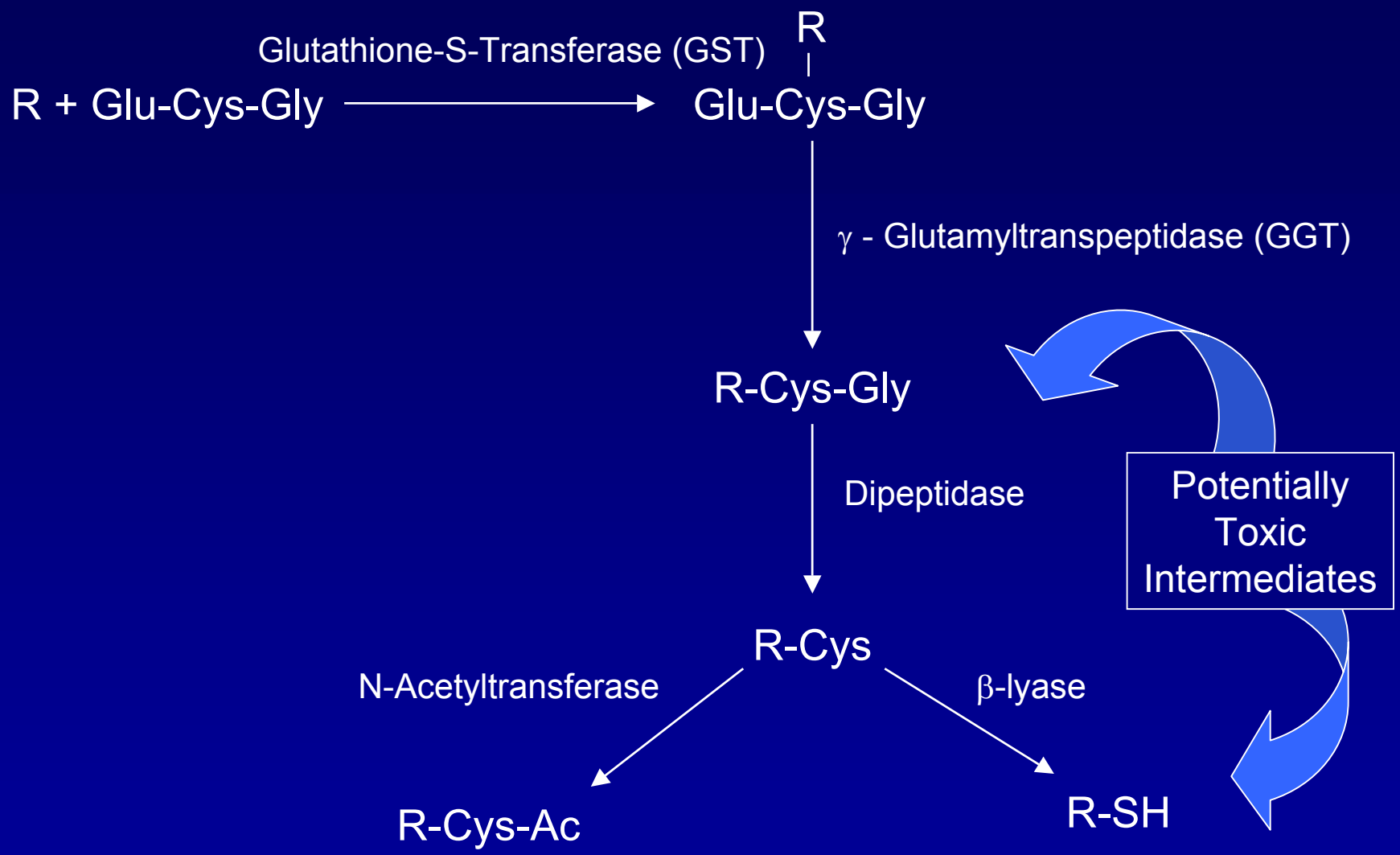


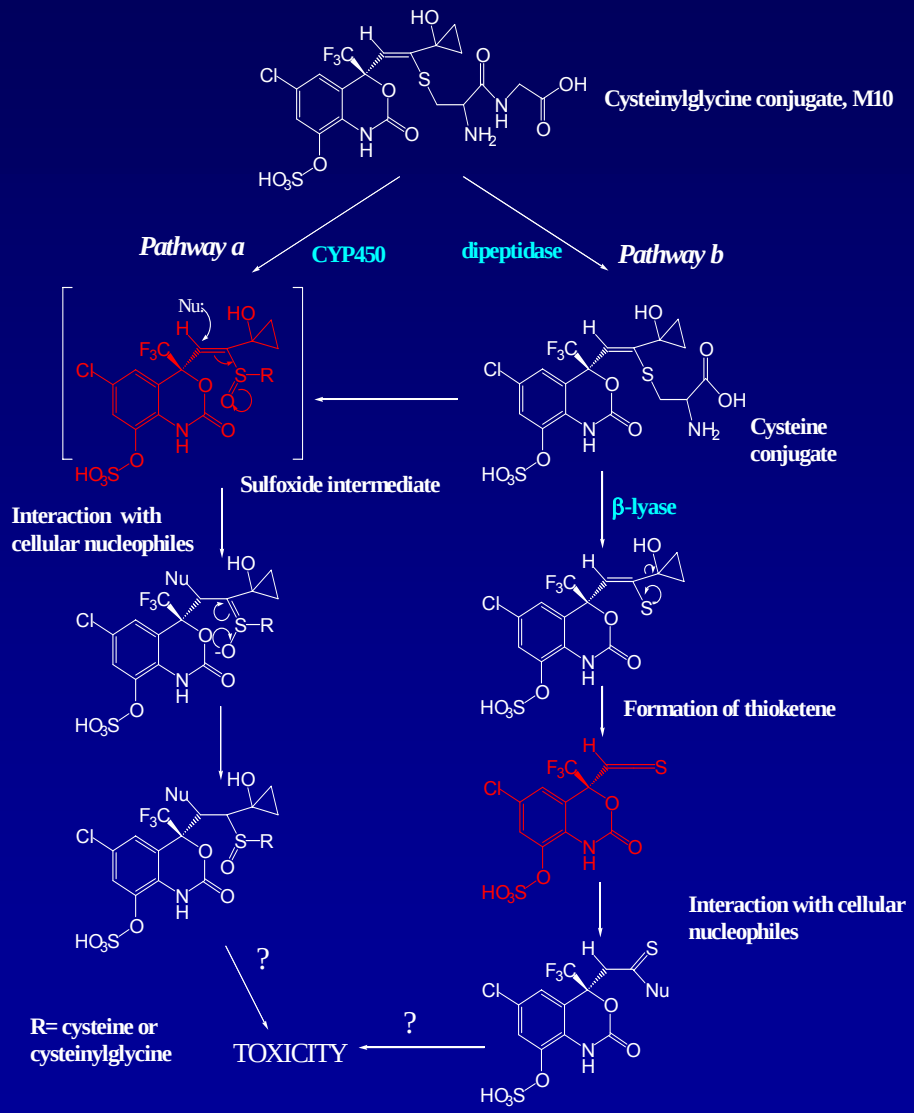
ACIVICIN PRETREATMENT DECREASES THE INCIDENCE AND SEVERITY OF NEPHROTOXICITY



RENAL PROCESSING OF GLUTATHIONE CONJUGATES



FORMATION OF POTENTIAL NEPHROTOXIC REACTIVE METABOLITES



CONCLUSIONS

- SELECTIVE DEUTERATION DIMINISHED THE CYP MEDIATED OXIDATION AND FORMATION OF THE CYCLOPROPANOL INTERMEDIATE, AN OBLIGATE SPECIES IN THE FORMATION OF THE ULTIMATE NEPHROTOXICANT

- CONJUGATION WITH GLUTATHIONE AND SUBSEQUENT RENAL PROCESSING OF THIS CONJUGATE ULTIMATELY LEADS TO THE RAT SELECTIVE NEPHROTOXICITY

- MECHANISMS AND RELEVANCE OF REACTIVE INTERMEDIATE FORMATION AND DISPOSITION CAN ONLY BE DETERMINED BY THE APPLICATION OF BIOANALYTICAL CHEMISTRY, DRUG METABOLISM, KINETICS AND BIOCHEMICAL TOXICOLOGY