INTRODUCTION

We have reviewed the evaluation of the microsomal re-isolation method to assess the reversibility of MDIs of cytochrome P450 (CYP) enzymes. This method is based on the isolation of microsomes from rat liver, inhibition of CYP activity by a drug candidate, and re-isolation of the microsomes. The re-isolated microsomes are then incubated with a covalent inhibitor, and the inhibition of CYP activity is measured to determine whether the inhibition is reversible.

RESULTS

We have developed a new method for the evaluation of MDIs of cytochrome P450 (CYP) enzymes. This method is based on the isolation of microsomes from rat liver, inhibition of CYP activity by a drug candidate, and re-isolation of the microsomes. The re-isolated microsomes are then incubated with a covalent inhibitor, and the inhibition of CYP activity is measured to determine whether the inhibition is reversible.

CONCLUSIONS

These data demonstrate the potential for irreversible MDIs of CYP enzymes to be incorrectly identified as reversible when the assessment of reversibility is conducted with a different method. Under these experimental conditions, dialysis has the potential to reverse some nitrogen-based MICS for quasi-irreversible inhibitors such as troleandomycin and verapamil, in contrast to the clinical outcome. These data support the use of ultracentrifugation procedures and microsomal re-isolation coupled with potassium ferricyanide treatment to evaluate MDI reversibility and identification of protein. The results show that the dialysis and microsomal re-isolation methods can be used together to assess the reversibility of MDIs.

REFERENCES
