**ABSTRACT**

Endoxifen (N-(4-hydroxytamoxifen) acetic acid) is an bioactive metabolite of tamoxifen being developed for use in breast cancer prevention. Endoxifen demonstrates dose-dependent growth inhibitory effects in breast cancer cells and in vivo efficacy in breast cancer prevention models in rodents. Although the effects of endoxifen were originally attributed to it being a more potent aromatase inhibitor than tamoxifen, recent studies have suggested that endoxifen is a more potent endocrine disruptor than tamoxifen. The metabolism and pharmacokinetics of endoxifen were investigated in various species, and the metabolism of endoxifen was assessed in primary hepatocytes from human, rat, minipig, and monkey. Endoxifen was metabolized to O-N-desmethyltamoxifen; 4-hydroxytamoxifen (4-hydroxy); 4-hydroxytamoxifen N-sulfate; and glucuronide derivatives of endoxifen and 4-hydroxytamoxifen.

**RATIONAL**

This study was a component of a larger preclinical program to characterize the toxicity, pharmacokinetics (PK), and pharmacodynamics (PD) profiles of endoxifen. Phase 2 metabolites were generated by incubation of endoxifen with hepatocytes from human, rat, minipig, and monkey. The relative production of Phase 2 metabolites between species was compared.

**MATERIALS AND METHODS**

**Study Design:** Commercially available pools of hepatocytes from humans, rats, minipigs, and monkeys were assayed for enzymatic activity (in vitro). Assays were performed for 2 hours at 37°C. Assays were performed in triplicate and the resulting data were compared to each other. The relative production of Phase 2 metabolites by hepatocytes from each species is tabulated in Table 4. As described for endoxifen glucuronidation, metabolites generated by rat and monkey hepatocytes were produced by only 1% of the administered endoxifen dose. The relative production of Phase 2 metabolites by hepatocytes from each species is limited to relative levels of parent compound and the O-sulfated metabolite.

**RESULTS**

Endoxifen glucuronidation and metabolite ChoSet were the only metabolites that were consistently identified. Other phases 2 metabolites were detected only in human hepatocytes. This study compared the toxicity, pharmacokinetics (PK), and pharmacodynamics (PD) profiles of endoxifen. Phase 2 metabolites were generated by incubation of endoxifen with hepatocytes from human, rat, minipig, and monkey. The relative production of Phase 2 metabolites between species was compared.

**CONCLUSIONS**

Endoxifen glucuronidation and metabolite ChoSet were the only metabolites that were consistently identified. Other phases 2 metabolites were detected only in human hepatocytes. This study compared the toxicity, pharmacokinetics (PK), and pharmacodynamics (PD) profiles of endoxifen. Phase 2 metabolites were generated by incubation of endoxifen with hepatocytes from human, rat, minipig, and monkey. The relative production of Phase 2 metabolites between species was compared.

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