Letter to the Editor

CYP1A1-MEDIATED ACTIVATION OF THALIDOMIDE AND SUPPRESSION OF EMBRYO FIBROBLAST PROLIFERATION

The article by Miyata et al. (2003) in the April issue of Drug Metabolism and Disposition reported that thalidomide inhibited the proliferation of microfibroblasts in the presence of microsomes from rabbit liver or HepG2 cells pretreated with 3-methylcholanthrene (3-MC). Mouse liver microsomes or microsomes from human HepG2 cells pretreated with vehicle did not cause inhibition. The inhibition was abolished by the addition of α-naphthoflavone, furafylline, or anti-rat CYP1A1 antibody. The authors concluded that CYP1A1 was responsible for the bioactivation of thalidomide to a reactive metabolite that resulted in inhibition of embryo fibroblast proliferation.

However, the data provided by the authors could not exclude the involvement of CYP1A2 in the bioactivation of thalidomide. In fact, the majority of human CYP1A inhibitor and substrate probes are nonspecific in their recognition of CYP1A1 and CYP1A2 with significant species differences (Tassaneeyakul et al., 1993; Eagling et al., 1998). For example, α-naphthoflavone inhibited CYP1A1- and 1A2-mediated phenacetin O-deethylation (Tassaneeyakul et al., 1993); furafylline as a selective inhibitor of CYP1A2 in humans can inhibit both CYP1A2 and 2C9 in rats (Eagling et al., 1998). Furthermore, anti-rat CYP1A1 antibody preparations can recognize CYP1A1/1A2 from the rat and other species (Zhou et al., 2000). As shown in Fig. 8, in Miyata et al. (2003) the existence of small amounts of CYP1A2 in microsomes from HepG2 cells treated with 3-MC (lanes 3 and 5 of Fig. 8B) is likely. 3-MC has been shown to induce CYP1A2 in HepG2 cells (Quattrochi et al., 1994; Pickwell et al., 2003), which may be attributable to the interaction of upstream enhancing factors with an E-box within the CYP1A2 5'-flanking gene (Pickwell et al., 2003). An increase in treatment time of HepG2 cells with 3-MC (24 h in this study) would allow the expression of CYP1A2. Additionally, Fort et al. (2000) observed enhanced toxicity of thalidomide to frog embryos in the presence of microsomes from the rat treated with either isoniazid or Aroclor 1254. However, the addition of 3-amino-1,2,4-triazole or α-naphthoflavone ameliorated the toxicity, suggesting the involvement of CYP1A1/2 and CYP2E1 in thalidomide bioactivation. It would be interesting to examine whether CYP2E1 is involved in embryo fibroblast inhibition by thalidomide.

Miyata et al. (2003) did not report the effect of hydrolysis products of thalidomide on embryo fibroblast proliferation. Thalidomide undergoes rapid hydrolysis (Eriksson et al., 2001), whereas CYP2C19-mediated metabolism (Ando et al., 2002) is considered to play a minor role. Furthermore, some studies demonstrated that the biological activities of thalidomide were dependent on the intact molecule (Shannon et al., 1997). Hydrolysis of thalidomide will abrogate its immunomodulating activity.

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References

We thank Dr. Shufeng Zhou for comments regarding our recent publication, Miyata et al. (2003). We are now analyzing human CYP forms involved in thalidomide-induced suppression of embryo fibroblast proliferation and are also identifying the structure of the metabolites. Because we will show these results in a future study, we choose not to respond to the letter at this time.

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