Synopsis of Original Research Paper

Development of photosafety testing strategy and its strategic harmonization

Satomi Onoue

Department of Pharmacokinetics and Pharmacodynamics,School of Pharmaceutical Sciences, University of Shizuoka

Photoreactivity and dermal/ocular deposition of compounds have been recognized as key considerations for evaluating the phototoxic risk of compounds. Because some drugs are known to cause phototoxic reactions via generation of potent phototoxic metabolites, photosafety assessments on parent drugs alone may lead to false predictions about their photosafety. This study aimed to establish a new photosafety assessment strategy for evaluating the in vivo phototoxic potential of both a parent substance and its metabolites. The in vivo phototoxic risk of fenofibrate (FF) and its metabolites, fenofibric acid (FA) and reduced fenofibric acid, were evaluated based on photochemical and pharmacokinetic analyses. FF and FA exhibited intensive UV absorption, with molar extinction coefficient values of 17,000 (290 nm) and 14,000 $M^{-1}cm^{-1}$ (295 nm), respectively. Superoxide generation from FA was significantly higher than from FF, and a marked increase in superoxide generation from FF was observed after incubation with rat hepatic S9 fractions, suggesting enhanced photoreactivity of FF after metabolism. FA showed high dermal/ocular deposition after oral administration (5 mg/kg, p.o.) although the concentration of FF was negligible, suggesting high exposure risk from FA. On the basis of these findings, FA was deduced to be a major contributor to phototoxicity induced by FF taken orally, and this prediction was in accordance with the results from *in vitro/in vivo* phototoxicity tests. Results from this study suggest that this new screening strategy for parent substances and their metabolites provides reliable photosafety information on drug candidates and would be useful for drug development with wide safety margins.