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PHOTOBIOLOGICAL AND PHARMACOKINETIC STUDIES ON PHOTOTOXIC POTENTIAL OF GRiseofulvin

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The phototoxic responses after topical and systemic administration of photosensitive pharmaceutics have been recognized as undesirable side effects, and require the exposure to light and the presence of drug in the skin. Recently, we proposed new screening methodologies to assess phototoxic potential of pharmaceutical substances on the basis of their photochemical and photobiological properties [Pharm Res (2008) 25:861; J Pharm Sci (2008) In press; J Chromatogr A (2008) 1188:50]. The present investigation is aimed at evaluating the phototoxic potential of griseofulvin by the new assay systems and pharmacokinetic studies. In reactive oxygen species (ROS) assay, generation of ROS from photoirradiated griseofulvin was observed, mechanism of which would be both type I and II photochemical reactions. In addition, griseofulvin could interact with DNA as detected by DNA-binding assay and spectroscopic analyses such as UV and circular dichroism. Capillary gel electrophoretic (CGE) studies also exhibited significant structural transition of plasmid pBR322 DNA, suggesting griseofulvin-induced photodynamic cleavage of DNA through interaction with DNA. The present in vitro studies suggest phototoxic and photogenotoxic potential of griseofulvin through radical-based reactions under light exposure. Pharmacokinetic studies using UPLC-MS exhibited the disposition of griseofulvin in the skin of rats after oral administration of griseofulvin, and in vivo photopatch testing indicated the inflammatory phototoxic skin responses against griseofulvin. Upon these findings, griseofulvin was deduced to be phototoxic and photogenotoxic after oral administration, and these observation could verify predictability of new in vitro screening strategies such as ROS assay and CGE screening system.

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INVESTIGATION INTO THE CAUSE OF LOW BIOAVAILABILITY, OBSERVED IDIOSYNCRATICALLY IN MONKEYS. -CONTRIBUTION OF INTESTINAL METABOLISM TO BIOAVAILABILITY IN MONKEYS-

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During the past decade, studies on many drugs often reported that monkeys exhibited low bioavailability (BA) than other animal species. We obtained similar results in a previous study using 13 commercially available drugs1. And, we speculated that lower intestinal availability (FaFg) may be the most significant factor affecting the low BA in monkeys; its influence may be greater than that of hepatic availability (Fh). In midazolam2 and quinidine (QD) 3, particularly, we reported that Fg is the major factor of low BA in monkeys.

In this study, we will show the contribution of Fg to low BA in monkeys using QD and caffeine (CAF), which has a low and high BA in monkeys, respectively. In order to determine the Fg, radioactivity and unchanged drug concentrations in blood were measured obtained by simultaneously sampling portal and peripheral blood after oral co-administration of 1H-QD and 1H-C-CAF. In all monkeys used in this study, it was confirmed that QD and CAF did not affected the PK parameters of QD and CAF each other.