Herb-Drug Interaction

Alterations of Gefitinib Pharmacokinetics by Co-administration of Herbal Medications in Rats*

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ABSTRACT Objective: To evaluate the potential pharmacokinetic interactions of the anticancer agent gefitinib (Iressa®) and the oriental medications Guipi Decoction (八物湯, GPD, Guibi-tang in Korean) and Bawu Decoction (八物湯, BWD, Palmul-tang in Korean). Methods: Methylcellulose (MC, control), GPD (1,200 mg/kg), or BWD (6,000 mg/kg) was orally administered to rats either as a single dose or multiple doses prior to gefitinib administration. To examine the effects of a single dose of the herbal medicines, gefitinib (10 mg/kg) was orally administered after 5 min or 1 h of MC or the herbal medicine pretreatments. To examine the effects of the multiple doses of the herbal medicines, gefitinib (10 mg/kg) was orally administered following 7 consecutive days of the administration of MC or each herbal medicine. The plasma concentrations of gefitinib were determined with a noncompartmental analysis. Results: Gefitinib was rapidly absorbed and showed a mono-exponential decline with an elimination half-life of 3.7–4.1 h. The pharmacokinetics of gefitinib was not affected by GPD pretreatment. However, a significantly lower maximum plasma concentration (C_{max}, P<0.05) and area under the curve (AUC, P<0.05) were observed in both single- and multiple-dose BWD-pretreated rats compared with the control rats. Conclusions: BWD and not GPD might delay and interfere with gefitinib absorption. Further evaluations of the clinical significance of these findings are needed.

KEYWORDS herb-drug interaction, pharmacokinetics, gefitinib, Guipi Decoction, Bawu Decoction

The use of herbal medicines in combination with pharmaceutical drugs has raised considerable concerns. The concurrent use of herbs and pharmaceutical drugs may mimic, augment, or oppose the pharmacokinetics (PK) or pharmacodynamics, which can then increase or decrease the pharmacological or toxicological effects of either constituent. In particular, patients with chronic medical conditions, such as cancer, are more likely to use complementary alternative herbal medicines, and they are therefore at greater risk for potential herb-drug interactions. Although some herbal medicines have shown potential benefits on cancer progression and relief of chemotherapy-related toxicities, reports of the interactions of herbal medicines and anticancer drugs are increasing, and herbal medicines have become a safety concern. Nevertheless, people tend to believe that traditional remedies are harmless and neglect to consider the potential interactions with conventional drugs.

Gefitinib (Iressa®) is a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that is approved for the treatment of advanced non-small cell lung cancer. Along with other EGFR tyrosine kinase inhibitors, such as erlotinib and afatinib, gefitinib is used as a first-line therapy for patients with advanced non-small cell lung cancer who have an activating EGFR mutation. Cytochrome P450 (CYP) isozymes are known to be involved in gefitinib metabolism, and studies have indicated CYP3A4-mediated drug interactions between gefitinib and other drugs. The involvement of several membrane transporters,
such as the organic anion-transporting polypeptides OATP1B1 and OATP1B3 and the organic cation transporters, in gefitinib uptake and disposition has been suggested.\(^\text{10,11}\) Gefitinib is a substrate of the efflux transporters ABCB1 (P-glycoprotein, P-gp) and ABCG2 (breast cancer resistance protein, BCRP), and this limits its tissue distribution.\(^\text{12,13}\) Interestingly, gefitinib also inhibits P-gp and BCRP.\(^\text{14-16}\) However, the potential drug interactions of gefitinib that are associated with drug transporters are less understood. Moreover, little is known regarding the drug interactions of gefitinib with herbal medications, despite the prevalent use of herbal prescriptions in cancer patients.

Guipi Decoction (归脾汤, GPD, Guibi-tang in Korean and Kihi-To in Japanese) and Bawu Decoction (八物汤, BWD, Palmul-tang in Korean) are herbal medications that have been traditionally used in Asian countries as tonifying agents for various diseases. The use of these tonifying drugs is popular in patients with severe chronic medical conditions or patients going through chemotherapy. GPD is a mixture of 12 herbal preparations and has long been used to treat amnesia, fatigue, insomnia, anemia, palpitations, and neurosis.\(^\text{17}\) BWD is composed of 8 herbs and exhibits various bioactivities, including immunomodulatory,\(^\text{18}\) anti-fatigue,\(^\text{19}\) and anti-allergic\(^\text{20}\) effects. In addition, the potential benefits of GPD\(^\text{21}\) and BWD\(^\text{22}\) in cancer treatment have been suggested. Therefore, the use of GPD or BWD, either as a tonifying agent or as a supplement, may benefit cancer patients being treated with chemotherapeutic agents, such as gefitinib.

In the present study, we evaluated the effects of the administration of the herbal medications GPD and BWD on the PK of gefitinib. The oral absorption and plasma drug concentration-time profiles of gefitinib were examined in rats that were pretreated with single or multiple oral doses of GPD or BWD. A better understanding of potential drug-herb interactions will be provided so that the benefits can be augmented and the adverse effects can be minimized.

**METHODS**

**Materials**

Diphenhydramine hydrochloride was purchased from Mallinckrodt (St. Louis, MO, USA), and formic acid was purchased from Sigma-Aldrich Co. LLC.

**Drugs**

Gefitinib was purchased from LC Laboratories (Woburn, MA, USA). GPD, consisting of Angelicae Gigantis Radix, Longan Arillus, Zizyphi Semen, Polygalae Radix, Ginseng Radix Alba, Astragali Radix, Atractylodis Rhizoma Alba, Hoelen Cum Radix, Aucklandiae Radix, Glycyrrhizae Radix, Zingiberis Rhizoma Crudus, and Zizyphi Fructus and BWD, consisting of Ginseng Radix, Glycyrrhizae Radix, Hoelen Cum Radix, Atractylodis Rhizoma, Angelicae Gigantis Radix, Cnidii Rhizoma, Paeniae Radix, and Rehmanniae Radix, were obtained from Hanzung Pharmaceutical Co., Ltd. (Daejeon, Republic of Korea) and Han Kook Shinyak Co., Ltd (Nonsan, Republic of Korea), respectively.

**Animal Study**

The animal study was approved by the Ethics Committee for the Treatment of Laboratory Animals at the Catholic University of Daegu and conducted according to standard operating procedures. Male Sprague-Dawley rats (8 weeks, 220–270 g; Samtako, Osan, Republic of Korea) were kept in plastic cages with free access to a standard diet (Samtako). The animals were maintained at a temperature of 23 ± 2 °C with a 12-h light-dark cycle and relative humidity of 50% ± 10%.

GPD and BWD were dissolved in 0.5% MC. A drug-free 0.5% MC solution (control, n=6) or an herbal medicine solution [GPD (1,200 mg/kg, n=5) or BWD (6,000 mg/kg, n=5)] was orally administered as a single dose or multiple doses for 7 consecutive days. The doses of GPD and BWD were selected based on the human clinical daily dose of 128 mg/kg for GPD and 683 mg/kg for BWD. In order to examine the effects of a single dose of the herbal medicines, GPD or BWD was administered to rats by oral gavage, which was followed by the oral administration of gefitinib that was dissolved in 0.5% MC (10 mg/kg) within 5 min or 1 h after the herbal medicine treatment. In order to examine the effects of multiple doses of the herbal medicines, gefitinib was dissolved in 0.5% MC (10 mg/kg) and given by oral gavage following 7 consecutive days of GPD or BWD administration. The rats were fasted for 12 h prior to gefitinib