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Enhanced paclitaxel bioavailability after oral coadministration of paclitaxel prodrug with naringin to rats

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Abstract

The aim of this study was to investigate the effect of naringin on the bioavailability and pharmacokinetics of paclitaxel after oral administration of paclitaxel or its prodrug coadministered with naringin to rats. Paclitaxel (40 mg/kg) and prodrug (280, 40 mg/kg paclitaxel equivalent) were coadministered orally to rats with naringin (1, 3, 10 and 20 mg/kg).

The plasma concentrations of paclitaxel coadministered with naringin increased significantly ($p < 0.01$ at paclitaxel, $p < 0.05$ at prodrug) compared to the control. The areas under the plasma concentration–time curve (AUC) and the peak concentrations (C_{max}) of paclitaxel with naringin significantly higher ($p < 0.01$) than the control. The half-life ($t_{1/2}$) was significantly ($p < 0.05$) longer than the control. The absolute bioavailability (AB, %) of paclitaxel with naringin was significantly higher (3.5–6.8%, $p < 0.01$) than the control (2.2%). Absorption rate constant (K_a) of paclitaxel with naringin increased, but not significantly. The AUC of paclitaxel after coadministration of prodrug with naringin to rats was significantly ($p < 0.05$) higher than the prodrug control. The relative bioavailability (RB, %) of paclitaxel after coadministration of prodrug with naringin was 1.35–1.69-fold higher than prodrug control. The absolute bioavailability (AB, %) of paclitaxel after coadministration of prodrug with naringin increased significantly ($p < 0.05$) from 6.6 to 9.0% and 11.2%. The bioavailability of paclitaxel coadministered as a prodrug with or without naringin was remarkably higher than the control. Paclitaxel prodrug, a water-soluble compound concerning with its physicochemical properties, passes through the gastrointestinal mucosa more easily than paclitaxel without obstruction of P-gp and cytochrome P-450 in the gastrointestinal mucosa. Oral paclitaxel preparations which is more convenient than the IV dosage forms could be developed with a prodrug form with naringin.

Keywords: Paclitaxel; Prodrug; Naringin; Pharmacokinetic; Bioavailability; Coadministration

1. Introduction

Paclitaxel (Taxol®) is an antineoplastic agent that is derived from the bark of the Pacific yew tree (*Taxus*

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brevifolia) (Wani et al., 1971). In contrast to Vinca alkaloids, the anticancer action of taxol is that it inhibits cellular growth by promoting and stabilizing the microtubule assembly by a non-covalent interaction with tubulin, which blocks cell replication in the late G_2 mitotic phase of the cell cycle (Kumar, 1981; Manfedi and Horwitz, 1984). Because of its poor water solubility, paclitaxel is currently dissolved in a mixture of polyoxyethyleneglycerol triricinoleate 35 (Cremophor EL) and dehydrated ethanol (1:1, v/v) for the IV dosage form. However, Cremophor EL itself is toxic and produces vasodilation, labored breathing, lethargy and hypotension when administered intravenously. One mediator of the hypersensitivity reactions is the endogenous histamine release and prophylaxis to counteract the histaminergic mechanisms and reduces the incidence of the hypersensitivity reactions (Rowinsly et al., 1993).

Paclitaxel has been used to treat ovarian carcinoma, breast carcinoma, leukemia, melanoma, prostate carcinoma, etc., and has become particularly important in managing ovarian and breast carcinoma (Rowinsky et al., 1990; McGuire et al., 1989; Sarosy et al., 1992; Holmes et al., 1991). The oral administration of the paclitaxel is problematic as it has poor absorption due to the poor solubility and efflux pump function of the drug for the multidrug transporter P-glycoprotein (P-gp), which is present abundantly in the gastrointestinal tract. Thus, this drug is mainly used for intravenous administration (Sparreboom et al., 1997).

Paclitaxel has a very large volume of distribution in the body, and is highly bound by the plasma protein, primarily albumin (95–98%) (Wiernik et al., 1987). In particular, it is much higher in the disposition of the liver and bile than in the other tissues (Fujita et al., 1994). Less than 6–10% of administered paclitaxel is recovered as the unchanged drug in the urine of treated patients (Wiernik et al., 1987; Brown et al., 1997). Paclitaxel is mainly metabolized though the liver and undergoes biliary excretion (Cresteil et al., 1994; Kumar et al., 1994; Rahman et al., 1994; Sonnichsen et al., 1995). In humans, the total fecal excretion is approximately 70% of the paclitaxel dose, with 6α-hydroxypaclitaxel being the major metabolite (Walle et al., 1995).

In an attempt to develop safer formulations, many studies have been directed towards a new oral formulation. However, paclitaxel is very poorly absorbed when administered orally. Several studies have reported that the poor bioavailability of paclitaxel would result from the metabolism by enzymes or counter-transport processes by P-gp in the gut wall. It has been suggested that, in some cases the poor absorption of drugs after oral administration results from the activity of a multidrug transporter, a membrane-bound P-gp, which functions as an energy-dependent transporter or an efflux pump to decrease the intracellular accumulation of the drugs by extruding xenobiotics from the cell (Sparreboom et al., 1997).

Flavonoids are regarded as a new class of chemosensitizers, which interact with both the cytosolic domains of P-gp and its ATP binding site (Conseil et al., 1998) and various CYP enzyme inhibitors (Peter et al., 2002). It also has been reported to have antiproliferative effect on cancer cell (Darwanto et al., 2000) and peroxidation activity and antioxidant agents (Ferguson, 2001), which exist in various plants and vegetable food as glycosides (Scambia et al., 1995).

Naringin as a member of the flavonoids class has been reported to possess the ability to inhibition of the P-gp efflux pump (Conseil et al., 1998; Scambia et al., 1995; Bailey et al., 1993; Takanaga et al., 1998). It also has been reported that naringin can inhibit CYP 3A, which is the main subfamily of the cytochrome P450 that is responsible for metabolizing paclitaxel (Kumar et al., 1994; Peter et al., 2002; Doostdar et al., 2000; Dupuy et al., 2003; Hodek et al., 2002). Quercetin, flavone, naringin, GF120918 and cyclosporine as the inhibitors of CYP3A and P-pg, have increased the bioavailability of some drugs, which are substrates of CYP3A and P-pg (Scambia et al., 1995; Bailey et al., 1993; Takanaga et al., 1998; Zhang et al., 2000; Choi et al., 2004a, 2004b; Bardelmeijer et al., 2000; Malingre et al., 2001). But there is no investigation about naringin if it potentiates the ability of inhibition of P-gp and CYP enzymes or not, with paclitaxel administered orally to rats.

A water-soluble prodrug compound, 7-mPEG 5000-succinyloxymethyloxycarbonyl-paclitaxel, was synthesized with a water-soluble polymer and paclitaxel (Jo, 2004). It is rapidly hydrolyzed by an esterase to generate the physiologically active paclitaxel.

The purpose of this study was to investigate the bioavailability of paclitaxel after oral administration of paclitaxel and paclitaxel prodrug alone or with naringin.