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Pharmacokinetic interaction between oltipraz and omeprazole in rats: Competitive inhibition of metabolism of oltipraz by omeprazole via CYP1A1 and 3A2, and of omeprazole by oltipraz via CYP1A1/2, 2D1/2, and 3A1/2

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ABSTRACT

In rats, oltipraz is metabolized via hepatic CYP1A1/2, 2B1/2, 2C11, 2D1/2, and 3A1/2, and omeprazole via hepatic CYP1A1/2, 2D1/2, and 3A1/2. Hence, pharmacokinetic interaction between oltipraz and omeprazole were evaluated after simultaneous single i.v. and p.o. administration of both drugs to rats. After i.v. administration of oltipraz (10 mg/kg) and omeprazole (20 mg/kg), the AUC of both drugs was significantly greater (32.3 and 28.1% increase for oltipraz and omeprazole, respectively) than those after each drug alone. This could have been due to a competitive inhibition of metabolism of oltipraz by omeprazole via CYP1A1 and 3A2, and of metabolism of omeprazole by oltipraz via CYP1A1/2, 2D1/2, and 3A1/2. This could be supported by the apparent inhibition constants (K_i) and the concentrations of each drug in the liver. After oral administration of oltipraz (30 mg/kg) and omeprazole (40 mg/kg), the AUC of oltipraz was significantly greater (68.8% increase) than that after oltipraz alone. This could have been primarily due to an inhibition of intestinal metabolism of oltipraz by omeprazole. However, comparable AUC values of omeprazole between p.o. administration of omeprazole alone and both drugs could have been due to insufficient inhibitory effect of oltipraz on omeprazole metabolism in both the liver and intestine.

1. Introduction

Oltipraz [5-(2-pyrazinyl)-4-methyl-1,2-dithiol-3-thione], a synthetic dithiolthione, was developed by Rhône-Poulenc (Virty-sur-Seine, France) in the treatment of schistosomiasis (Bueding et al., 1982.). Recently, therapeutic effects of oltipraz in rat model of liver cirrhosis induced by N-dimethylnitrosamine have been reported (Kang et al., 2002; Bae et al., 2006). Based on the results (Kang et al., 2002; Bae et al., 2006), oltipraz is being evaluated in phase II clinical trial in Korea as an oral (p.o.) agent to treat patients with liver fibrosis and cirrhosis induced by chronic hepatitis types B and C. Bae et al. (2005a) reported that oltipraz was primarily metabolized via hepatic microsomal cytochrome P450 (CYP) 1A1/2,

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2B1/2, 2C11, 2D1/2, and 3A1/2, but not via CYP2E1, in male Sprague–Dawley rats.

Omeprazole, 5-methoxy-2-[{(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl} sulfoxide]-1H-benzimidazole, is a gastric parietal cell proton pump inhibitor. The drug has greater antisecretory activity than histamine H_2-receptor antagonists and has widely been used in the treatment of peptic ulcer, efflux oesophagitis, and Zollinger–Ellison syndrome (Berglindh and Sachs, 1985; Im et al., 1985). Lee et al. (2006) recently reported that omeprazole was primarily metabolized via hepatic CYP1A1/2, 2D1/2, and 3A1/2, but not via CYP2B1/2, 2E1, and 2C11, in male Sprague–Dawley rats.

Gerson and Triadafilopoulos (2001) reviewed that proton pump inhibitors, such as omeprazole, may interact with other drugs through numerous mechanisms including a competitive inhibition of hepatic CYP isozymes involved in drug metabolism and alteration of absorption of other drugs due to changes in gastric pH level. Moreover, there have been a number of reports that omeprazole interacts with several drugs via inhibition of CYP isozymes (VandenBranden et al., 1996; Funck-Brentano et al., 1997; Niwa et al., 2005) indicating that omeprazole carries a considerable potential for drug interactions. Langouët et al. (1995) reported that oltipraz acts as a competitive inhibitor of CYP1A2 and 3A4 in human hepatocytes. As mentioned above, CYP isozymes responsible for the metabolism of oltipraz (Bae et al., 2005a) and omeprazole (Lee et al., 2006) are partially identical each other (CYP1A1/2, 2D1/2, and 3A1/2). Thus, pharmacokinetic interaction between oltipraz and omeprazole would be expected.

Several studies reported that peptic ulcer occurs with an increased frequency among patients with liver cirrhosis (Kirk et al., 1980; Rabinovitz et al., 1989, 1990; Ichiyanagui et al., 1995; Siringo et al., 1995) and *Helicobacter pylori* infection is implicated in pathogenesis of peptic ulcer in patients with liver cirrhosis (Zullo et al., 1999). Omeprazole has been frequently used in patients with liver cirrhosis to treat peptic ulcer disease, and has also been used for healing of mucosal lesions after endoscopic sclerotherapy of esophageal varices in liver cirrhosis and extrahepatic portal vein obstruction, EHPVO (Kumar et al., 2003). Moreover, it has already been reported that there were significant pharmacokinetic changes of oltipraz or omeprazole in cirrhotic rats and humans (Rinetti et al., 1991; Sauvet and Schouler, 1992; Pique et al., 2002; Bae et al., 2004; Lee et al., 2007). Thus, this study was performed with oltipraz and omeprazole in rats to find whether pharmacokinetic interaction between the two drugs would be observed or not.

This paper reports pharmacokinetic interaction between oltipraz and omeprazole with respect to a competitive inhibition of metabolism of oltipraz by omeprazole via CYP1A1 and 3A2, and of omeprazole by oltipraz via CYP1A1/2, 2D1/2, and 3A1/2 after simultaneous single intravenous (i.v.) and p.o. administration of the two drugs to male Sprague–Dawley rats.

2. Methods and materials

2.1. Chemicals

Omeprazole and torasemide [an internal standard for the high-performance liquid chromatographic (HPLC) analysis of omeprazole] were donated by Yungjin Pharmaceutical Company (Seoul, South Korea) and Roche Pharmaceutical Company (Mannheim, Germany), respectively. Oltipraz was supplied from R & D Center of Pharmaceuticals, Institute of Science & Technology, CJ Corporation (Ichon, South Korea). Polyethylene glycol 400 (PEG 400) and dimethylsulfoxide were products from Yakuri Pure Chemical Company (Kyoto, Japan). Rat recombinant CYP isoforms expressed in insect cells were purchased from Gentest Corporation (Woburn, MA). Dimethylacetamide, the reduced form of β-nicotinamide adenine dinucleotide phosphate (NADPH; as a tetrasodium salt), tris(hydroxymethyl)aminomethane (Tris)-buffer, dithiothreitol, histidine, phenylmethanesulfonylfluoride (PMSF), and ethylenediamine tetraacetic acid (EDTA) were purchased from Sigma–Aldrich Corporation (St. Louis, MO). Other chemicals were of reagent grade or HPLC grade.

2.2. Animals

The protocol for this animal study was approved by the Animal Care and Use Committee of the College of Pharmacy of Seoul National University, Seoul, South Korea. Male Sprague–Dawley rats, 6–9 weeks old and weighing 270–330 g, were purchased from the Taconic Farms Inc. (Samtako Bio Korea, O-San, South Korea). They were maintained in a clean room (Animal Center for Pharmaceutical Research, College of Pharmacy, Seoul National University) at a temperature of 20–23 °C with 12-h light (07:00–19:00 h) and dark (19:00–07:00 h) cycles and a relative humidity of 50 ± 5%. The rats were housed in metabolic cages (Tecniplast, Varese, Italy) under filtered pathogen-free air and with food (Samyang Company, Pyeongtaek, South Korea) and water available ad libitum.

2.3. Intravenous administration of oltipraz and omeprazole to rats

The procedures used for the pretreatment of rats including cannulation of the carotid artery (for blood sampling) and the jugular vein (for drug administration) were similar to previously reported methods (Kim et al., 1993). Oltipraz [suspended (Bae et al., 2003, 2004, 2005a,b,c, 2006) in PEG 400:dimethylacetamide:distilled water = 40:40:20, v/v/v] at a dose of 10 mg/kg with (n = 9; total injection volume of 3 ml/kg) or without (n = 9; total injection volume of 3 ml/kg) omeprazole [dissolved in a 0.1 M carbonate buffer (pH 9.8)] at a dose of 20 mg/kg were infused for 1 min via the jugular vein of rats. A blood sample (approximately 0.12 ml) was collected via the carotid artery at 0 (control), 1 (at the end of the infusion), 3, 7, 15, 30, 45, 60, 90, 120, 180, and 240 min after the start of the i.v. infusion of the drug(s). A heparinized 0.9% NaCl-injectable solution (15 units/ml), 0.3 ml, was used to flush the cannula immediately after each blood sampling to prevent blood clotting. Blood sample was immediately centrifuged and a 50-μl aliquot of plasma sample was collected in a 1.5 ml polyethylene tube, and was stored at −70 °C (Revco ULT 1490 D-N-S; Western Mednics, Ashville, NC) until the HPLC analysis of oltipraz (Bae et al., 2001). The procedures for collecting and handling the 24-h urine samples and gastrointestinal tract (including is contests and feces) samples at 24 h were similar to reported methods (Lee et al., 2006, 2007).