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Regular article

Paroxetine decreased plasma exposure of glyburide partly via inhibiting intestinal absorption in rats

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ABSTRACT

Accumulating evidences have shown that diabetes is often accompanied with depression, thus it is possible that oral antidiabetic agent glyburide and antidepressive agent paroxetine are co-administered in diabetic patients. The aim of this study was to assess interactions between glyburide and paroxetine in rats. Effect of paroxetine on pharmacokinetics of orally administered glyburide was investigated. Effect of naringin (NAR), an inhibitor of rat intestinal organic anion transporting polypeptides 1a5 (Oatp1a5), on pharmacokinetics of glyburide was also studied. The results showed that co-administration of paroxetine markedly reduced plasma exposure and prolonged T_{max} of glyburide, accompanied by significant increase in fecal excretion of glyburide. Co-administration of naringin also significantly decreased plasma exposure of glyburide. Data from intestinal perfusion experiments showed that both paroxetine and naringin significantly inhibited intestinal absorption of glyburide. Caco-2 cells were used to investigate whether paroxetine and naringin affected intestinal transport of glyburide and fexofenadine (a substrate of Oatp1a5). The results showed that both paroxetine and naringin greatly inhibited absorption of glyburide and fexofenadine. All results gave a conclusion that co-administration of paroxetine decreased plasma exposure of glyburide in rats via inhibiting intestinal absorption of glyburide, which may partly be attributed to the inhibition of intestinal Oatp1a5 activity.

1. Introduction

Glyburide (GLB) is a second-generation sulfonylurea and is widely used to treat type 2 diabetes. It stimulates insulin release from pancreatic β-cells by inhibiting ATP-sensitive potassium channels [1]. Glyburide in compound formulation is also co-administrated with metformin for treating type 2 diabetes. Clinical trials have shown that combination of glyburide and metformin is more efficacious in improving glycemia than metformin monotherapy or glyburide monotherapy [2]. Glyburide is absorbed through gastrointestinal tract and extensively metabolized in liver [3]. Like other sulfonylureas, glyburide metabolism in human liver is mainly mediated by CYP2C9 [4]. Other CYP450s, such as CYP3A4, CYP2C8 and CYP2C19 are also involved in glyburide metabolism [5]. Glyburide shows high intestinal permeability. Several reports have demonstrated that in addition to breast cancer resistance protein (BCRP), some drug influx transporters including organic anion transporting polypeptides (OATPs) mediate drug absorption via gastrointestinal tract [6–9]. In human small intestine, two OATP transporters: OATP1A2 and OATP2B1 have been identified [10]. Accumulating evidences have shown that intestinal OATPs play important roles in intestinal transport of substrates including fexofenadine (FEX) and aliskiren [11,12]. For example, the decreased absorption of fexofenadine by naringin was considered to be partly attributed to inhibition of intestinal OATP1A2 [10]. In rat small intestine, the predominant Oatp isoforms are Oatp1a5 and Oatp2b1 [13]. The rat Oatp1a5 is generally believed to be an ortholog of human OATP1A2 based on the combination of amino acid identity, substrate similarity, and syntenic chromosomal localizations, which transport many common substrates such as taurocholate, estrone-3-sulfate and fexofenadine [14,15]. The rat Oatp2b1 also

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shares 77% amino acid identity with human OATP2B1 [16]. Both OATP2B1 and OATP1A2 have been reported to mediate transport of glyburide. Glyburide is also a substrate of hepatic OATP2B1 [9,17]. All these results indicate that like human OATPs, rat Oatps also mediate drug absorption in small intestine, which has been evidenced by the findings that Oatp1a5 mediates the absorption of ciprofloxacin and pitavastatin [18,19] and the Oatp-mediated absorption of drugs may be inhibited by naringin in the rat intestine such as pravastatin [20].

The prevalence of co-morbid mental and physical disorders becomes high in recent years [21]. Among the most commonly occurring comorbities is that of depression and diabetes. Both depression and diabetes are disabling disorders which would lead to negative outcomes [22,23]. It may increase the odds for functional disability and mortality when these two disorders occur together. The selective serotonin reuptake inhibitors (SSRIs) including paroxetine (PA) were reported to be the most studied group of antidepressant medications for treating co-morbid depression in patients with diabetes [24]. It is possible that oral antidiabetic drug glyburide and oral antidepressive agent paroxetine could be co-administered to treat the co-morbid depression in diabetic patients. It is generally accepted that paroxetine is a potent inhibitor of CYP2D6. At the same time, paroxetine also possesses inhibitory effects on CYP2C9 [25,26]. Our previous study showed that co-administration of paroxetine significantly increased plasma exposure of pravastatin (OATP1B1 substrate) partly via inhibiting hepatic OATP1B1-mediated uptake of pravastatin [27]. All these results give a clue that potential drug–drug interaction may occur when paroxetine is co-administrated with glyburide.

Given the possibility that glyburide and paroxetine are co-administered, we aimed to assess the drug–drug interaction potential between glyburide and paroxetine following oral administration in rats. Naringin served as the positive control to examine whether paroxetine altered pharmacokinetics of orally administered glyburide via affecting activity of intestinal Oatps.

2. Materials and methods

2.1. Materials

2.1.1. Chemicals

Glyburide and paroxetine were purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Naringin and fexofenadine were purchased from Tokyo Chemical Industry Co., Ltd. Glucose-6-phosphate, glucose-6-phosphate dehydrogenase (TypeV) and β-nicotinamide adenine dinucleotide phosphate (NADP) were from Sigma Chemical Co. (St Louis, MO, USA). Normal laboratory rodent chow was purchased from Jiangsu Xietong Organism Co., Ltd (Nanjing, China). All other reagents used were of analytical grade and from commercial sources.

2.1.2. Animal

Male Sprague–Dawley (SD) rats, were purchased from SIPPR/BK Experimental Animal Co., Ltd (Shanghai, China). The rats were housed in an air-controlled room (temperature, 22.0 ± 2 °C; humidity, 50 ± 5%) with a 12-h light/dark cycle. They were allowed free access to food and water. Rats were fasted overnight (12 h), but allowed free access to water prior to experiments. The study was approved by the Animal Ethics Committee of China Pharmaceutical University (No. CPU-PCPK-S1210313). Every effort was made to minimize suffering to the animals.

2.1.3. Effect of paroxetine on pharmacokinetics of glyburide in rats

Glyburide administered alone or co-administrated with paroxetine was orally given to SD rats. In brief, the experimental rats were randomly divided into GLB and GLB + PA rats, which orally received glyburide (10 mg/kg) alone and glyburide (10 mg/kg) co-administrated with paroxetine (10 mg/kg), respectively. The oral dosages of glyburide and paroxetine were based on previous reports [7,27]. Blood samples (about 0.25 mL) were collected from rats of each group under light ether anesthesia via the oculi chorioideae vein at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 14 and 24 h after oral administration of glyburide. After 3 or 4 samplings, an appropriate amount of normal saline was administered to the rats via the tail veins to compensate for blood loss. Plasma samples were obtained by centrifugation and stored at −20 °C until analysis.

Another subset of rats was used to document effect of naringin, an inhibitor of Oatp1a5, on pharmacokinetics of glyburide. Briefly, the rats were randomly divided into GLB and GLB + NAR rats, which orally received glyburide (10 mg/kg) and glyburide (10 mg/kg) at 0.5 h following oral dose of naringin (0.145 mg/kg). The dosage of naringin was cited from previous report [28]. Plasma samples were obtained as described above and stored at −20 °C until analysis.

2.1.4. Effect of paroxetine and naringin on excretion of glyburide via feces of rats

The experimental rats, fasted overnight, were randomly divided into GLB and GLB + PA rats, which orally received glyburide (10 mg/kg) alone and glyburide (10 mg/kg) co-administrated with paroxetine (10 mg/kg), respectively. Another batch of rats were randomly divided into GLB and GLB + NAR rats, which orally received glyburide (10 mg/kg) alone and glyburide (10 mg/kg) at 0.5 h following oral dose of naringin (0.145 mg/kg), respectively. Then, the rats were individually housed in metabolic cages. Feces were collected before dosing and at 0–12, 12–24, 24–36 h after administration. The weight of each feces was recorded. The feces were homogenized in water (1:10, w/v). All fecal samples were stored at −20 °C until analysis.

2.1.5. In situ single-pass intestinal perfusion experiments

In situ single-pass intestinal perfusion experiments were performed to evaluate the effect of paroxetine and naringin on the small intestinal absorption of glyburide according to the method described previously [29]. Briefly, male SD rats, weighing 200–250 g, were fasted for 12 h with free access to water prior to the experiment and received intra-peritoneal injection of 45 mg/kg pentobarbital sodium salt (dissolved in 0.9% saline solution). A midline abdominal incision was made and the small intestine was exposed. The jejunum (10 cm) was isolated and flushed with 10 mL of saline pre-warmed to 37 °C to reach a steady state. The manipulation should be performed carefully in order to minimize the surgery and to maintain an intact blood supply.

For absorption experiments, the inlet concentrations (C_{in}) of glyburide and paroxetine were kept to be 10 μg/mL in the perfusion buffer. In general, after perfusion of pre-warmed saline at 37 °C, the Krebs-Henseleit buffer containing drugs (GLB, GLB + PA or GLB + NAR200 μmol/L) were perfused for about 30min until steady state was achieved. The outlet perfusate samples were collected every 15 min for 120 min perfusion period. The areas of the perfused segments were measured at the end of the experiment and finally the animals were euthanized. The concentration of naringin was cited from previous report [30]. All samples were stored at −20 °C until analysis.

The cumulative fraction of absorption was estimated. The outlet concentrations were corrected by multiplying the inlet concentration with C_{in} (phenol red)/C_{out} (phenol red). The P_{eff} was calculated according to the following equation: $P_{eff} = -Q\ln(C_{out[corrected]}/C_{in})/$