PHARMACOKINETICS AND DISPOSITION

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Plasma protein binding of tamsulosin hydrochloride in renal disease: role of $\alpha_1$-acid glycoprotein and possibility of binding interactions

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Abstract

Objective: To investigate the factors that affect the plasma protein binding of tamsulosin in patients with lowered renal function compared with that in healthy subjects and to evaluate the possibility of binding interactions.

Methods: Blood was donated from patients with renal dysfunction and from healthy subjects. The binding of $^{14}$C-tamsulosin to plasma proteins was determined by the ultrafiltration method. In addition, plasma protein binding interactions were investigated between tamsulosin and other drugs used concomitantly.

Results: The mean percentage of unbound $^{14}$C-tamsulosin was 0.90% in the healthy subjects (control) and was 0.71% in the patients. The unbound fraction in the patients with $\alpha_1$-acid glycoprotein ($\alpha_1$-AGP) levels over 0.9 mg/ml was significantly lower than that in the healthy subjects. In contrast, the unbound fraction in the patients with $\alpha_1$-AGP levels less than 0.7 mg/ml, which is the mean normal level, was almost equal to the control levels. A significant correlation existed between the $C_b/C_u$ of tamsulosin and plasma $\alpha_1$-AGP level ($r^2=0.580$, $P<0.001$), while no correlation existed between the $C_b/C_u$ and plasma albumin level ($r^2=0.021$, $P=0.381$) in both groups. No apparent binding interactions were observed between tamsulosin and the other drugs examined.

Conclusions: Tamsulosin is highly bound to $\alpha_1$-AGP. The extent of plasma protein binding of tamsulosin correlated with the $\alpha_1$-AGP level but not with the albumin level. Furthermore, there appears to be no or little possibility of binding interactions between tamsulosin and other drugs in clinically concomitant use, despite its strong binding to $\alpha_1$-AGP.

Key words Tamsulosin · Protein binding · Renal disease

Introduction

Tamsulosin hydrochloride (Harnal, Omnic) is a potent and selective $\alpha_1$-adrenoceptor antagonist (Honda and Nakagawa 1986; Honda et al. 1987; Yamada et al. 1994). This drug is used clinically in Japan and several European countries as an oral medication to ameliorate the bladder-outlet obstruction associated with prostatic hypertrophy. In previous studies, it was revealed that tamsulosin was highly bound to human plasma proteins (Matsushima et al. 1997) and was primarily eliminated by hepatic metabolism (Matsushima et al. 1998). It is well known that changes in the plasma protein binding alter the pharmacokinetic disposition of highly bound drugs. Therefore, it is necessary to evaluate the possibility of binding interactions for such drugs. Tamsulosin is a basic drug which possesses a secondary amine function. Many basic drugs are known to be highly bound to $\alpha_1$-acid glycoprotein ($\alpha_1$-AGP), one of the acute-phase proteins. It has been reported that the level of $\alpha_1$-AGP increases in disease states such as cancer, myocardial infarction, trauma and renal disease, and that the extent of plasma protein binding increases with increase in plasma $\alpha_1$-AGP levels for several basic drugs (Kremer et al. 1988). Moreover, changes in plasma protein binding can lead to alteration of plasma drug levels (Terao and Shen 1983; Yasuhara et al. 1985). Previously, an increase in the plasma tamsulosin level was observed in some patients with renal impairment. If this increase was caused by the elevation of the $\alpha_1$-AGP level, plasma protein binding of tamsulosin would be correlated to $\alpha_1$-AGP levels. Therefore, characterization
of tamsulosin binding to plasma proteins will be helpful to investigate the mechanism for alteration of plasma tamsulosin level in the patients.

In the present study, the in vitro plasma protein binding of \(^{14}\)C-tamsulosin in patients with lowered renal function was determined using an ultrafiltration method to investigate the factors that cause the alteration of plasma protein binding of tamsulosin in patients with complicated renal disease. In addition, the plasma protein binding interactions between tamsulosin and drugs that are often co-administered with tamsulosin clinically have been examined to evaluate the possibility of binding interactions.

**Methods**

**Patients and healthy subjects**

Thirty male patients (34–82 years old), whose creatinine clearance decreased to less than 70 ml/min, donated plasma samples after giving informed consent. They were inpatients and outpatients of Mito General Hospital. Six patients presented with chronic renal failure or renal insufficiency, seven with chronic glomerulonephritis, ten with diabetes mellitus, three with hyperuricemia, one with nephrotic syndrome, one with polycystic kidney and two with benign prostatic hypertrophy. The control group consisted of nine healthy male volunteers (24–33 years old) who worked at Yamanouchi Pharmaceutical Co., Ltd. Blood was collected using heparinized syringes. After centrifugation, plasma was separated and stored at \(-20°C\) until further studies. The concentrations of \(^{1\alpha}\)-AGP and albumin were determined using the single radial immunodiffusion (SRID) method and the bromocresol green (BCG) method, respectively. The patients were stratified into three groups according to the plasma level of \(^{1\alpha}\)-AGP (high, medium and low levels) and so that the size of each group was similar (n = 9–11 patients per group).

**In vitro binding study**

**Binding to plasma protein in patients and healthy subjects**

The plasma protein binding of \(^{14}\)C-tamsulosin (specific activity: 3.6 MBq/mg; Amersham International plc, Buckinghamshire, UK) was determined using an ultrafiltration method (Matsushima et al. 1998). \(^{14}\)C-Tamsulosin was added to yield a final concentration of 1 \(\mu\)g/ml to achieve quantitative determination. After incubation of 2.1 ml plasma containing \(^{14}\)C-tamsulosin for 30 min at \(37°C\), a 0.2-ml aliquot was taken to measure the total concentration. A 1.8-ml aliquot of remaining plasma was transferred to an ultrafiltration tube (Ultracent-10, Tosoh, Tokyo, Japan), then centrifuged for 15–30 min (\(37°C\), 1870 \(g\)). After centrifugation, a 0.2-ml aliquot of the filtrate was taken for the measurement of unbound concentration. The aliquots of plasma and filtrate were diluted to 1 ml with distilled water and, to each 10 ml of liquid, scintillation cocktail (Aquasol-2, New England Nuclear, Boston, Mass.) was added. Samples were counted for radioactivity using a liquid scintillation counter (2000CA, Packard Instruments Co., Meriden, Conn.).

**Binding to isolated proteins**

The binding of \(^{14}\)C-tamsulosin to \(^{1\alpha}\)-AGP (Sigma, St. Louis, Mo.) or human serum albumin (HSA; Sigma) was determined to identify the primary binding protein with tamsulosin. \(^{1\alpha}\)-AGP solution was prepared in isotonic phosphate buffer (pH 7.4) to make a concentration of 0.7 mg/ml. Albumin solution was similarly prepared to make a concentration of 40 mg/ml. In addition to the mono-protein solutions, a solution that contained both \(^{1\alpha}\)-AGP (0.7 mg/ml) and albumin (40 mg/ml) was prepared. \(^{14}\)C-Tamsulosin was added to the sample solution to yield a concentration of 1 \(\mu\)g/ml. The protein binding was determined using the ultrafiltration method as described above.

**Protein-binding interaction study**

Using pooled plasma donated by healthy volunteers, possible plasma-protein-binding interactions were investigated between tamsulosin and other drugs that are highly bound to plasma protein and are often used concomitantly with tamsulosin. The drugs examined in this study are as follows: diazepam (Yamanouchi, Tokyo, Japan), propranolol (Wako Pure Chemical, Osaka, Japan), trichlormethiazide (Shionogi and Co., Ltd., Osaka, Japan), chloramdinone acetate (Sigma), amitriptyline (Sigma), diclofenac (Sigma), glibenclamide (Sigma), simvastatin and its \(\beta\)-hydroxycacid metabolite (Merck, Rahway, N.J.), and warfarin (Sigma). Trichlormethiazide, simvastatin and its active metabolite were gifts and all other compounds except for diazepam were purchased commercially.

**Binding of tamsulosin**

The plasma protein binding of \(^{14}\)C-tamsulosin in the presence or absence of other drugs was determined using the ultrafiltration method as described above. \(^{14}\)C-Tamsulosin was added to yield a final concentration of 600 ng/ml, which is much higher than the maximum concentrations (10–20 ng/ml) observed at clinical doses (0.2–0.4 mg), to achieve quantitative determination. The other drugs were, however, added to yield a concentration close to that of corresponding maximum found after oral dosing of a conventional clinical dose (Hillestad et al. 1974; Vervloet et al. 1977; Sketris et al. 1981; Bax et al. 1984; Tsukamoto et al. 1988; Coppack et al. 1990; Hartter and Hiemke 1992; Pentikainen et al. 1992; Thakker et al. 1992).

**Binding of diazepam, propranolol, glibenclamide and warfarin**

The plasma protein binding of these four drugs in the presence or absence of tamsulosin was determined using the ultracentrifugation method using radiolabeled compounds, i.e., \(^{3}^{3}\)C-diazepam (specific activity: 7.0 MBq/mg; Amersham), \(^{3}^{3}\)H-propranolol (3.29 GBq/mg; Amersham), \(^{3}^{3}\)H-glibenclamide (6.29 GBq/mg; Amersham) and \(^{14}\)C-warfarin (6.81 MBq/mg; Amersham). Tamsulosin concentration was set at 200 ng/ml, which is 10–20 times higher than the therapeutic concentration, to avoid underestimation of the potency of binding interaction, while the others were set as described earlier. A 3-ml or 5-ml aliquot of plasma containing the test compounds was incubated for 1 h at \(37°C\); then a 0.5-ml aliquot was taken for measurement of total concentration. The remaining plasma was ultracentrifuged for 18 h at \(37°C\) and 170,000 \(g\). After ultracentrifugation, a 0.5-ml aliquot of the supernatant was taken for measurement of the unbound concentration. To each aliquot of plasma and supernatant, 10 ml of liquid scintillation cocktail (Aquasol-2) was added and measured for radioactivity by means of liquid scintillation counting.

**Binding of trichlormethiazide, chloramdinone acetate, amitriptyline and diclofenac**

The plasma protein binding of these four drugs in the presence or absence of tamsulosin was investigated by the ultracentrifugation method as described above. As the drugs used in the experiment were non-radiolabeled compounds, the drug concentrations in the plasma and supernatant were measured by means of high-performance liquid chromatography (HPLC–ultraviolet (UV) methods.