PHARMACOKINETICS AND DISPOSITION

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Pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers

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Abstract Background: Quercetin is a flavonoid with a wide range of biological activities. It mainly occurs in plants as glycosides, such as rutin (quercetin rutinoside) in tea. Quercetin and rutin are used in many countries as vasoprotectants and are ingredients of numerous multivitamin preparations and herbal remedies.

Objectives: The primary objective was to characterise and compare the absorption and the pharmacokinetics of quercetin from quercetin aglycone and rutin. A secondary objective was to investigate which forms of quercetin are present in plasma.

Methods: In this double blind, diet-controlled, two-period cross-over study, 16 healthy volunteers received three different doses of quercetin and rutin orally. The doses corresponded to 8 mg, 20 mg and 50 mg quercetin aglycone. Blood samples were obtained between 0 h and 32 h post-dose.

Results: The overall kinetic behaviour of quercetin differed remarkably after ingestion of quercetin aglycone or rutin. The mean area under the plasma concentration-time curve from 0 h to 32 h [AUC$_{0-32}$] and maximum plasma concentration (C$_{max}$) values of the two treatments were similar. However, time to reach C$_{max}$ (t$_{max}$) was significantly shorter after the quercetin aglycone treatment than after the rutin treatment (1.9, 2.7 and 4.8 versus 6.5, 7.4 and 7.5 h, for doses 1, 2 and 3, respectively). Also, the absorption of quercetin from quercetin aglycone was predictable and inter-individual variation was small. In contrast, after ingestion of rutin, inter-individual variations in AUC$_{0-32}$ and C$_{max}$ values were considerable and seemed to be associated with gender and use of oral contraceptives. Quercetin and rutin were found in plasma as glucuronides and/or sulfates of quercetin and as unconjugated quercetin aglycone, but no rutin was detected.

Conclusions: In clinical trials, studying the effects of quercetin from rutin, bioavailability must be taken into consideration and plasma quercetin concentrations monitored. Whether our results apply to other glycosidic drugs as well, especially other rutosides, should be investigated.

Key words Quercetin · Rutin · Flavonoids

Introduction

Flavonoids are a group of polyphenols widely occurring in plants. These compounds, especially the flavon quercetin, exhibit a multitude of biological activities such as antircarcinogenic [1, 2], antioxidative [3] and enzyme-modulating activities [4, 5, 6]. Epidemiological studies indicate an inverse association between dietary intake of flavonoids (mainly quercetin) and cardiovascular disease [7] and cancer [8]. Recent studies also specifically suggest a protective effect of drinking tea on cardiovascular disease [9, 10]. One of the main constituents of tea is rutin (quercetin rutinoside), which is a common quercetin glycoside in plants in general.

Quercetin, and especially rutin (Fig. 1), are used in many countries to relieve capillary impairment and to treat venous insufficiency of the lower limbs. Quercetin and rutin are also ingredients of a large number of multivitamin preparations and herbal remedies. At present, over 130 preparations containing quercetin or rutin are registered as drugs worldwide and in 1998 sales of flavonoids belonging to the rutin group (rutin, ruta extract, troserutin and quercetin) was estimated as US $430 million [11]. Clinical studies that support the use of quercetin and rutin in the treatment of the above-mentioned conditions are few, but at least two studies
indicate that buckwheat tea, which contains high amounts of rutin, is useful in the treatment of chronic venous insufficiency [12, 13]. More comprehensive data on the vasoprotectant effects of flavonoids are available for the hydroxyethyl rutosides, which are synthetic derivatives of rutin [14].

Despite the wide use of flavonoids and the fact that hundreds of studies suggest promising pharmacological activity for these compounds, especially quercetin, little is known about their bioavailability. In fact, no information is available about the pharmacokinetics of quercetin aglycone except for a pilot study performed in our laboratory [15]. Quercetin aglycone is the form of quercetin usually used in in vitro experiments. Some information is available on the absorption of quercetin glycosides, which seems to depend on the type and position of the sugar moieties [16]. The mechanisms of absorption, however, have been a matter of much controversy. It has been suggested that quercetin bound to glucose moieties could be absorbed intact from the small intestine [16], but recent studies [17, 18] indicate that they could be hydrolysed by β-glucosidases present in the small intestine prior to absorption as well. It has been shown previously that enzymes hydrolysing glycosides, such as rutin, are present in the colon [19] and it is likely that rutin is hydrolysed prior to absorption as quercetin aglycone.

The main objectives of our study were to characterise and compare the pharmacokinetics of quercetin from quercetin aglycone and rutin in healthy volunteers in a double-blind, cross-over, diet-controlled design. A recently developed method for the quantitation of total quercetin from human plasma [15] was used and was further developed to enable determination of unconjugated quercetin aglycone and rutin in plasma.

**Methods**

**Subjects**

The study population consisted of 16 healthy, non-smoking volunteers (seven females and nine males). Subject characteristics were as follows (mean±SD): age 22.1±3.5 years (range 18–33 years), weight 65.2±9.4 kg (range 54–94 kg) and body mass index (BMI) 21.7±3.1 kg/m² (range 18.1±26.3 kg/m²). The subjects were checked to be in good health and were free of medication, with the exception of four women who used oral contraceptives. At screening, medical history evaluations and physical examinations were made and electrocardiograms and clinical chemistry tests were taken. The subjects that were included in the study were randomised into two groups. Four females and four males were given the treatments in sequence quercetin aglycone-rutin, and three females and five males received the treatments in the opposite order. In both groups two subjects (one male and one female) discontinued and thus 12 subjects completed the study. The reasons for discontinuing the study were personal (two subjects), tachycardia (one subject) and fever, nausea and vomiting (one subject). None of these was related to the study compound.

The clinical part of the study was conducted at the Clinical Pharmacological Laboratory of Leiras Oy (Helsinki, Finland). All subjects gave written informed consent before participating in the study. The study was conducted in accordance with the ethics principles of the declaration of Helsinki and the study protocol was reviewed and approved by the ethics committees of the National Public Health Institute and Leiras.

**Study design**

This was a double blind, diet-controlled, two-period cross-over study conducted to characterise and compare the pharmacokinetics of quercetin from quercetin aglycone and rutin. The study consisted of two study periods, two treatments and three different doses within both treatments. The term treatment refers to quercetin aglycone and rutin, but not to the individual doses used. The selected doses were 8 mg, 20 mg and 50 mg quercetin aglycone and 16 mg, 40 mg and 100 mg rutin, designated as doses 1, 2 and 3, respectively. The respective doses of quercetin aglycone and rutin contained equimolar amounts of quercetin aglycone. The sequence of treatments was randomised, but within a treatment the study drug was given in ascending dosages. A dosing schedule is shown in Fig. 1. Within the treatments the wash-out interval between doses 1 and 2 was 2 days, and between doses 2 and 3 it was 3 days. Between periods the wash-out interval was 9 days. Each volunteer received a capsule belonging to each dose and treatment once. A study nurse administered the capsules at the study site. The test drug was taken orally in the morning after an overnight fast with a glass of water on an empty stomach. A glass of water (200 ml) was given 2 h after taking the study drug. Lunch was served 4 h after drug administration, dinner 8 h and snacks 6 h and 10 h after drug administration. Blood samples were collected into vacuum tubes containing ethylene diamine tetracetic acid (EDTA) at 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 24 h and 32 h post-dose. A baseline blood sample was taken 20–30 min before administration of the study drug. Plasma was separated using a refrigerated centrifuge and stored at −70 °C until analysed (within 6 months).

**Diet**

As the doses used in this study were close to the amounts of quercetin attainable from the diet, it was essential that the intake of quercetin from the diet was as low as possible. The subjects maintained a low quercetin diet 5 days prior to and during both study periods. To ensure compliance with the diet, lunch and