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Issues with Human Bioavailability Determinations of Bioactive Curcumin

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Abstract

The health benefits of curcumin which is extracted from turmeric (Curcuma longa) are well known. However, curcumin is poorly absorbed in the gastrointestinal tract and undergoes rapid metabolism to inactive forms. The free form of curcumin is more bioactive than its conjugates. Various formulations have been developed to increase curcumin bioavailability. Most curcumin pharmacokinetic studies measure and report total (free plus conjugated) curcumin, not free, bioactive curcumin as a result of enzymatic hydrolysis of plasma samples prior to extraction and analysis. Hydrolysis results in approximately a 10-fold over-estimation of the amount of total curcuminoids in plasma and greater than a 10-fold over-estimation of free, bioactive curcumin, therefore producing a misrepresentation of the results. As a consequence, caution is warranted in interpreting published pharmacokinetic results and claims involving curcumin products.

Keywords: Curcumin; Conjugates; Enzymatic hydrolysis; Bioactive forms

Introduction

Curcumin is the active polyphenolic constituent in turmeric from the rhizomes of Curcuma longa, and exhibits anti-inflammatory, antioxidant, metabolism regulating, chemoprotective, immuno-modulating, antibacterial, antiviral, anti-fungal, antineoplastic, and anti-depressant properties [1-11]. However, unformulated [regular] curcumin is poorly absorbed and exhibits poor bioavailability, limiting its effects and usefulness. Therefore, various formulations have been developed to enhance curcumin bioavailability, including formulations with micelles, liposomes, interaction with macromolecules such as gelatin and various polysaccharides, and nano-particulate preparations including nano-emulsions, nano-micelles, nano-gel, dendrimers, polymers, conjugates and solid dispersions [12,13].

Curcumin Metabolism

Orally consumed curcumin is rapidly conjugated in the small intestine, liver and kidneys to curcumin glucuronide and curcumin sulfate which undergo rapid excretion in the urine and feces [4-7,11-16]. Curcumin occurs in the blood primarily as these physiologically and pharmacologically inactive conjugates with relatively little free, bioactive curcumin. Curcumin also undergoes extensive metabolic reduction to dihydrocurcumin, tetrahydro curcumin and hexahydro curcumin by intestinal microorganisms [5,11-17]. However, these metabolites also undergo conjugation, converting them into physiologically inactive constituents that are excreted in the urine and feces [5,11-17]. Curcumin is more physiologically active as compared to its conjugated forms, and therefore free curcumin reflects its bio-efficacy as compared to conjugated metabolites [5,11-14]. Pharmacokinetic studies have been conducted with various curcumin formulations. The major pharmacokinetic index used for determining extent of absorption of various curcumin products is a plot of blood plasma concentration of the active constituent(s) against time, yielding the area under the curve (AUC). Data from pharmacokinetic studies of various products can be compared by normalization of the results on the basis AUC/mg curcumin administered.

Enzymatic Hydrolysis

With few exceptions [13,18,19], plasma samples are routinely subjected to enzymatic hydrolysis with β-glucuronidase and sulfatase to yield total curcumin [20-32]. Therefore, most pharmacokinetic studies involving curcumin formulations have not demonstrated an increase in free, bioactive curcumin in the blood. Curcumin glucuronide and curcumin sulfate are the primary, physiologically inactive conjugates of curcumin. Therefore, the results do not provide information regarding the potential pharmacokinetic benefits of the formulations with respect to an increase in free, bioactive curcumin. When plasma

samples are directly extracted without hydrolysis, free curcumin, curcumin glucuronide and curcumin sulfate are detected. Extraction following enzymatic hydrolysis results in the detection of curcumin, tetrahydro curcumin, desmethoxycurcumin and bis-desmethoxycurcumin. Total curcuminoids detected in plasma following hydrolysis increase by a factor of approximately 10-fold or more as compared to direct extraction without hydrolysis.

In a pilot study, free curcumin in plasma after the administration of a liquid droplet nano micellar formulation (BioCurc®) represented approximately 15-20% of the total curcuminoids detected in plasma following direct solvent extraction without enzymatic hydrolysis, while free curcumin after hydrolysis of the plasma samples constituted approximately 25-30% of the total curcuminoids. Therefore, curcumin content after hydrolysis may not directly correlate with free curcumin in the plasma, with the curcumin content after hydrolysis being as much as 14-fold higher than the free curcumin content determined without hydrolysis. Unfortunately, the effect of hydrolysis is not discussed or considered in most pharmacokinetic studies involving curcumin. Biologically inactive curcumin glucuronide constitutes approximately 75% of the directly extracted curcuminoids without enzymatic hydrolysis and analyzed by high performance liquid chromatography and tandem mass spectrometry. Tetrahydorcurcumin constitutes over 60% of the total curcuminoids extracted from plasma after enzymatic hydrolysis, while no free, bioactive tetrahydro curcumin was detected in the plasma samples extracted without hydrolysis.

Summary and Conclusion

Pharmacokinetic studies with almost all commercial formulations have used enzymatic hydrolysis to free conjugated curcumin prior to analysis. It is not known how these various formulations affect the amount of free curcumin in plasma as compared to the total amount that is reported (free plus conjugated form). Enzymatic hydrolysis of plasma samples prior to solvent extraction may result in at least a 10-fold over-estimation of the amount of free, bioactive curcumin, thus resulting in exaggerations of the efficacy of the formulations. Conjugates of curcumin cannot be compared to the actions of free curcumin. Enzymatic hydrolysis of plasma samples does not provide an accurate reflection of the plasma levels of free, bioactive curcumin, its bio-efficacy or therapeutic potential.

Conflict of Interest

S.D.R. has no perceived conflict of interest to report. S.J.S. has served as a consultant for Boston Biopharm Inc.

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