Osteoarthritis and Cartilage 18 (2010) 1104–1105

Osteoarthritis and Cartilage

Letter to the Editor

About oral absorption and human pharmacokinetics of chondroitin sulfate

Dear Editor,

A recent paper by Jackson *et al.*[1] investigates the pharmacokinetics (PK) of glucosamine (GlcN) and chondroitin sulfate (CS) when taken separately or in combination as a single dose. As concerns CS, the authors report that the endogenous concentration and CS disaccharide composition were not detectably altered by ingestion of CS. As a consequence, the authors state "we found no evidence for absorption of oral CS into the circulation under any dosing regimen".

However, many previous studies on man [see Refs. 2 and 3], animals[4] and *in vitro* models[5] using CS or similar natural biomacromolecules, i.e., dermatan sulfate, desulfated CS, fucosyl CS, heparin, or mixtures [see Refs. 2 and 3] clearly demonstrated the oral absorption of these polysaccharides. As a consequence, how is it possible to explain the "absence" of CS oral absorption in man observed in[1]? The key point is related to the study protocol and analytical procedures and methodologies adopted in their research. This is more important when oral PK and bioavailability of highly structurally complex and heterogeneous macromolecules like CS are under investigation. This is more complex when studies are performed on human biological fluids, such as plasma, in which endogenous CS is present[2,3], and a large individual variability is expected.

Keeping this in mind, we should consider that two PK studies have been performed on oral absorption of CS. To this aim, 4000 mg of CS were orally administered to 20 human volunteers[2,3]. According to these studies, a total absorption of 2.5–5% (mean ~3.5%) CS was observed. Considering that Jackson *et al.* performed their study on 1200 mg CS[1], that the total blood volume in a man is ~1/12 of his weight[6] and that plasma constitutes ~55% of the entire blood[6], and that the recovery obtained in[1] is ~75%, we can calculate a maximum of CS absorption of ~10–15 μg/mL plasma, possibly evaluated under a curve between 2 and 6 h, as demonstrated for a similar CS[2]. As a consequence, the possible increase of a single concentration-time between 2 and 6 h in[1] blood sample obtained at 2, 2.5, 3, 4 and 6 h along with other points may be expected at a maximum of 4–8 μg/mL. Under these conditions and considering that Jackson *et al.* determined a mean CS endogenous concentration of approx. 20 μg/mL with a possible individual variation of 5 μg/mL (25%) and 40–45% variation in AUC values after CS administration (see Tables IV and VI)[1] (similar values to those obtained in studies Refs. 2, 3), it is hard to obtain any significant plasma CS variation. To confirm this, a trend toward higher CS concentrations was observed by the authors but differences were found to be non-significant, also perhaps due to the small number of subjects, 9–10, studied[1].

Closely related to the first point, is the possibility to determine any increase of 6-sulfated disaccharide (Di6s) in human plasma after oral administration of CS composed of ~45% of this disaccharide (generally present in endogenous CS plasma in trace amounts)[2,3]. In fact, in previous studies[2,3] a maximum increase of ~20% of Di6s was observed after administration of 4000 mg CS. By performing the same approach as previously reported, we can expect a maximum Di6s presence in plasma of 0.9–1.3 μg/mL. Jackson *et al.* measured ~10% (~2 μg/mL) Di6s in endogenous CS and, considering as above the huge % variations, also in this case it is very hard to observe any significant value.

Along with detection limits, other factors may influence CS recovery from plasma. For example, previous studies, contrary to research in Ref. 1, accurately avoid the use of heparin (a polysaccharide with similar anionic properties to CS), interfering in particular with the extraction procedures. Furthermore, Jackson *et al.* measured a CS endogenous amount of ~20 μg/mL[1], virtually 2–4 times more than several other studies performed by various analytical approaches [see Refs. 2 and 3]. Additionally, due to the anionic properties of these macromolecules, absorbed CS may interact with several blood components, in particular with endothelium reported, for example, to have the power to remove up to 80% heparin from circulation after administration[7]. Finally, part of the absorbed CS reaching the plasma compartment may be rapidly taken up by liver cells where polysaccharides are most recovered in experimental animals[8].

According to the above-illustrated considerations and the data available in International Scientific Literature, the statement reported in the paper of Jackson *et al.*[1] should be changed to the more correct statement "no evidence for absorption of oral CS into the circulation under any dosing regimen has been found *under the experimental conditions used in this study*".

Author contribution

NV is the only author of this work.

Conflict of interest

Declaration: the author declares that he has no competing financial interests.

Acknowledgments

Grant support: none.

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doi:10.1016/j.joca.2010.02.018

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N. Volpi
Department of Biology, University of Modena & Reggio Emilia, Modena, Italy

Address correspondence and reprint requests to: Nicola Volpi, Department of Biology, University of Modena & Reggio Emilia, Via Campi 213/D, 41100 Modena, Italy.
Tel: 39-59-2055543; Fax: 39-59-2055548.
E-mail address: volpi@unimo.it