Controversy on glucosamine

A pharmacokinetic matter?

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Glucosamine is a natural aminosugar, largely utilised both in drugs (principally in the European Union) and dietary supplements to treat osteoarthritis (OA), with a good safety profile. However, despite favourable evidence obtained in animal studies, controversial results have been obtained in clinical trials on its effect in modifying disease progression or alleviating symptoms of OA.

A recent article was published with the aim of presenting and discussing the potential sources of this controversy about the effect of glucosamine [1].

Inconsistency of commercial products and labelled glucosamine content

The Authors reported that 13 out of 14 tested formulations had a glucosamine content considerably lower than the stated amount (ranging from 41 to 82%). This could be due to the fact that glucosamine crystals are highly instable and are often co-crystallised with KCl: manufacturers might have used the diluted crystals without allowing for the co-crystallisation in their quality control. Unfortunately the Authors considered only the Canadian market, but this exercise should be extended to the products containing glucosamine available in other countries. Thus in negative trials glucosamine could have been under-dosed, highlighting the requirement of clinical trials using higher controlled products or formulations giving higher plasma concentrations.

Dose-effect relationship and bioequivalence

Although almost all clinical trials have been done with a daily dose of 1.5 g of glucosamine, this dose gives plasma levels considerably lower than those effective *in vitro* or in animal studies. However, according to the Authors, no attempt was made to test higher doses in the clinical trials carried out so far. Moreover, the minimum effective dose of glucosamine has not been determined even in animal studies, and this is another gap in the knowledge of the product's efficacy.

Also, the bioavailability of the different formulations could play a role: the reported plasma peak concentration in different trials after the 1.5 g dose varies from 2.75 (obtained with glucosamine HCl) to 15.4 μ M (obtained with glucosamine sulphate). To address this point the Authors reported their own results in rats, demonstrating that after oral administration of

100 mg/kg as HCl or sulphate salts, no significant differences in bioavailability are observed. Moreover, they compared the two formulations in a preliminary study in healthy volunteers by measuring the intact glucosamine urinary excretion after a single oral dose of 1.5 g glucosamine sulphate or its equivalent HCl salt. Although these results need to be confirmed in a larger study, they found that the two formulations were bio-equivalent, thus ruling out a possible effect of formulation differences in the different trials' results.

Metabolism

Another possible source of variability in trial results is inflammation, since it may inhibit the hepatic metabolism of compounds (first pass effect). However, according to the Authors, there is no evidence of hepatic glucosamine metabolism, since its low bioavailability seems to be related to loss in the gut.

Outcome assessment

The sensitivity of methods used to assess the effectiveness of glucosamine in OA may be another source of variability in trial results. Outcome measures commonly utilised are the WOMAC arthritis index, different pain scales, radiographic techniques and joint space narrowing. Indeed in one trial a sub-group of patients have not been able to differentiate between placebo and celecoxib, thus a re-evaluation of assessment measures is recommended for further OA trials in order to detect moderate beneficial effects. Also, the inclusion of patients with low pain at baseline might also have contributed to negative trial results.

Other bias

The Authors considered also possible industry bias. Although this could have affected in some way the outcome measures in non-independent studies, it is unlikely to play a role in the differences in plasma concentrations. Thus the low bioavailability for the HCl formulation used in some trials is still an open question.

In conclusion, the article provides a critical discussion of the controversial results obtained with glucosamine, and highlights the pharmacokinetic properties, bioavailability and inconsistency of commercially available products as determinant. New clinical trials using higher doses or formulations with greater bioavailability, and revision of the outcome assessment should be planned to clarify the glucosamine controversy.

References

1. Aghazadeh-Habashi A, Jamali F (2011) The glucosamine controversy: a pharmacokinetic issue. J Pharm Pharm Sci 14:264–273

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