Active Ingredient Consistency of Commercially Available Glucosamine Sulfate Products

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ABSTRACT. ***Objective.*** To assess the content of active ingredient in over-the-counter (OTC) glucosamine sulfate (GLS) preparations.

Methods. We analyzed in a coded, blind manner 14 commercially available capsules or tablets of GLS, plus one herbal mixture as a control. We used a high performance liquid chromatography system as described.

Results. The amount of free base varied from 41 to 108% of the mg content stated on the label; the amount of glucosamine varied from 59 to 138% even when expressed as sulfate.

Conclusion. If GLS is used as a therapeutic agent, it is important that the products conform to a standard in their description. The content is probably best expressed in terms of free base. (J Rheumatol 2002;29:2407–9)

Key Indexing Terms:
GLUCOSAMINE CONTENT OVER-THE-COUNTER PREPARATIONS

Glucosamine derives from the natural amino monosaccharide and is a normal constituent of glycosaminoglycans in cartilage and synovial fluid[1]. There have been several short term and one longterm study suggesting that commercial preparations of glucosamine are effective in the treatment of patients with osteoarthritis of the knee, and perhaps other areas[2,3]. While in Europe it is regarded as a medication, and is thus subject to the usual quality controls, this is not so in either Canada or the US. In Canada it is widely available as a nutritional supplement and is not subject to even rudimentary checks on purity. Glucosamine sulfate is very hygroscopic and unstable. Hence, during manufacturing, varying amounts of potassium or sodium chloride are added to improve stability. Because of concerns that the labeling description may not always be valid, we analyzed a variety of preparations for their glucosamine content.

MATERIALS AND METHODS

Fourteen preparations containing glucosamine were selected on the basis of their ready availability in Edmonton stores (see appendix for listing). One other non-glucosamine mixed supplement was used as a control. All lots were within one year of the noted expiry date, and all contained glucosamine as sulfate, between 300 and 1500 mg in each capsule (11 were labeled 500 mg). Two indicated that they contained chondroitin in addition. One preparation noted that it contained glucosamine sulfate, hydrochloride, and KCl, and that each tablet contains 500 mg of glucosamine. The others all indicated that they contained their weight in glucosamine sulfate without giving the weight of free base. Preparation 9 contained D-glucosamine sulfate, preparation 5 indicated that glucosamine sulfate was obtained from KCl complex. All were noted to be sodium-free. Thus, it would be expected from the label that all should contain the weight as glucosamine sulfate with the exception of preparation 1, which was expressed as pure glucosamine.

Determination of glucosamine in preparations. Two of the preparations (1 and 9) were tablets, all the others were capsules. Five tablets or capsules from each container were weighed and transferred to a mortar. They were ground and 3 portions of the resulting powder each equivalent to 10% of the total weight were dissolved in 1 l of water. The resultant was filtered and 1 ml of the filtrate was diluted to 2.5 ml with water. To 0.05 ml of this solution was added aspartic acid aqueous solution as internal standard, and 0.06 ml methanol. The mixture was evaporated and glucosamine in the residual was derivatized with 1-naphthyl isothiocyanate at the amino group. The excess amount of derivatizing reagent was extracted with chloroform. A 0.1 ml volume of the eluted solution was injected into an isocratic high performance liquid chromatography system consisting of a C18 column, a mobile phase of acetonitrile:H_2O:acetic acid:triethylamine (4.5:95.5:0.1:0.05) with a flow rate of 0.9 ml/min, and a UV detector set at 254 nm. Glucosamine and the internal standard appeared 11 and 21 minutes postinjection, respectively. Standard solutions were prepared in water. The outcomes [slope, intercept, and percent coefficient of variation (CV)] were the same as those observed in the presence of plasma except that the chromatograms were cleaner. The assay[4] was linear over the range of 1.25–400 μg/ml (CV < 10%) with a limit of quantification of 1.25 μg/ml. All analyses were run with quality control samples of known drug concentrations (the analyst was blinded), prepared from the same material used for the standards. This was laboratory grade glucosamine HCl (based on glucosamine base) extracted and purity confirmed in our own laboratory using nuclear magnetic resonance and liquid chromatography-mass spectrophotometry.

RESULTS

The results of the assays are noted in Table 1. One preparation of glucosamine (preparation 1) contained 542 mg per tablet. Another contained 409 mg per tablet. All others were well below the 394 mg expected if the tablet actually contained 500 mg of glucosamine sulfate. Some preparations indicated KCl extraction was used (preparation 5) and on specific enquiry agreed their dosage was based on the glucosamine sulfate to KCl (MW 605) formula. Such a preparation should contain 296 mg of glucosamine, but this still did not explain the wide variation seen. It should be

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Submitted November 7, 2001; revision accepted May 21, 2002.

Table 1. Content of glucosamine (mg/capsule or tablet) as base.

Preparation	Capsule or Tablet	Labeled Content, mg	Sulfate or Chloride	Glucosamine, mg	Glucosamine, mg Expressed as Sulfate	% of Stated Amount (as base)
1	T	500	S + C	542	688	108
2	C	500	S	409	519	82
3	C	500	S	277	351	55
4	C	500	S	325	445	65
5	C	500	S	330	419	66
6	C	Nil	—	0	—	—
7	C	500	S	248	315	50
8	T	1500	S	634	804	42
9	C	500	S	233	295	41
10	C	500	S	298	378	60
11	C	500	S	231	293	46
12	C	500	S	274	348	55
13	C	500	S	238	302	48
14	C	300	S	169	214	56
15	C	500	S	262	332	52

noted that the stated strengths also varied, one preparation being labeled 1500 mg, and another labeled 300 mg. All preparations indicated they were sodium-free, suggesting that this should not therefore have been a contaminant.

DISCUSSION

Many reports on the use of glucosamine have used glucosamine sulfate 500 mg tablets or capsules[2]. It is not always clearly stated whether this represents 500 mg of glucosamine base or salt. The glucosamine may have been extracted along with KCl, but it is not indicated in the reports whether this should be considered in the total dosage. The ratio of molecular weights of glucosamine to glucosamine sulfate is 358 to 454. Without considering the potassium or sodium content, therefore, 500 mg of commercially available glucosamine sulfate contains at most 394 mg of glucosamine base (i.e., 78.6%).

To improve stability, glucosamine salts are usually crystallized in the presence of sodium or potassium chloride[5,6]. The amount of salt added, however, is not constant and varies by several fold. The powder used as the active ingredient to manufacture tablets or capsules of glucosamine therefore contains varying amounts of the base depending on the amount of KCl (or NaCl) used. No commercially available product that we tested contained any information as to the quantity of KCl used, and only one indicated the amount of glucosamine included as base.

In usual doses, glucosamine is not a toxic substance and its use is unlikely to be associated with serious side effects even when relatively large amounts are taken. However, the efficacy of the drug presumably depends on the amount used as the base. As it stands, the amount of glucosamine stated on product labels is not an accurate reflection of the active ingredient contained.

A further confusing problem, reviewed by Houpt, *et al*[5], is that glucosamine as a sulfate contains some 50% less bioactive base than does the chloride. This is partly because of the need for added potassium and occasionally sodium chloride as a stabilizing agent, and is one explanation for the variability in glucosamine base content seen with our assay. The presence of KCl is occasionally noted in small print, but none of the labels indicated that this was part of the designated mg content. This is the cause of additional confusion as to how much base is contained in each capsule.

We recommend that the exact amount of glucosamine base contained in the products be clearly stated on the product label if there is a supposition that the dosage bears some relationship to response. Even where this is not clear, it would still seem appropriate that as a general rule all over-the-counter health care products be correctly and accurately labeled.

APPENDIX

Nature Made GLS 500 mg (tablets)
Webber Naturals GLS 500 plus chondroitin
Wampole GLS 500 mg
Webber GLS 500 mg
Organika GLS 500 mg
Jamieson GLS 500 mg
Holista GLS 500 mg
Quest GLS 1500 mg
Natural Factors GLS 500 mg
Enzymatic Therapy GLS 500 mg
Prairie Naturals GLS 500 mg
SISU GLS 500 mg
Organika LIGA GLS 300 mg (plus chondroitin)
Enerex GLS 500 mg

ACKNOWLEDGMENT

We would like to express our gratitude to the reviewers for their helpful and constructive comments.

REFERENCES

1. Barclay TS, Tsourounus C, McCart GM. Glucosamine. Ann Pharmacother 1998;32:574-9.
2. Deal CL, Moskowitz RW. Nutraceuticals as therapeutic agents in osteoarthritis: the role of glucosamine, chondroitin sulphate and collagen hydrolysate. Rheum Dis Clin North Am 1999;25:379-95.
3. Reginster JY, Deroisy R, Rovati LC, et al. Long term effects of glucosamine sulphate on osteoarthritis progression: a randomized placebo controlled clinical trial. Lancet 2001;357:251-6.
4. Aghazadeh A, Sattari S, Pasutto FM, Jamali F. High performance liquid chromatographic determination of glucosamine in rat plasma. J Pharm Pharm Sci (in press).
5. Houpt JB, McMillan R, Wein C, Paget-Dellio SD. Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. J Rheumatol 1999;26:2423-30.
6. Nutrasense. Glucosamine hydrochloride vs. sulfate. www.nutrasense.com/glucosaminehcl/html