Medicines Q&As

Q&A 143.4

Glucosamine – what are the adverse effects?

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Summary

- Glucosamine supplements are widely used for the relief of pain and symptoms associated with osteoarthritis. They appear to be well tolerated, with a reported frequency of adverse effects similar to that with placebo.
- Mild gastrointestinal disturbance is the most common adverse effect. Other adverse effects include headache, drowsiness, insomnia and skin reactions.
- Although glucosamine should not precipitate allergic reactions in patients sensitive to shellfish, as the non-synthetic preparations are derived from the shell and not the flesh of shellfish, some sources recommend cautious use or avoidance of these products in patients at risk.
- Glucosamine does not appear to adversely affect plasma blood glucose in patients without diabetes. However, data relating to its effects in patients with diabetes are lacking. It may be wise for patients with diabetes to monitor their blood glucose levels more closely if they start to take glucosamine, increase their dose or change the product taken.
- Glucosamine should be used with caution in patients with renal impairment or those taking nephrotoxic medication.

Background

Glucosamine is a naturally occurring sugar that is a basic building block of several important constituents of articular (joint) cartilage. It is important for maintaining the elasticity, strength and resilience of cartilage in joints, which helps to reduce joint damage (1). The administration of glucosamine is believed to stimulate production of cartilage components and allow rebuilding of damaged cartilage (1).

Glucosamine is commonly used for the relief of pain and symptoms associated with osteoarthritis and other joint disorders. It is available in the form of tablets and capsules as glucosamine sulphate, glucosamine hydrochloride and N-acetyl-D-glucosamine (NAG). It is sometimes used in combination with chondroitin sulphate. Glucosamine supplements are either produced synthetically or derived from the shells of shellfish (2). Products vary in their content and strength of active ingredients.

Glucosamine appears to be well tolerated, at least in the short-term. The incidence of adverse effects in clinical studies has generally been comparable to that with placebo. (3,4). Side effects associated with this supplement are discussed below.

Answer

When taken orally, the most common adverse effect of glucosamine is mild gastrointestinal disturbance. Symptoms, which include nausea, heartburn, diarrhoea, constipation and epigastric pain, may be reduced if glucosamine is taken with or after food (4,5,6). Other adverse effects include headache, drowsiness and insomnia, and skin reactions such as erythema and pruritus (6). Peripheral oedema and tachycardia have been reported in a few patients in larger clinical trials investigating oral or intramuscular glucosamine, but a causal relationship has not been established (6).

Allergy

It has been suggested that non-synthetic glucosamine products may cause allergic reactions in people sensitive to shellfish. Shellfish allergy is caused by IgE antibodies to antigens in the flesh of shellfish, and not to the shell. Therefore it should be safe for patients with shellfish allergy to take glucosamine supplements (7). This assertion is supported by a small study in six subjects with a history of systemic reaction and a positive skin test to shellfish; all six had a negative skin test to glucosamine and an

uneventful oral challenge (7). However, the Australian Adverse Drug Reactions Advisory Committee has received 51 reports of allergic skin reactions to glucosamine, including angioedema, and note that in some cases, patients tolerated a different glucosamine product without adverse effect. The report implies that these patients may have initially reacted to shellfish-derived products (8). Some sources recommend that people who are allergic to shellfish should use glucosamine sourced from shellfish with caution or avoid it entirely (9). The Summary of Product Characteristics (SPC) for the licensed brands of glucosamine, *Alateris*, *Dolenio* and *Glusartel*, all contraindicate the use of the glucosamine in patients who are allergic to shellfish (10, 11, 12).

The possibility of an allergic response to glucosamine in patients with asthma has been raised by a single case report. Exacerbation of the condition occurred in a woman with a ten-year history of asthma, after she started taking a preparation containing glucosamine 500mg plus chondroitin 400mg three times daily for arthritis (13). The exacerbation was marked by periodic attacks of wheezing, shortness of breath and decreases in peak expiratory flow rate and pulse oxygenation. Symptoms did not respond to oral steroids but within twenty-four hours of discontinuing glucosamine/chondroitin, asthma symptoms resolved completely. A lack of collaborating evidence from clinical trials or in the form of other case reports suggests that asthma should not be viewed as a contraindication to glucosamine treatment at this time. The SPC for glucosamine advises that asthmatic patients starting on glucosamine should be aware of potentially worsening symptoms of asthma (10, 11, 12).

Blood glucose levels

Concern has been raised about the possibility that glucosamine may interfere with blood glucose control. A review of the literature on this topic concluded that although alterations in glucose metabolism have been noted in animals given high-doses of intravenous (but not oral) glucosamine, similar effects have not been consistently documented in humans following usual oral doses (14). The review reports on a number of studies evaluating the long-term use of oral glucosamine for osteoarthritis. In two studies of similar design, non-obese patients with knee osteoarthritis but without 'substantial metabolic abnormalities' were randomised to either 1,500mg daily or placebo for three years. In the first trial (n=212) fasting plasma glucose concentrations determined annually decreased slightly in glucosamine treated patients (15). In the second study (n=202), although no specific data on glucose parameters were given, no differences in annual laboratory tests were reported between the treatment and placebo groups (16). Smaller, shorter-term studies in subjects without diabetes, have also reported that glucosamine does not affect glucose tolerance or insulin resistance (14).

Only one placebo-controlled double-blind trial assessing the effects of glucosamine on glucose control in patients with type 2 diabetes has been identified (17). In this study, patients with type 2 diabetes who were not receiving insulin were randomised to receive glucosamine 1,500mg plus chondroitin 1,200mg daily (n=26), or placebo (n=12) for 90 days. HbA1c values increased slightly (0.05%) in the active treatment group and decreased slightly in the placebo group (0.16%). These changes did not reach statistical significance. The patients in this study had well-controlled type 2 diabetes and it is unclear whether these results would apply to patients with less well-controlled disease, or to those with type 1 diabetes.

On the basis of the data included in this review, glucosamine would not be anticipated to have an adverse effect on glucose control in many patients. However data are limited and the effects of glucosamine in patients with diabetes are not well studied. Until further information becomes available, it is suggested that patients with diabetes should monitor their blood glucose levels more closely when glucosamine is initiated, the dose is increased or the product being taken is changed (10, 11, 12,14,18).

Other adverse effects

Hypercholesterolaemia has been reported in three women aged 60 to 66 taking glucosamine (doses unknown) for between six to twelve months. Increases in total cholesterol ranged from 0.9 to 2.4mmol/l while taking the supplement. In one case, total cholesterol returned to pre-treatment levels when glucosamine was discontinued; outcomes in the other patients are unknown (19). Changes in lipid levels have not been reported in long-term clinical trials (15,16). The SPC for glucosamine advises monitoring blood lipid levels in patients taking glucosamine who have known risk factors for cardiovascular disease, based on these reports, but notes that causality has not been established (10, 11, 12).