INTRODUCTION

Dietary glucosamine is now widely used as a therapeutic alternative to anti-inflammatory drugs for the relief of joint pain associated with osteoarthritis. Our understanding of the mode of action of glucosamine is however very limited. The commonly held view that dietary glucosamine promotes joint health by promoting cartilage matrix production has not been experimentally verified. On the other hand, glucosamine exerts anti-catabolic effects on cartilage and chondrocytes (1,2) and anti-inflammatory effects on neutrophils (3) when added to cell cultures in the 100uM-20 mM (20ug/ml-4mg/ml) range. Whether these observations on cellular activity are relevant to the apparent therapeutic effects of dietary glucosamine in human osteoarthritis (4) depends on whether these concentrations are reached in serum and joint fluid following a typical glucosamine dose of 20mg/kg/day. To address this we have determined the pharmacokinetics of oral (nasogastric) and intravenous glucosamine in the serum and synovial fluid of adult horses following a 20mg/kg dose.

METHODS

Eight adult female horses, with a mean age of 10 years (6 – 15 years) and weight of 500 kg (442 – 546 kg) were studied. All were free of clinical evidence of joint disease and were randomly assigned to two groups of four. After overnight fast, glucosamine hydrochloride (20mg/kg body weight; Sigma (G1514) at 100mg/ml in 0.9 % sterile saline, pH 6) was administered to one group by nasogastric intubation and to the other by intravenous injection. Naso-gastric dosing included 500 ml of 0.9% sterile saline immediately post-glucosamine. Intravenous injection was via an intravenous catheter in the right jugular vein. Blood samples were collected via an intravenous catheter in the left jugular vein before dosing and at 5, 15, 30, 60, 120, 180, 240, 360, 480 and 720 min post dosing. Synovial fluids were collected by aseptic arthrocentesis, 48 h before dosing (predose) in both radiocarpal joints, at 1h post-dosing in the left joint and 12h post-dosing in the right joint. Synovial fluids and blood were kept on ice, centrifuged (3000 rpm 20 min at 4º C) and cell-free supernatants stored at – 70º C until assayed for glucosamine. Horses were evaluated twice weekly by flexion tests and joint palpation, for heat, pain and lameness (C until assayed for glucosamine. Horses were evaluated twice weekly by flexion tests and joint palpation, for heat, pain and lameness (C until assayed for glucosamine.

RESULTS

The pre-dose level of glucosamine in sera and synovial fluids was below 0.1 uM. With intravenous dosing, a peak serum concentration of about 180 uM was observed in all horses between 5 and 15 min post-dose (Figure 1, right panels). This was followed by a rapid decrease to ~ 50 uM after 2 h and a return to essentially pre-dose control levels (~ 0.5 uM) by 12 h. Oral dosing resulted in a peak serum concentration between 4 and 10 uM in all horses, and depending on the animal, this was achieved between 30 min and 2 h post-dose (Figure 1, left panels). Again, a decrease to pre-dose levels was seen within 12 h. With I.V. dosing the synovial fluid levels were 25-50 uM at 1h which was similar to the serum levels at this time. With oral dosing, synovial fluid concentrations were 1-2 uM at 1h, which was about 50% of that in serum at this time.

DISCUSSION

The data provided clearly shows that following a single oral (nasogastric) dose of glucosamine in horses at clinically relevant levels (20 mg/kg) the peak concentration in serum (about 10uM) and synovial fluid (about 5 uM) is markedly (10-1000-fold) lower than that required to affect cellular activity in culture(1,2,3). Importantly, the serum concentration reported here for horses dosed naso-gastrically with 20mg/kg is similar to that we have determined for rabbits and normal humans at this oral dosage (Plaa and Sandy, unpublished).

The study reported here in horses (monogastric animals) is therefore clearly relevant to the human clinical situation and has shown for the first time that oral glucosamine at the recommended dosage results in a peak glucosamine concentration in serum within 1-3 h after ingestion and that predose levels are re-established within 6h of intake. Further, we have been able to show that an increase in serum glucosamine concentration is accompanied by an increase in the synovial fluid concentration to a value of about 30% of the peak in the serum. If, as seems likely, the therapeutic effects of glucosamine on joint pain (4) are a result of glucosamine altering cells within articular or periarticular tissues, then the present study suggests that these effects are achieved by a maximum concentration of about 5 uM glucosamine within 1-3h of ingestion. However, the nature of the target cell(s) and the mechanism of action of glucosamine at these in vivo concentrations remains to be determined.

REFERENCES:


** Department of Veterinary Medicine, University of Montreal, *Department of Internal Medicine and *** Shriners Hospital, Department of Pharmacology, University of South Florida.