Effects of allopurinol on plasma uric acid levels in normouricaemic and hyperuricaemic green iguanas (*Iguana iguana*)

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A two-phase cross-over therapeutic study was performed with 19 green iguanas (*Iguana iguana*) maintained within a preferred optimum temperature range of 26 to 37°C. During phase 1, they were fed a normal vegetarian diet and medicated orally with either allopurinol or a placebo control once a day for seven days. Uric acid concentrations, total protein, packed-cell volumes (PCV) and bodyweights were recorded from each lizard before and after treatment to determine the effects of allopurinol. In phase 2, after a 10-day washout period, the iguanas were fed a high protein diet to induce hyperuricaemia. Normo- and hyperuricaemic iguanas that received 24·2 (3·2) mg/kg allopurinol had significantly lower mean (sd) uric acid concentrations (100·3 [53·1] μmol/l) than the controls (159·3 [100·3] μmol/l). There were no detectable interactions between the doses of allopurinol or placebo, and the iguanas' diet, weight, PCV or total protein. The allopurinol was well tolerated, and there was no significant clinical, gross or histological evidence of hepatic or renal toxicity in the iguanas that received the drug. However, in the kidneys of the hyperuricaemic iguanas that did not receive allopurinol there were proliferative changes in the glomeruli and degeneration of tubular epithelia. Allopurinol given orally at 25 mg/kg daily is able to reduce plasma uric acid levels by 41 to 45 per cent, and is therefore recommended for the treatment of hyperuricaemia in the green iguana.

REPTILES are popular zoo exhibits and companion animals. They have been reported to suffer from kidney disease and gout, and the green iguana (*Iguana iguana*) has received particular attention in terms of both diagnosis and treatment (Keymer 1978a, b, Maxwell and Jacobson 2004, Hernandez-Divers and others 2005, Hernandez-Divers and Innis 2006, Mader 2006, Selleri and Hernandez-Divers 2006). Reptiles differ significantly from mammals in their renal anatomy and physiology (Dantzler 1976, Fitzsimons and Kaufman 1977, Guo and others 1996, Braun 1998, Benson and Forrest 1999, Hernandez-Divers and others 2005), in that they have paired metanephric kidneys, each containing a few thousand nephrons, compared with the million or so in most mammals. The reptilian nephron does not possess a loop of Henle, and the convoluted tubule (not the glomerulus) is supplied by a renal portal circulation. The distal tubule of mature male lizards undergoes hyperplasia during breeding periods, which causes gross and histological changes. The main nitrogenous product of most reptiles is uric acid; however, their renal function is otherwise not dissimilar from that of mammals and birds, with the osmoregulation of electrolytes and water balance being primary functions. Reptiles cannot concentrate urine above the concentration of plasma, although in several species there is significant post-renal modification of the urine across the bladder or cloacal membranes (Dantzler and Schmidt-Nielson 1966, Dantzler 1976).

The overproduction of, or failure to excrete, uric acid results in hyperuricaemia, which can lead to systemic or localised precipitation of urates in tissues (Agudelo and Wise 1991, Choy 2005, Kang and Nakagawa 2005). This condition is termed gout and is known to be painful in human beings. In captive reptiles, hyperuricaemia and gout have been associated with excess dietary protein and severe nephropathy (Keymer 1978a, b Montali and others 1979, Figureres 1997, Campbell 2006, Hernandez-Divers and Innis 2006, Mader 2006, Selleri and Hernandez-Divers 2006). Continued efforts in human medicine to improve the treatment of renal disease, hyperuricaemia and gout led to the development of allopurinol (4-hydroxypurinol), an isomer of hypoxanthine. Allopurinol is metabolised to oxypurinol by xanthine oxidase, and acts as a competitive antagonist of the enzyme that catalyses the conversion of hypoxanthine and xanthine to uric acid. It has been shown to be effective for decreasing blood uric acid levels in human beings, chimpanzees, chickens, turkeys and dogs (Weir and Fisher 1970, Czarnecki and others 1987, Smith and Wright 1987, Komoriya and others 1993, Bartges and others 1995, 1997b,) and has also been recommended for the treatment of ischaemia and leishmaniosis in dogs (Puig and others 1989, Emerit and Fabiani 1990, Liste and Gascon 1995, Kamau and others 2000, Colakoglu and others 2006, Pacher and others 2006).

The pharmacokinetics of allopurinol and its therapeutic effects have been studied in a variety of mammals and birds (Murrell and Rapeport 1986, Smith and Wright 1987, Bartges and others 1997a, b, Ling and others 1997, Poffers and others 2002). The bioavailability of allopurinol is unaffected by the presence of food but varies between species, being reportedly low in horses (14 per cent) and high in dogs and human beings (90 per cent) (Murrell and Rapeport 1986, Mills and others 1995, Bartges and others 1997b). The elimination half-life of allopurinol is short while that of its main metabolite, oxypurinol, is longer, and it accounts for most of the therapeutic effects. The drug is excreted mainly by the kidneys, but oxypurinol may accumulate in animals with renal dysfunction (Murrell and Rapeport 1986). In the red-tailed hawk (*Buteo jamaicensis*) oral allopurinol at 25, 50 and 100 mg/kg failed to prevent normal post-prandial hyperuricaemia, and at the higher doses caused toxic effects including vomiting and renal dysfunction (Poffers and others 2002). There have been several reports describing the beneficial effects of allopurinol in treating chelonians with hyperuricaemia and gout (Figureres 1997, Martinez-Silvestre 1997). However, there have been no controlled studies of the effects of allopurinol in any species of reptile.

To investigate the ability of allopurinol to decrease plasma uric acid levels in reptiles a therapeutic trial was conducted using the green iguana as a laboratory model. Green iguanas, maintained on either a normal vegetarian diet or a high protein (uricogenic) diet were medicated with either allopurinol or a placebo control for seven days. The effects of allopurinol were assessed by comparing the animals' bodyweights, plasma uric acid levels, plasma total protein and packed-cell volumes (PCV) before and after the treatment. In addition, possible microscopic changes were investigated by histology.

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MATERIALS AND METHODS

All the methods were evaluated and accepted by the University of Georgia's Institutional Animal Care and Use Committee. Nineteen green iguanas were maintained in facilities approved by the Association for Assessment and Accreditation of Laboratory Animal Care within the College of Veterinary Medicine. The lizards were two- to three-year-old subadult males weighing between 0·66 and 1·18 kg that had been maintained on an indigenous plant diet in outdoor enclosures in El Salvador during the previous 12 months. They were group housed in a dedicated animal room measuring 8 m X 6 m, with environmental control. Ten self-ballasted mercury vapour lamps (UVHeat; Westron Corporation) provided basking areas at 37°C and broad spectrum lighting during the day, and the diurnal air temperature in the room varied from 26 to 29°C. The relative humidity varied from 60 to 90 per cent, and the photoperiod was set to 12 hours light and 12 hours dark. The iguanas were provided with fresh water ad libitum, and mixed green leafy vegetables, supplemented with calcium carbonate, every morning. A hosepipe was left trickling and the room was sprayed daily to provide additional humidity and drinking opportunities. The iguanas were acclimatised for seven days before the start of the study, and all of them were eating, drinking, urinating, defecating and behaving normally.

Experimental design

The cross-over study was conducted in two phases. During phase 1, the 19 iguanas were fed a normal vegetarian diet and medicated orally with either allopurinol or a placebo control, once a day for seven days. Their bodyweights, plasma uric acid and total protein and PCV were recorded before and after the treatment to determine the effects of allopurinol. In phase 2 after a 10-day washout period, all the iguanas were fed a high protein diet to induce hyperuricaemia before they were treated in the same way.

Therapeutic trial

An oral suspension of 20 mg/ml allopurinol was compounded by using 100 mg tablets (Allopurinol; Qualitest Pharmaceuticals) in syrupalta syrup (Huma Texarkana) according to published guidelines (Dressman and Poust 1983). The 19 iguanas were physically examined, accurately weighed, individually numbered, and randomly assigned to one of two treatment groups. The 10 iguanas in group A received 1 ml of the allopurinol suspension (20 mg) and the nine in group B received 1 ml of syrupalta syrup by stomach tube every day for seven days. On day 1 the iguanas were examined, weighed and a blood sample (0·5 ml) was collected from the caudal (ventral tail) vein with a 3 ml syringe and 23 G 2·54 cm needle into a lithium heparin plasma separator tube (Microtainer; Becton Dickinson Vacutainer Systems), which was kept on ice and processed within an hour of collection. Each iguana was restrained in a vertical position with its mouth held open by a rubber gag. A 4·7 mm (14 Fr) feeding catheter (Tyco Healthcare) with dosing syringe attached was advanced into the stomach and the 1 ml dose was administered followed by 5 ml of sterile saline (Braun Medical).

Two haematocrit tubes were filled with blood from the heparin blood tube, and centrifuged at 5000 g for five minutes; the PCV was read from both tubes with a haematocrit reader (Damon-IEC Division) and the mean value was recorded. The tubes were then broken above the buffy coat, and the plasma total protein concentration was measured with a hand-held refractometer (Reichert). The heparin separator tubes were centrifuged at 13,460 g for five minutes and the plasma was decanted and stored at –70°C in microcentrifuge tubes (Eppendorf North America) until processed.

On day 8, the iguanas were again examined, weighed and blood samples were collected in the same way.

All the plasma uric acid determinations were run as a single batch within two weeks of collection using an enzymatic colorimetric assay (UA Plus, BMC Liq Uric Acid kit # 1661868; Roche Diagnostics) run on a BMC 912 chemistry analyser (Hitachi Nissei Sangyo America).

In phase 2, the iguanas were all maintained under the same management system, but each animal was supplemented with 10 ml Hills a/d (Hills Pet Nutrition) starting three days before the start of the drug trial. The nine iguanas remaining in group A now received 1 ml of syrupalta syrup and the nine in group B received 1 ml of allopurinol suspension by stomach tube every day for seven days. The same method was used except that the stomach tubes were flushed with 10 ml Hills a/d rather than sterile saline after dosing. On day 8 the animals were examined, weighed and blood samples were taken as before.

Postmortem examinations

The 19 iguanas were euthanased with intravenous pentobarbitone (Beuthanasia; Schering-Plough Animal Health) one week after the study was completed. They were examined thoroughly and, together with any abnormal tissues, samples of liver and kidney were removed from each iguana, placed into 10 per cent neutral buffered formalin, and examined histologically. Representative sections were processed, embedded in paraffin, sectioned at 5 μm, and stained with haematoxylin and eosin, periodic acid-Schiff, reticulin and periodic acid methanamine silver, and examined by light microscopy.

Statistical analysis

The data were analysed by using SAS v 9.1 (SAS Institute). A Student's t test ($\alpha=0·05$) was used to determine whether the diets affected the iguanas' uric acid, total protein, PCV or weight before they were treated, and a two-factor analysis of variance was used to determine whether the allopurinol or the diets affected the variables. An interaction term between the diets and the drug was also included, such that if P<0·10, indicating a potential interaction between them, then a Student's t test for effect of the drug was applied to each diet separately.

RESULTS

All the iguanas were clinically healthy as determined by physical examinations, their normal feeding and behaviour, and ultimately postmortem examinations. The mean (sd) and 95 per cent confidence intervals of their weight, uric acid, total protein, PCV and dose of allopurinol were determined (Table 1). During the 10-day washout period, one male iguana in group A sustained tail damage during an aggressive encounter with a second male; it was subsequently removed from the study and did not participate in phase 2.

No macroscopic abnormalities were observed postmortem but five random liver and kidney samples from group A and five from group B were evaluated histologically. The livers were normal. In the kidneys mild to marked sexual segment differentiation of the distal tubule was observed in three animals. The apical parts of the epithelial cells contained the characteristic eosinophilic globules present in sexually active male squamates. On slides where epididymal tubules were present spermatozoa were frequently observed. There were mild, adverse renal changes in only one of the lizards in group A, including protein deposition in the glomerular capillaries, mild thickening of the capillary basement membranes, and proximal tubular irregularity and broadening of the brush borders.

The five lizards in group B were more severely affected, with protein deposits in the glomerular capillaries and

thickening or splitting of the capillary basal membranes in three of them, proliferation of visceral epithelial cells of the Bowman's capsule in four, and proliferation of the parietal epithelium of the Bowman's capsule in two. In one animal, the urinary space of a few glomeruli contained a proteinaceous deposit. In three of the lizards the brush borders of the proximal tubules were irregular and broadened, there was cloudy swelling or vacuolation of the cellular protoplasm, pyknosis of the nuclei, and proteinaceous material within the lumen. In three of them there was necrosis of the epithelial cells, and degenerative changes in the distal tubules and collecting ducts ranging from vacuolation to necrosis. In one iguana the lumen of both the proximal and distal segments contained necrotic cells and the proteinaceous remnants of urate globules suggesting urinary stasis.

DISCUSSION

The dose of allopurinol that has been most commonly reported for reptiles is 20 mg/kg daily by mouth (Martinez-Silvestre 1997, Divers 1998, Diethelm 2005), but in one case report an allometrically scaled dose of 3·31 mg/kg was used (Figureres 1997). Given the lack of pharmacokinetic data in reptiles, the iguanas were all given approximately 20 mg/kg. The similarity in their bodyweights (0·81 [0·9] kg) resulted in a mean dose rate of 24·2 (3·2) mg/kg.

In an attempt to induce hyperuricaemia, the iguanas were fed a high protein supplement; their protein intakes from the vegetarian and high protein diets were estimated to be 1·0 g/kg/day and 2·5 g/kg/day, respectively. When fed the high protein diet their mean uric acid concentration was 218·3 (106·2) μmol/l, significantly higher (P=0·0028) than when they were fed the vegetarian diet (129·8 [70·8] μmol/l). On the high protein diet their total protein concentration was 83 (9) g/l, compared with 74 (6) g/l on the vegetarian diet (P=0·029). The high protein diet had no significant effect on their weight or PCV. Feeding a high protein diet, like Hills a/d, reliably induced hyperuricaemia and hyperproteinaemia in these iguanas, compared with those fed the lower protein vegetarian diet (Divers and others 1996, Harr and others 2001).

When the normo- and hyperuricaemic iguanas were treated with 24·2 (3·2) mg/kg allopurinol daily for seven days they had significantly lower uric acid values (100·3 [53·1] μmol/l) than the placebo-treated controls (159·3 [100·3] μmol/l) (P=0·020) and previously published reference ranges (Divers and others 1996, Harr and others 2001), a reduction of 41 to 45 per cent. There were no detectable interactions between the doses of allopurinol or placebo and the iguanas' diet, weight, PCV or total protein concentrations. During phase 1, both the pre- and post-treatment weights were significantly greater for group A (day 1, 0·88 [0·15] kg; day 8, 0·88 [0·14] kg) than group B (day 1, 0·76 [0·06] kg; day 8, 0·76 [0·06] kg); however, there were no significant interactions between their weight and uric acid, total protein, PCV, or treatment. This result was associated with the random selection of larger iguanas for group A.

Temperature has been shown to have inconsistent effects on drug pharmacokinetics in reptiles. For example, the pharmacokinetics of amikacin are affected by temperature in gopher snakes (*Pituophis melanoleucus catenifer*) (Mader and others 1985), but not in royal pythons (*Python regius*) (Johnson and others 1997). In the gopher tortoise (*Gopherus polyphemus*), the clearance of amikacin is affected by temperature but its half-life is not (Caligiuri and others 1990). The iguanas in this study were provided with a species-specific preferred optimum temperature range of 26 to 37°C, rather than a fixed temperature. It is possible that the variable environmental temperature may have affected the pharmacokinetics of allopurinol and its effects, but lizards' metabolic

processes tend to plateau rather than change proportionately with temperature when they are able to select a preferred body temperature from within their optimum range (Templeton 1964, Shoemaker and others 1966).

Allopurinol appeared to be well tolerated and did not cause any significant microscopic changes in the kidneys of the treated iguanas. In contrast there were several pathological changes in the placebo group. The aetiology of these changes is unclear; however, they may have been caused by high uric acid concentrations (or some other biochemical change) that was prevented by the treatment with allopurinol.

The oral dose of 24·2 (3·2) mg/kg of allopurinol daily for seven days appeared to be well tolerated and without adverse clinical or histological effects on these green iguanas. This dose can therefore be recommended for the treatment of hyperuricaemia in iguanas.

TABLE 1: Mean (sd) values and 95 per cent confidence ranges of the doses of allopurinol and the bodyweight, plasma uric acid, total protein, and packed-cell volume (PCV) of the green iguanas when they were fed a vegetarian or high protein diet, and medicated orally with either allopurinol or a placebo daily for seven days

Measurement		Phase 1 (vegetarian diet)*		Phase 2 (high protein diet)†	
		Group A (n=10) (allopurinol)	Group B (n=9) (placebo)	Group A (n=9) (placebo)	Group B (n=9) (allopurinol)
Allopurinol dose (mg/kg)		22·7 (3·8) 20·3-25·1	NA	NA	25·3 (2·6) 23·6-27·0
Weight (kg)	Day 1	0·88 (0·15) 0·79-0·97	0·76 (0·06) 0·73-0·80	0·80 (0·08) 0·75-0·86	0·8 (0·08) 0·74-0·85
	Day 8	0·88 (0·14) 0·79-0·97	0·76 (0·07) 0·72-0·80	0·81 (0·08) 0·76-0·86	0·81 (0·09) 0·75-0·87
Uric acid (μmol/l)	Day 1	130·4 (82·4) 51·1-79·3	123·2 (65·4) 82·7-163·8	207·8 (116·9) 131·5-284·2	226·2 (95·9) 163·5-288·8
	Day 8	77·3 (33·7) 20·9-56·4	99·6 (46·9) 70·6-128·7	213·1 (109·1) 141·8-284·4	123·9 (66·8) 80·2-167·6
Total protein (g/l)	Day 1	76 (6) 72-80	76 (7) 71-80	78 (10) 71-84	84 (8) 79-90
	Day 8	75 (6) 71-79	73 (6) 70-77	83 (8) 78-88	83 (11) 76-90
PCV (l/l)	Day 1	0·36 (0·03) 0·34-0·38	0·37 (0·04) 0·35-0·40	0·38 (0·05) 0·34-0·41	0·39 (0·06) 0·35-0·43
	Day 8	0·35 (0·03) 0·33-0·36	0·36 (0·04) 0·34-0·38	0·33 (0·03) 0·31-0·35	0·31 (0·05) 0·28-0·35

* Estimated protein intake 1·0 g/kg/day
† Estimated protein intake 2·5 g/kg/day
NA Not applicable

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