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ORIGINAL ARTICLE

Effects of cyclooxygenase inhibitor treatment on the renal toxicity of cisplatin in rats

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Abstract
Purpose The purpose of this study was to determine the effects of a nonselective cyclooxygenase (cox) inhibitor and of a selective cox-2 inhibitor on the renal toxicity of cisplatin.
Methods Cisplatin with or without a cox-1 inhibitor (SC560), a cox-2 inhibitor (SC236), or a nonselective cox inhibitor (piroxicam) was administered to Sprague–Dawley rats. Renal toxicity was assessed by serum creatinine concentration (SCR), urine specific gravity (USG), and histopathologic lesion score (HLS).
Results Acutely, the SCR was significantly higher in rats receiving cisplatin/SC560 (1.62 ± 0.34 mg/dl) or cisplatin/piroxicam (2.0 ± 0.41 mg/dl) than in rats receiving cisplatin alone (1.09 ± 0.40 mg/dl). The apparent increase in SCR in the rats receiving cisplatin/SC236 (1.58 ± 0.31) was not significantly different from that of rats receiving cisplatin alone (1.09 ± 0.40 mg/dl). No significant differences in USG or HLSs were noted between rats receiving cisplatin alone and cisplatin combined with any cox inhibitor. In a chronic study, no differences in renal toxicity were found between rats treated with cisplatin alone and cisplatin/SC236 or cisplatin/piroxicam.
Conclusions The acute rise in SCR following cisplatin treatment can be worsened by the addition of cox inhibitors, especially those that inhibit cox-1.

Keywords Cisplatin · Cyclooxygenase inhibitor · Cox-2 inhibitor · Renal toxicity

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Introduction

Cisplatin is a widely used chemotherapeutic agent for the treatment of several forms of cancer including urinary bladder cancer [1, 2]. World Health Organization figures indicate that more than 300,000 people develop urinary bladder cancer worldwide, and more than 130,000 people die from the cancer yearly. The most aggressive and lethal form of bladder cancer is intermediate to high grade invasive transitional cell carcinoma (InvTCC). Improved medical therapy for InvTCC is needed. Cisplatin is considered one of the most active chemotherapeutic agents for InvTCC [1, 2]. The nonselective cyclooxygenase (cox) inhibitor, piroxicam, has greatly enhanced the antitumor activity of cisplatin in pet dogs with naturally occurring InvTCC where the cancer closely mimics the human condition [3, 4]. In a randomized study, the remission rate was significantly greater in dogs receiving cisplatin/piroxicam (71%) than in dogs receiving cisplatin alone (<20%) [3]. Unfortunately, cisplatin/piroxicam was associated with unacceptable renal toxicity [reduction in glomerular filtration rate (GFR) as well as decrease in USG]. The renal toxicity was thought to be due to renal tubule damage induced by cisplatin and

reduced renal blood flow exacerbated by cox inhibition [5–8]. With the predominant form of cox in renal arterioles being cox-1, a selective cox-2 inhibitor would be expected to have less effect on renal blood flow and on cisplatin renal toxicity [9–14]. The predominant isoform of cox in InvTCC cells is cox-2 [15, 16], and there is evidence that cox-2 inhibitors also have antitumor activity against bladder cancer [17]. The objective of this study was to determine the renal toxicity of cisplatin alone compared to cisplatin combined with a selective cox-2 inhibitor. The hypothesis was that cisplatin combined with a cox-2 inhibitor would be no more toxic to the kidneys than cisplatin alone. For comparison, treatment groups also included cisplatin/nonselective cox inhibitor and cisplatin/selective cox-1 inhibitor. Rats were selected for the proposed studies because cisplatin toxicity is well characterized in the rats and appears similar to cisplatin toxicity in humans and dogs [18–20].

Materials and methods

All animal studies were performed in the Clinical Discovery Laboratory, Department of Veterinary Clinical Sciences, Purdue University with approval of the Purdue Animal Care and Use Committee. Subjects for the studies were male, Sprague–Dawley rats (250–300 g) which were acclimated to the facility for 3–5 days prior to study. Work included a pilot study in rats to select the most appropriate dose of cisplatin for subsequent studies, a 5-day acute toxicity study, and a 1-month chronic toxicity study. Cisplatin (AmerisourceBergen, Chesterbrook, PA, USA) and the nonselective cox inhibitor, piroxicam (PCCA, Houston, TX, USA) were purchased. SC236 (selective cox-2 inhibitor) and SC560 (selective cox-1 inhibitor) were provided by J. Masferrer, Pharmacia Corporation (Skokie, IL, USA). SC236 and SC560 were selected for their 1,000-fold specificity for cox-2 and cox-1, respectively, and also for their well-defined pharmacology and dosing in rats ([11, 21–23], unpublished data, J. Masferrer, Pharmacia/Pfizer).

Pilot study to select cisplatin dose

A pilot study was performed to determine a dose of cisplatin that would cause moderate toxicity, and thus the opportunity to detect more severe toxicity in rats receiving combination treatment in subsequent studies. Doses used in the pilot study were selected from studies in the literature [24, 25]. Assessment of renal toxicity included differences in serum creatinine concentration (SCR) and histopathologic changes in kidney tissue (HLS).

Rats were randomized (4 rats/group) to receive the following cisplatin doses: 2.5, 4.0, 6.0, and 7.5 mg/kg. Cisplatin was diluted to a total volume of 2.5 ml in normal saline and given intraperitoneally (ip). Performance status was monitored, and toxicity was categorized as in Table 1. Any rat having unacceptable performance (having two or more criteria in Group I or one or more criteria in Group II) was to be humanely killed. Four days following cisplatin injection, rats were euthanatized [1 ml, 55 mg/ml of pentobarbital ip (Beuthanasia D solution, Schering-Plough Corporation, Union, NJ, USA)]. Blood was collected for measurement of SCR, and renal tissue harvested for scoring morphologic changes in the kidneys (HLS).

Histopathology of formalin-fixed paraffin-embedded tissues was performed by a board-certified veterinary pathologist (J. Ramos-Vara). Five micrometer thick sections were stained with hematoxylin and eosin (H&E), and both kidneys were examined. While reading histopathology slides, the pathologist was blinded to the treatment of each rat. Histopathologic changes in the renal tubules were assessed in 6 categories: (1) necrosis, (2) dilation of tubule lumens, (3) epithelial desquamation, (4) presence of casts, (5) inflammation, and (6) regeneration as described previously in cisplatin toxicity studies [24–27]. Renal lesions were scored on a scale of 0–3 (0 = no lesions detected in renal tubules, 1 = minimal lesions, 2 = moderate lesions, and 3 = severe lesions). To help summarize the differences in histopathologic findings, a single HLS was generated for each rat by averaging the score for each of the first five categories in that rat. The desired cisplatin dose selected for further study was one that caused detectable renal toxicity (HLS 1–2), but not overly severe renal toxicity.

Acute toxicity study of cisplatin alone and cisplatin combined with cox inhibitors

Rats were randomized to the following treatment groups (8 rats/group): (1) cisplatin [dose determined in the pilot study, on treatment day 1], (2) selective cox-2 inhibitor SC236 (6 mg/kg by oral gavage given once the day before cisplatin), (3) selective cox-1 inhibitor SC560 (6 mg/kg/day by oral gavage), (4) nonselective cox inhibitor piroxicam (6 mg/kg twice daily by oral gavage), (5) cisplatin/SC236, (6) cisplatin/SC560, (7) cisplatin/piroxicam, (8) ip saline (cisplatin vehicle) on treatment day 1, and (9) ip saline on

Table 1 Criteria of performance alteration in rats

Group I Criteria	Group II Criteria
Absence of grooming behavior	Inability to eat or drink
Eyes fully/partially closed	Failure to right itself when placed on back
Markedly diminished resistance to restraint	Dyspnea
Markedly decreased movement	

treatment day 1 and vehicle for cox inhibitor via gavage. Administration of the cox inhibitors was begun the day before cisplatin was given. The same doses of cisplatin and cox inhibitors were used in the single agent treatments and in the combination treatments. Cox inhibitor treatments were administered between 8:00 and 10:00 a.m. (to avoid any differences in drug metabolism that could occur if the drugs were given at variable times during the rat-photoperiod). The afternoon dose of piroxicam was given between 3:00 and 5:00 p.m. (half-life indicated BID dosing). Cisplatin was given in the middle of the day (at least 2 h after the morning cox inhibitor dosing).

Cisplatin treatments were given on Monday (treatment day 1). On Friday (treatment day 5), rats were euthanized. At the time of death, blood was collected to measure SCR, and urine was collected to measure USG. (Note: initial plans had included measuring urine osmolality and biochemical assays of cisplatin-induced tubular damage, but the volume of urine collected was not sufficient for those analyses.) Necropsy was performed with collection of renal tissue. Renal lesions viewed on H&E stained slides were scored by Dr. Ramos-Vara as described in the pilot study.

Chronic toxicity study of cisplatin alone and cisplatin combined with cox inhibitors

The chronic toxicity study was performed similar to the acute toxicity study except the cox inhibitor treatment was given for 4 weeks. Treatment groups (8 rats/group) included: (1) cisplatin alone (dose selected from pilot study, given once at the beginning of the 4 week period), (2) cisplatin/SC236 with the SC236 being given weekly, (3) cisplatin/piroxicam with the piroxicam being given twice daily, and (4) vehicle control. SC236 has a half-life of 117 h in rats, and cox-2 inhibition has been detected at least for a week followed by dosing (unpublished data, J. Masferrer, Pharmacia/Pfizer). Rats were euthanized after 4 weeks of treatment.

Confirmation of selective cox-1 or cox-2 inhibition by whole blood assay

Cox-1 activity was assessed by thromboxane B_2 release from platelets during coagulation. Cox-2 activity was assessed by prostaglandin E_2 release from stimulated peripheral blood monocytes. For the cox-1 function assay, blood (1–2 ml) was collected and immediately incubated for 10 min at 37°C in a clot tube. Following incubation, the tube was centrifuged for 10 min, and the serum collected and frozen at −80°C until analyzed. Thromboxane B_2 formed when the clotted blood was measured with a competitive ELISA (Assay Designs, Ann Arbor, MI, USA). For the cox-2 function assay, blood (2 ml) was collected, and aliquots of 1 ml each was placed in tubes with sodium heparin. LPS (endotoxin, final concentration 10 μg/ml) used to stimulate cox-2 activity in monocytes was added to one tube. Both tubes were incubated for 24 h at 37°C. Tubes were then centrifuged for 10 min, and the plasma collected and frozen at −80°C until analyzed. Prostaglandin E_2 was measured with a competitive ELISA (Cayman Chemical, Ann Arbor, MI, USA).

Statistical analyses

Statistical analysis was performed using SAS (Version 9.1) for Windows. Treatment groups were summarized using the sample mean and standard deviation. In both the acute and chronic studies, a set of specific pairwise treatment comparisons (*t* tests) of interest were included across several different end-points. To handle this multiple testing problem, the Bonferroni multiple comparison adjustment was implemented using PROC MULTTEST. The group means were deemed significant when the adjusted *P* value was less than 0.05.

Results

Pilot study to select cisplatin dose

Dose-related renal toxicity was observed in the pilot study. The cisplatin dosage of 6 mg/kg was selected for the subsequent studies. The mean SCR in rats receiving this dose was 2.0 ± 1.22 mg/dl (reference range 0.05–0.65 mg/dl). HLSs were moderate in rats in this treatment group (mean HLS 1.75). Rats in this group had good performance status.

Acute toxicity study of cisplatin alone and cisplatin combined with cox inhibitors

Change in body weight

During the 5-day acute toxicity study, rats in treatment groups that received cisplatin lost body weight, while rats not receiving cisplatin gained weight (Fig. 1). Rats in all groups remained active, and did not demonstrate signs of toxicity listed in Table 1.

Change in SCR

The SCRs in rats treated with single agent either SC560 or SC236 were not different from that of untreated rats (Fig. 2). Rats receiving piroxicam alone had a slight (although not significant) increase in SCR (Fig. 2). The SCR was significantly higher ($P < 0.05$) for rats in all cisplatin-containing treatment groups than in control animals. The SCR was higher ($P < 0.05$) in rats receiving cisplatin/SC560

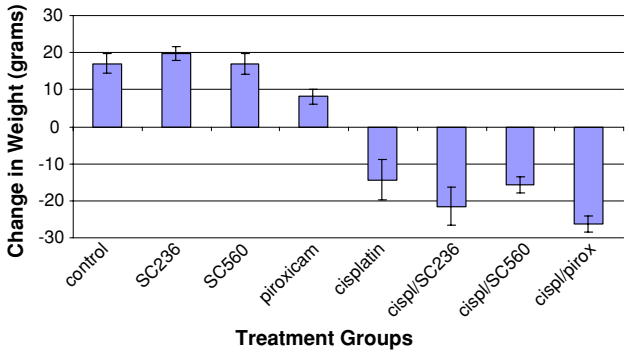

Fig. 1 Change (mean ± SE) in body weight (grams) in rats (8 rats/group) over the 5-day treatment period

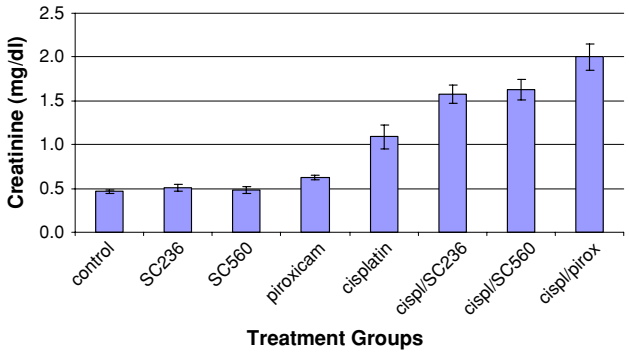

Fig. 2 Serum creatinine concentration (SCR, mg/dl; mean ± SE) in rats (8 rats/group) treated with drugs listed or with vehicle control for 5 days. Rats received cisplatin on treatment day one. Euthanasia was performed, and blood was collected for SCR measurement on treatment day 5. The SCR was significantly higher in rats treated with cisplatin (alone or in combination with cox inhibitors) than in control rats. The SCR was significantly higher in rats treated with cisplatin/SC560 or cisplatin/piroxicam than in rats treated with cisplatin alone

(1.62 ± 0.34 mg/dl) and in rats receiving cisplatin/piroxicam (2.0 ± 0.41 mg/dl) than that of rats receiving cisplatin alone (1.09 ± 0.40 mg/dl). There was a trend for SCR in rats receiving cisplatin/SC236 (1.58 ± 0.31) to be higher than of rats receiving cisplatin alone, but significant differences ($P < 0.052$) were not found. The highest mean SCR was noted in rats receiving cisplatin combined with the nonselective cox inhibitor piroxicam (2.0 ± 0.41 mg/dl).

Results of the whole blood assay confirmed the selective inhibition of SC560 for cox-1 and of SC236 for cox-2 (data not shown).

Change in HLS

Morphologic changes in the kidneys were noted in rats receiving cisplatin and in rats receiving cisplatin and any of the cox inhibitors (Figs. 3, 4). Changes in each of the individual categories of histopathologic lesions were determined, i.e., (1) necrosis, (2) dilation of tubule lumens,

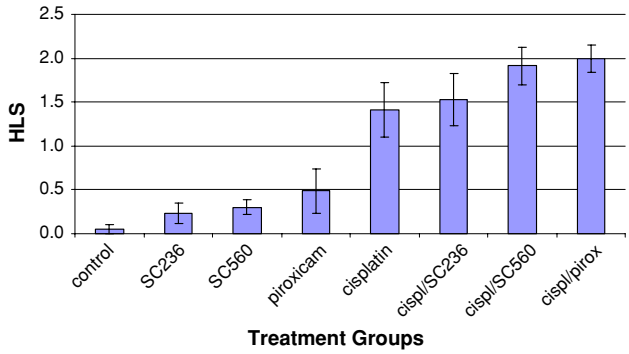

Fig. 3 Histopathologic lesion score (HLS, as defined in text) for rats receiving cisplatin alone, cisplatin/cox inhibitor, or vehicle control in the 5 day study. The mean HLS was calculated by averaging the scores for necrosis, lumen dilation, epithelial desquamation, casts, and inflammation. The mean ± SE of the HLS for each group of 8 rats is reported here. The HLS was significantly higher for rats treated with cisplatin (alone or in combination with any of the cox inhibitors) than in control rats. There were no significant differences in HLSs between rats in any of the cisplatin-containing treatment groups

(3) epithelial desquamation, (4) presence of casts (5) inflammation, and (6) regeneration. Significantly higher lesion scores ($P < 0.05$) were noted in lesion categories 1–4 between rats in the control group and rats in any of the cisplatin-containing treatment groups. No significant differences were noted in the lesions between rats receiving cisplatin and rats receiving cisplatin/cox inhibitor treatment. Similarly, when combining scores in lesion categories 1–5 for an overall "HLS", scores were significantly higher for rats receiving cisplatin (1.43 ± 0.92) than for rats in the control group (0.05 ± 0.2). Although the HLS appeared higher in rats treated with cisplatin/SC560 (1.93 ± 0.79) or with cisplatin/piroxicam (2.0 ± 0.56) than the rats treated with cisplatin alone (1.43 ± 0.92), significant differences were not noted. An apparent slight, but insignificant increase in HLS was noted in rats receiving single agent piroxicam compared to control rats.

Change in USG

The USG was significantly lower ($P < 0.05$) in rats treated with cisplatin (1.023 ± 0.003), cisplatin/SC236 (1.023 ± 0.003), cisplatin/SC560 (1.022 ± 0.002) or cisplatin/piroxicam (1.022 ± 0.004) than that in control rats (1.035 ± 0.011).

Chronic toxicity study of cisplatin alone and cisplatin combined with cox inhibitors

Change in body weight

Initial weight loss was noted in rats receiving cisplatin or cisplatin/cox inhibitor treatment, similarly to that observed in the acute study. By week 2, however, the body weight

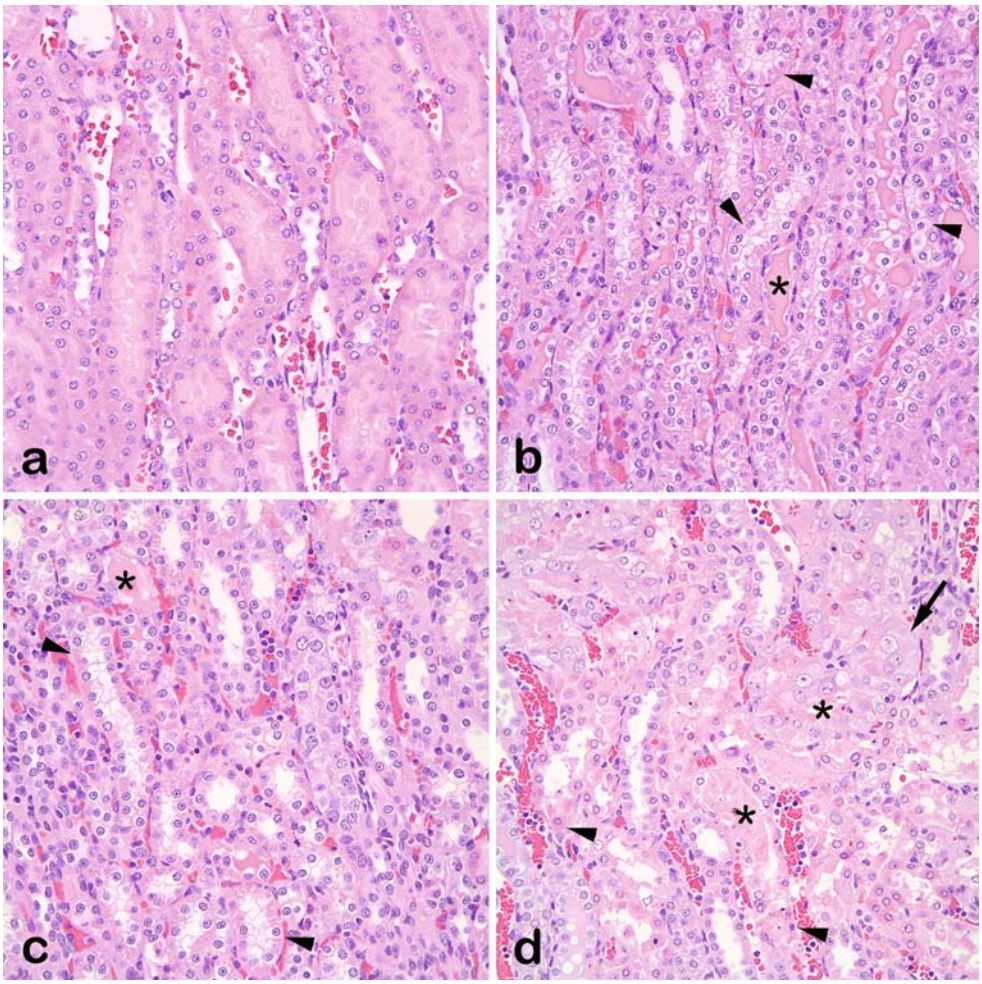

Fig. 4 **a** Photomicrograph of kidney from control rat. No evidence of tubular degeneration or necrosis is noted. **b** Kidney from rat treated with cisplatin alone. Note tubular degeneration which is characterized by marked cytoplasmic vacuolation of the apical border of lining epithelial cells (*arrowheads*). Proteinaceous material within tubular lumens (*asterisk*) is noted. **c** Kidney from rat treated with cisplatin and SC236. Tubular degeneration (*arrowheads*) is similar in severity to that present in the kidneys of rats treated with cisplatin alone. Protein within tubular lumen (*asterisk*) is noted. **d** Kidney from rat treated with cisplatin and piroxicam. Severe tubular degeneration and necrosis are present. Casts (*asterisks*) of cellular debris in several tubular lumens are noted. Most tubules contain necrotic epithelial cells (*arrowheads*). There is evidence of regeneration in tubular epithelial cells (*arrow*)

was beginning to increase in treated rats. After 1 month the average weight gain was 78 ± 10 g in control rats, 54 ± 12 g in rats receiving cisplatin, 56 ± 15 g in rats receiving cisplatin/SC236, and 36 ± 9 g in rats receiving cisplatin/piroxicam.

Change in SCR

The SCR at 4 weeks post cisplatin treatment was not different between rats in the treatment and control groups (Fig. 5).

Change in HLS

The HLSs were higher in rats receiving cisplatin (1.0 ± 0.57) or cisplatin/cox inhibitor (1.0 ± 0.63) than in rats receiving only vehicle alone (0.05 ± 0.2) (Fig. 5). There were no differences in HLS between rats receiving cisplatin/SC236, cisplatin/piroxicam or cisplatin alone.

Change in USG

There were no significant differences in USG between rats treated with cisplatin (1.037 ± 0.005), cisplatin/SC236 (1.036 ± 0.008), cisplatin/piroxicam (1.025 ± 0.007) or vehicle control (1.034 ± 0.013).

Discussion

Cisplatin is one of the most active chemotherapeutic agents for the treatment of InvTCC [1, 2]. This cancer takes the

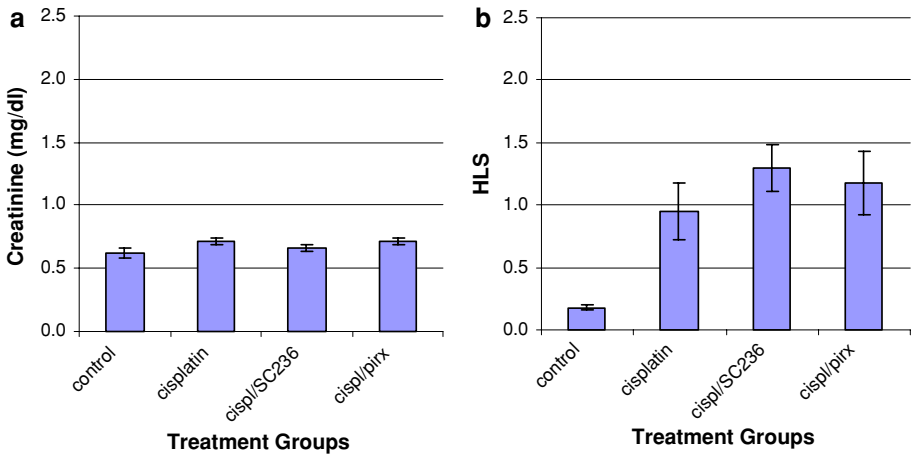

Fig. 5 Serum creatinine concentration (SCR, mg/dl, **a**), and histopathologic lesion scores (HLS, as defined in text, **b**) in rats treated with cisplatin, cisplatin/cox inhibitor or vehicle control (4-week treatment). The mean ± SE for each group (8 rats/group) is reported. Blood samples were collected 4 weeks after cisplatin administration. The HLSs in rats treated with any of the cisplatin-containing treatments were significantly higher than in control rats

lives of more than 130,000 people worldwide every year. One strategy for improving therapy of InvTCC is to increase the efficacy of cisplatin-containing protocols. Intriguing enhancement of cisplatin antitumor effects by a nonselective cox inhibitor has been observed in dogs with naturally occurring InvTCC where the cancer closely mimics the human condition [3, 4]. Unfortunately, the addition of the nonselective cox inhibitor to a cisplatin protocol in dogs resulted in unacceptable renal toxicity. It was anticipated, however, that selective cox-2 inhibitors could also enhance the antitumor activity of cisplatin because the predominant isoform of cox expressed in InvTCC is cox-2 [15, 16] and that cox-2 inhibitors would have less deleterious effects on kidney function when combined with cisplatin. Cox-1 is the predominant isoform of cox in renal arterioles, and is thought to have a major role in the regulation of renal blood flow [9–14]. This is important when considering cisplatin effects on the kidneys. Following cisplatin tubular damage, a reduction in GFR occurs due to tubuloglomerular feedback and reduction in renal blood flow [5, 6, 28]. Prostaglandins, predominantly of cox-1 origin, counter balance afferent renal vessel constriction thus limiting the reduction in renal blood flow induced by tubular damage. Inhibition of cox-1 can exacerbate the reduction in renal blood flow and GFR. It is acknowledged, however, that the kidneys of rats, dogs, and humans are not devoid of cox-2 expression [9–14], and cox-2 metabolites have been implicated in mediation of renin release, regulation of sodium excretion, and maintenance of renal blood flow to some extent [29].

The results of this study in rats confirm that drugs that inhibit cox-1 (nonselective cox inhibitors and selective cox-1 inhibitors) when combined with cisplatin result in a significantly greater reduction in GFR (measured as SCR) when compared to cisplatin alone. Because of similarities between cisplatin toxicity in rats and humans [18–20], the results of the rat study raise potential concern for the clinical use of cisplatin combined with nonselective cox inhibitors. Studies to define the risks (potential increase in renal toxicity) and benefits (possible increase in antitumor activity) of cisplatin/nonselective cox inhibitor treatment in humans have been limited. Pending results of any further studies, it would appear appropriate to take caution in situations where cisplatin and a nonselective cox inhibitor could be administered together.

In addition to the significant effects of nonselective cox inhibitors on the renal toxicity of cisplatin, a trend (although not significant) was observed for worsening of the cisplatin-induced reduction in GFR by a cox-2 inhibitor. Further studies are indicated to define the risk: benefit ratio of combining cisplatin with a cox-2 inhibitor in urinary bladder cancer and other cancers. Studies that include multiple doses of cisplatin and more prolonged therapy may also be important. A study is ongoing at our institution to determine the effects of a selective cox-2 inhibitor in enhancing the antitumor activity of cisplatin (multiple doses) and effects on renal toxicity in dogs with naturally occurring InvTCC, where the cancer closely mimics human invasive urinary bladder cancer. In this canine study, the use of cisplatin doses that are typically well tolerated and the inclusion of a saline diuresis protocol are expected to minimize toxicity, i.e., to follow an approach more similar to what is used in humans. Iohexol clearance assessment is also being included in the dog study to detect more subtle changes in GFR.

The results of this study were encouraging in that the addition of the cox inhibitors to cisplatin treatment did not cause any worsening of the HLS or changes in USG in the acute study. This was also true in the chronic toxicity study in which there were no differences in HLSs between rats receiving cisplatin and rats receiving cisplatin combined with the cox inhibitors. Although histopathologic lesions persisted, it was not unexpected that the chronic toxicity study also demonstrated normalization of the SCR. Following cisplatin renal toxicity in humans and dogs, some improvement in GFR may be noted when the drug is withdrawn [3, 30].

At the onset of this study, the intent was to include additional tests of tubular function to assess cisplatin-induced tubular damage (urine osmolality, urine GGT/creatinine ratio, other biochemical tests) although the expectation was that tubular damage would be similar across all cisplatin-treated groups. Unfortunately, the volume of urine available from the rats was not sufficient for these additional assays. The inclusion of these types of assays in future studies would assist in more precisely localizing the site of tubular damage in the rats treated with cisplatin and various cox inhibitors. Assessment of creatinine clearance could also be considered in future studies. Although SCR reflects global kidney function, this test is insensitive for detecting damage until greater than 60–75% of nephrons are non-functional. More subtle change in kidney function may be detected by creatinine clearance or other measures of GFR, especially if less toxic doses of cisplatin are studied.

In conclusion, this study demonstrated worsening of cisplatin-induced renal toxicity (as measured by changes in SCR) by drugs that inhibit cox-1 activity. There was a trend for worsening of this toxicity by a selective cox-2 inhibitor. Further studies are ongoing to define the risk:benefit ratio of cisplatin combined with a selective cox-2 inhibitor.

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