

Effects of Tepoxalin and Medetomidine on Glomerular Filtration Rate in Dogs

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(Received 10 February 2012/Accepted 29 August 2012/Published online in J-STAGE 14 September 2012)

ABSTRACT. The objective of this study was to evaluate glomerular filtration rate (GFR) and the cardiovascular effects of the combination of tepoxalin (TPX) and medetomidine (MED) in dogs. Six healthy dogs of either sex (5 males and 1 female), aged 2.5 ± 2.2 years and weighing 14.7 ± 4.4 kg, were studied. Each dog received four randomized treatments with a minimum of 1 week between treatments: no medication as the control group (C); MED ($750 \mu\text{g}/\text{m}^2$, intravenously [IV]); TPX (10 mg/kg orally for 3 days); and MT (TPX 10 mg/kg orally for 3 days plus MED $750 \mu\text{g}/\text{m}^2$, IV). Iohexol (300 mg iodine/kg, IV) was injected in all dogs in each treatment as an indicator of GFR. Blood samples for serum iohexol clearance analysis were collected before and 1, 2, 5, 10, 15, 20, 60, 120, 240 and 360 min after the iohexol administration. Rectal temperature, heart rate, respiratory rate and direct arterial pressure (AP) were obtained before and 5, 10, 15, 20, 60, 120, 240 and 360 min after the iohexol injection. GFR did not differ between treatments. Heart rate was significantly lower in the MED and MT groups than in C or TPX. Mean AP was significantly higher with MT than TPX, but only at 5 min after the iohexol injection. TPX, MED and the combination of these two drugs do not alter GFR. The combination has minimal effect on cardiovascular variables at these doses in healthy dogs.

KEY WORDS: canine, glomerular filtration rate, medetomidine, tepoxalin.

doi: 10.1292/jvms.12-0062; *J. Vet. Med. Sci.* 75(1): 69–74, 2013

Non-steroidal anti-inflammatory drugs (NSAIDs) are a widely used group of agents in veterinary medicine. Use of NSAIDs may be associated with significant adverse effects and numerous different active agents have been manufactured in recent years. Drugs having higher cyclooxygenase (COX)-II selectivity are preferred by many veterinarians, because of a potential lower incidence of these adverse effects. Potential adverse effects associated with NSAID administration include gastrointestinal injury, renal injury, and hepatic injury in animals [29], and also cardiovascular risks such as thromboembolic disease in humans [7, 38]. Prostaglandins (PGs) may be synthesized in response to a variety of insults, and these compounds act as mediators contributing to pain and inflammation. Inhibition of the production of PGs synthesized in response to insults can reduce inflammation and provide analgesia [2, 6]. PGs having beneficial effects are produced normally in the absence of inflammatory insults and serve to maintain blood flow and function to the renal, hepatic, and cardiovascular systems [2, 6, 13, 29]. Documented adverse effects of NSAIDs are a result of the ability of these agents to inhibit the production of beneficial PGs as well as those mediating inflammation. The NSAIDs may inhibit one or more of several pathways

of PG formation. The cyclooxygenase-1 (COX-1) pathway produces PGs that are constitutive and have activity in renal arterioles, collecting ducts, and glomeruli as well as in many other organs [6]. These COX-1-derived PGs function to maintain blood flow and function to a variety of tissues. The COX-2 pathway is inducible, and the effects of its PG end products on the kidney differ depending upon species. The COX-2-derived PGs are thought to be generated primarily due to the effects of inflammation [2, 6, 13, 29]. Highly COX-2 selective NSAIDs are not always associated with minimal effects on renal function [29]. In contrast to the vasodilation produced by PGs, leukotrienes (LTs) which are produced by oxidation of arachidonic acid by 5-lipoxygenase (LOX) have been shown to produce renal vasoconstriction. Inhibition of COX-1, COX-2 or both COX-1 and 2 enzymes has been shown to divert arachidonic acid to the 5-LOX pathway with resultant increased production of leukotrienes [2]. This imbalance between COX and LOX metabolites can ultimately result in untoward renal consequences [13]. The contribution of LOX-derived LTs to inflammation has encouraged development of NSAIDs that inhibit both the COX and LOX pathways. These dual inhibiting agents may enhance gastrointestinal safety and provide improved analgesia compared with COX inhibition alone [29].

Tepoxalin is a dual acting NSAID that effectively inhibits both COX and LOX pathways, and also inhibits the production of thromboxane, PGE_2 , $\text{PGF}_{2\alpha}$ and LTB_4 in dogs [6, 29]. The drug has a gastrointestinal safety profile that matches other higher COX-2 selective inhibitors and, due to LOX inhibition, may have greater gastrointestinal safety

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and anti-inflammatory efficacy [1, 2, 20]. Tepoxalin is also reported to have little renal toxicity in dogs and rats [21].

Medetomidine is an α_2 -adrenoceptor agonist that exhibits potent sedation, muscle relaxation, analgesia, and reversibility. Clinically, the drug has been used to provide sedation and analgesia in patients presenting for procedures such as radiography, bandaging, wound debridement, and physical examination. Similar to the effects of all clinically used α_2 adrenoceptor agonist sedatives, medetomidine has profound cardiovascular effects that are due primarily to α_{2B} -adrenoceptor mediated peripheral vasoconstriction as well as α_{2A} -adrenoceptor mediated central sympathetic effects [24, 26]. These significant cardiovascular effects may have negative effects on renal physiology.

A variety of NSAIDs are administered to clinical patients presenting for painful orthopedic conditions, and many of these patients may also require sedation with an α_2 adrenoceptor agonist drug. Several NSAIDs, including tepoxalin, have been shown to have no adverse effects on renal function during general anesthesia [3–5, 9, 18, 22]. The α_2 -adrenoceptor agonist guanabenz was shown to decrease renal blood flow when it was administered following a NSAID drug indomethacin [35]. However, there are no reports of the renal effects of concurrent administration of medetomidine and tepoxalin in dogs. The objective of this study was to assess the glomerular filtration rate (GFR) in healthy dogs administered tepoxalin, medetomidine or the combination of tepoxalin and medetomidine.

MATERIALS AND METHODS

Six healthy dogs (4 Beagles and 2 mixed hound dogs; 5 intact males and 1 intact female), weighing 10.5 to 22 kg (14.7 ± 4.4 kg, average \pm SD) and aged 10 months to 6 years old (2.5 ± 2.2 years old), were studied. All dogs were fed twice daily and given water *ad libitum*. Food, but not water, was withheld for 12 hr prior to the study. The experimental protocol was approved by the Washington State University Institutional Animal Care and Use Committee.

Physical examination, complete blood count, blood chemistry profile, and urine analyses were completed in all dogs one week prior to the first study day. Each dog received the following four treatments with at least a one-week wash out period in randomized order: no medication as control (group C); tepoxalin (Zubrin, Schering-Plough Animal Health, Summit, NJ, U.S.A.) 10 mg/kg, orally (PO) for 3 days (group T); medetomidine (Domitor, Pfizer, New York, NY, U.S.A.) 750 mg/m², intravenously (IV) (group M); tepoxalin 10 mg/kg, PO for 3 days and medetomidine 750 mg/m², IV (group TM.) Calculation of body surface area (BSA, m²) was accomplished using the following formula [30].

$$BSA (m^2) = \frac{10.1 \times BW (g)^{2/3}}{10^4}$$

Instrumentation: On the day of the study, 3 intravascular catheters and an arterial catheter were inserted aseptically in each dog facilitated by lidocaine (Lidocaine Hydrochloride Injectable 2%, Vetco, Saint Joseph, MO, U.S.A.) local

analgesia. A 4.78 cm-20 SWG indwelling catheter (BD Insyte, Becton Dickinson, Sandy, UT, U.S.A.) was placed into a cephalic vein to permit injection of medetomidine and iohexol. A 4.78 cm-18 SWG indwelling catheter (BD Insyte, Becton Dickinson; in Beagles) or a 30.5 cm-19 SWG catheter (Intracath, Becton Dickinson; in mixed hound dogs) was placed into the jugular vein to permit sampling of blood, and a 2.54 cm-22 SWG indwelling catheter (BD Insyte, Becton Dickinson) was placed into the dorsal pedal artery to permit recording of arterial blood pressure. Heart rate (HR) was obtained by palpation of the chest and respiratory rate (RR) was counted by palpation or observation of the chest movements. The HR and RR data were counted for 60 sec. Body temperature (BT) was measured using a rectal thermometer (Model 600, Diatek, San Diego, CA, U.S.A.). Direct arterial pressure (AP) was determined using a patient monitor (M1092A, Hewlett Packard, Andover, MA, U.S.A.) connected to a calibrated pressure transducer (TruWave Disposable Pressure Transducer with Stopcock PX600, Edwards Lifesciences, Irvine, CA, U.S.A.) that was placed and zeroed to the level approximating the dog's sternum.

Study design: In groups T and TM, tepoxalin was administered orally on the morning of the study day and each morning for the two days prior to the study day. A small biscuit (Gentle Snackers, Purina, St. Louis, MO, U.S.A.) was fed with tepoxalin to facilitate absorption. One to three hr following tepoxalin administration on the day of the study, the catheters were inserted and the following baseline measurements were recorded: HR, RR, BT, systolic (SAP), diastolic (DAP) and mean (MAP) direct arterial blood pressure. In groups M and TM, medetomidine was administered after measurement of baseline values and 15 min prior to the injection of the GFR indicator, iohexol. In all groups, HR, RR, BT, SAP, DAP and MAP were determined 5, 10, 15, 20, 60, 120, 240 and 360 min after the injection of iohexol.

Glomerular filtration rate measurements: The GFR of each dog was estimated by serum iohexol concentration analysis using high performance liquid chromatography (HPLC). Following recording of baseline values, iohexol (Omnipaque injection 300, GE Healthcare, Princeton, NJ, U.S.A.) (300 mg iodine/kg, IV) was injected through the cephalic catheter. Three ml of blood was obtained from the jugular catheter before and 1, 2, 5, 10, 15, 20, 60, 120, 240 and 360 min after the injection of iohexol. Prior to each blood sample collection, 3 ml of blood was aspirated through the catheter to clear the catheter of any flush solution. Following each sample collection, the catheter was flushed with 3–5 ml of heparinized saline. Serum was harvested by centrifugation of the blood sample and immediately stored at -20°C for subsequent analysis.

The HPLC determination of serum iohexol concentrations was obtained using the method of Meucci *et al.* [27]. Briefly, *p*-aminobenzoic acid (*p*-aminobenzoic acid, MP Biomedicals, Solon, OH, U.S.A.) and 50 mM sodium dihydrogen phosphate (sodium phosphate monobasic, MP Biomedicals) buffer with 0.5 mM tetrabutylammonium chloride (tetrabutylammonium chloride, Acros Organics, Fair Lawn, NJ, U.S.A.) were used as the internal standard and the mobile

Table 1. Body temperature (BT), heart rate (HR), respiratory rate (RR), systolic arterial pressure (SAP), mean arterial pressure (MAP), diastolic arterial pressure (DAP)

| Groups | | Time (min) | | | | | | | | |
|----------------|----|------------|------------|------------|------------|------------|--------------|--------------|-------------|------------|
| | | Baseline | 5 | 10 | 15 | 20 | 60 | 120 | 240 | 360 |
| BT (C°) | C | 38.9 ± 0.4 | 38.7 ± 0.4 | 38.6 ± 0.3 | 38.5 ± 0.2 | 38.5 ± 0.1 | 38.8 ± 0.4 | 38.7 ± 0.2 | 38.5 ± 0.2 | 38.5 ± 0.2 |
| | T | 38.8 ± 0.2 | 38.5 ± 0.2 | 38.4 ± 0.1 | 38.4 ± 0.2 | 38.4 ± 0.3 | 38.7 ± 0.4 | 38.2 ± 0.5 | 38.3 ± 0.5 | 38.3 ± 0.3 |
| | M | 38.8 ± 0.4 | 38.4 ± 0.5 | 38.3 ± 0.3 | 38.1 ± 0.4 | 38.1 ± 0.4 | 37.5 ± 0.5*† | 37.0 ± 0.6*† | 37.3 ± 0.4† | 38.7 ± 0.3 |
| | TM | 39.0 ± 0.3 | 38.5 ± 0.3 | 38.4 ± 0.4 | 38.3 ± 0.3 | 38.3 ± 0.5 | 37.9 ± 0.6* | 37.2 ± 0.5 | 37.5 ± 0.5* | 39.0 ± 0.4 |
| HR (bpm) | C | 90 ± 18 | 81 ± 18 | 80 ± 14 | 81 ± 18 | 81 ± 17 | 73 ± 13 | 76 ± 10 | 71 ± 12 | 70 ± 11 |
| | T | 74 ± 14 | 68 ± 15 | 72 ± 23 | 69 ± 19 | 69 ± 21 | 73 ± 15 | 65 ± 11 | 67 ± 12 | 65 ± 13 |
| | M | 77 ± 17 | 37 ± 4*† | 37 ± 6*† | 41 ± 7*† | 42 ± 6*† | 40 ± 5*† | 36 ± 5*† | 58 ± 20 | 61 ± 20 |
| | TM | 87 ± 33 | 44 ± 13*† | 46 ± 10*† | 48 ± 11* | 44 ± 8*† | 46 ± 14*† | 41 ± 7*† | 57 ± 10 | 79 ± 17 |
| RR (bpm) | C | 22 ± 9 | 20 ± 10 | 19 ± 9 | 17 ± 4 | 18 ± 7 | 19 ± 9 | 17 ± 3 | 17 ± 3 | 15 ± 4 |
| | T | 19 ± 4 | 15 ± 3 | 16 ± 4 | 16 ± 5 | 13 ± 3 | 18 ± 3 | 15 ± 3 | 15 ± 2 | 15 ± 2 |
| | M | 18 ± 2 | 11 ± 3 | 12 ± 3 | 10 ± 4 | 12 ± 5 | 10 ± 3 | 11 ± 5 | 13 ± 3 | 13 ± 4 |
| | TM | 21 ± 14 | 11 ± 2 | 11 ± 2 | 12 ± 3 | 9 ± 3 | 11 ± 1 | 10 ± 2 | 15 ± 5 | 15 ± 3 |
| SAP (mm Hg) | C | 127 ± 13 | 126 ± 14 | 119 ± 15 | 126 ± 12 | 122 ± 12 | 123 ± 11 | 118 ± 9 | 121 ± 9 | 117 ± 9 |
| | T | 118 ± 12 | 110 ± 10 | 120 ± 10 | 117 ± 9 | 112 ± 10 | 112 ± 7 | 113 ± 7 | 119 ± 9 | 116 ± 7 |
| | M | 123 ± 10 | 145 ± 8 | 140 ± 10 | 130 ± 17 | 127 ± 12 | 118 ± 6 | 110 ± 9 | 114 ± 8 | 112 ± 9 |
| | TM | 126 ± 12 | 140 ± 10 | 133 ± 11 | 132 ± 9 | 128 ± 11 | 113 ± 9 | 110 ± 10 | 112 ± 9 | 112 ± 11 |
| MAP (mm Hg) | C | 109 ± 7 | 105 ± 4 | 104 ± 6 | 105 ± 5 | 104 ± 7 | 108 ± 10 | 105 ± 7 | 112 ± 5 | 109 ± 5 |
| | T | 108 ± 14 | 102 ± 9 | 108 ± 10 | 106 ± 10 | 101 ± 7 | 104 ± 6 | 105 ± 8 | 107 ± 9 | 106 ± 7 |
| | M | 106 ± 6 | 123 ± 14 | 121 ± 15 | 116 ± 15 | 113 ± 10 | 103 ± 5 | 99 ± 7 | 108 ± 9 | 105 ± 9 |
| | TM | 114 ± 9 | 129 ± 7† | 123 ± 11 | 120 ± 8 | 116 ± 9 | 103 ± 6 | 103 ± 13 | 107 ± 9 | 107 ± 9 |
| DAP (mm Hg) | C | 96 ± 7 | 94 ± 5 | 90 ± 8 | 90 ± 2 | 89 ± 7 | 96 ± 11 | 97 ± 10 | 102 ± 6 | 99 ± 5 |
| | T | 98 ± 16 | 93 ± 9 | 97 ± 12 | 97 ± 11 | 93 ± 11 | 97 ± 7 | 97 ± 11 | 96 ± 12 | 96 ± 10 |
| | M | 98 ± 7 | 115 ± 9 | 113 ± 14 | 105 ± 12 | 100 ± 10 | 91 ± 5 | 86 ± 8 | 99 ± 14 | 100 ± 4 |
| | TM | 105 ± 9 | 117 ± 9 | 110 ± 12 | 108 ± 11 | 104 ± 9 | 90 ± 9 | 93 ± 11 | 101 ± 8 | 103 ± 9 |

Values are expressed as means ± SD. C, control; T, tepoxalin 10 mg/kg PO for 3 days; M, medetomidine 750 mg/m² IV; TM, tepoxalin 10 mg/kg PO for 3 days and medetomidine 750 mg/m² IV; *, significantly different ($P < 0.05$) from group C; †, significantly different ($P < 0.05$) from group T.

phase, respectively. The flow rate was set at 1 ml/min with an ODS2 Luna column (Luna 5 μ m C18 100 Å Column 250 × 4.6 mm, Phenomenex, Torrance, CA, U.S.A.), and the UV detector (SPD-10A, Shimadzu, Columbia, MD, U.S.A.) was set at 254 nm.

Statistical analysis: One way-ANOVA was used for iohexol clearance analysis. For other variables, two-way repeated-measures ANOVA with a *post hoc* Bonferroni multiple comparison test was used. A P -value < 0.05 was considered significant.

RESULTS

Measured GFRs in groups C, M, T and TM were 1.09 ± 0.26 , 1.07 ± 0.21 , 1.01 ± 0.19 , and 1.07 ± 0.20 ml/min/kg (mean ± SD), respectively. No significant difference in the GFR was detected between groups.

The HR was significantly lower in groups M and TM compared with groups C and T from 5 through 120 min after injection of iohexol (Table 1). Values for BT were decreased in groups M and TM from 60–120 min following iohexol administration. The MAP was higher in group TM compared with group T only 5 min following iohexol injection. Values for RR, SAP, and DAP were not different between groups.

DISCUSSION

The study was initiated within 1–3 hr after the administration of the last dose of oral tepoxalin, because the mean peak concentrations of tepoxalin and its metabolites occur within 1–2 and 1–3 hr following the administration, respectively [21].

Renal GFR is determined primarily by the balance of pressures across the glomerular membrane. Hydrostatic pressure exerted by the renal arterioles acts to increase filtration pressure, while glomerular capillary colloid osmotic pressure and Bowman's capsule pressure act to decrease filtration. The filtration coefficient (K_f) is a constant and determines the volume of filtrate per net filtration pressure. Afferent and efferent arteriolar vessel tone may greatly influence glomerular hydrostatic pressure and thus impact GFR. Dilation of the afferent arteriole will increase glomerular hydrostatic pressure and result in increased GFR, whereas dilation of the efferent arteriole will decrease glomerular hydrostatic pressure and result in decreased GFR. The tonic balance of these two arterioles thus has a profound effect on GFR. NSAIDs are known to constrict afferent arterioles by inhibiting the COX-2 pathway and may be associated with a decrease in GFR [25]. Tepoxalin has not been reported to have adverse renal effects in dogs at dosages up to 150 mg/kg twice a

day for 6 months [21]. In dogs administered tepoxalin for 7 days, no significant changes in GFR was observed [11]. The results of our present study are in agreement with these prior studies, as no changes in GFR associated with administration of tepoxalin were observed.

The α_2 -adrenoceptor agonist, medetomidine, can cause profound peripheral vasoconstriction via activation of α_{2B} adrenergic receptors [23, 26]. In the kidney, α_2 -adrenoceptor agonist-mediated vasoconstriction occurs preferentially on efferent arterioles and may result in increases in GFR [35], although the effect is dependant upon administration route and dose [32]. Administration of medetomidine 50 $\mu\text{g}/\text{kg}$, IV decreases renal uptake of technetium 99m-labeled diethylenetriamine pentaacetic acid ($^{99\text{m}}\text{Tc}$ -DTPA) for 15 min after administration in dogs [12] and 10 $\mu\text{g}/\text{kg}$, IV of dexmedetomidine decreased renal blood flow by 30% in dogs anesthetized with chloralose and urethane or fentanyl and halothane [23]. In contrast, medetomidine (11 $\mu\text{g}/\text{kg}$, IV) administered with butorphanol (0.22 mg/kg, IV) increased GFR in dogs [15]. In human thoracotomy patients, administration of a dexmedetomidine infusion was shown to enhance renal function, including indices of glomerular filtration as well as urine flow rate [10]. The varied effects on renal blood flow and GRF exhibited by the α_2 -adrenoceptor agonists may be due to the biphasic cardiovascular effects of these drugs that are often reported in several species [23, 26, 31, 32]. An initial hypertension is observed immediately following IV bolus administration of α_2 -adrenoceptor agonists and is thought to be due to activation of peripheral α_{2B} adrenergic receptors [23]. The resultant increase in systemic vascular resistance is associated with a profound decrease in cardiac output (CO) and a baroreceptor-mediated reduction in heart rate. Since renal blood flow is influenced by CO, a reduction in GFR may result from decreased CO [34]. Following the initial hypertension, a reduction in sympathetic tone mediated by central α_{2A} adrenergic receptors is associated with a reduction in systemic blood pressure and a continued reduction in CO [26]. In contrast to the reduction in GFR associated with decreased CO, stimulation of peripheral α_{2C} adrenergic receptors may reduce circulating norepinephrine levels, attenuate afferent arteriolar constriction and tend to increase GFR [37]. Coupled with the fact that the vasoconstrictive effect of medetomidine and that of other α_2 -adrenoceptor agonists occurs primarily on efferent rather than on afferent renal arterioles, administration of α_2 -adrenoceptor agonist drugs is usually associated with an increase in GFR. In this present study, GFR did not change in dogs administered medetomidine (750 $\mu\text{g}/\text{m}^2$, IV bolus). It is not clear why GFR did not change, but there are several possible explanations. The effects of medetomidine on renal blood flow have been shown to be less than the effects seen in other abdominal organs [28], and post-synaptic α_2 -adrenoceptor receptors in renal vessels are either less numerous or less efficiently coupled to contractile elements compared with those in other vascular beds [36]. Alternatively, the dose of medetomidine used in this study might not have been high enough to have had any effects on GFR when used as a sole agent. Another possible explanation

for the lack of change in GFR might be the duration of this study and the method that was used to estimate GFR. In this present study, GFR was estimated as iohexol plasma clearance over the 6 hr plasma sampling period [14, 17]. Other methods of GFR determination such as renal scintigraphy measures GFR using a 3 min sampling time [19]. In this present study, a HPLC method using iohexol was chosen to estimate GFR over other methods, because iohexol clearance does not require sedation, urine collection, or the use of radionucleotides. Since the animals within the control group in our study could not be sedated, estimation of GFR using iohexol clearance was the obvious choice. Considering that the half-life of medetomidine (80 $\mu\text{g}/\text{kg}$, IV) in dogs is 0.97 hr [33], any possible early changes in GFR may have recovered during the 6-hr sampling period and thus have hidden any early changes. When a plasma clearance of a tracer is used as a GFR measurement method, the sampling times and the number of plasma samples can be factors that affect the results [8, 17]. In this present study, the combination of tepoxalin and medetomidine did not affect GFR. We thus conclude that there is no additive or synergistic effect of these two drugs on GFR in healthy dogs at the dosages used.

Values for MAP were significantly higher 5 min post injection of iohexol in group TM compared with group T. As medetomidine was administered 15 min prior to the iohexol injection, dogs in the TM group were likely still in the initial hypertensive phase of the α_2 -adrenoceptor agonist. In humans, administration of NSAIDs has been associated with an increase in blood pressure, thromboembolic events, myocardial infarction and cerebral vascular accidents [7, 38]. To our knowledge, there are no reports of serious cardiovascular effects associated with the administration of tepoxalin in humans or in dogs. Whilst it is possible that tepoxalin had a slight additive or synergistic hypertensive effect in combination with medetomidine, any putative difference was not clinically significant. Despite the initial hypertension seen in groups M and TM, values for MAP remained in the range of autoregulation of GFR (80–170 mm Hg) [16] throughout the study in all groups.

Although BT decreased significantly in groups M and TM, all the dogs' BT were maintained within a clinically acceptable range. This agrees with the report by Pypendop *et al.* [31] and likely due to reduction of heat production by muscular activity and/or due to a direct effect on noradrenergic hypothalamic mechanisms implicated in thermoregulation.

In conclusion, healthy, adult dogs administered medetomidine (750 mg/m^2 , IV) in conjunction with tepoxalin (10 mg/kg, PO for 3 days) had no changes in GFR as estimated by iohexol clearance.

ACKNOWLEDGMENTS. The authors appreciate Merck Animal Health and GE Healthcare for providing tepoxalin and iohexol, respectively. We also thank Dr. Neal Davies, Dr. Yusuke Ohgami, and Jody Takemoto for advice on the HPLC analysis, Dr. Karina Vega-Villa for help with the PK analysis, and Dr. Yu Ueda, Dr. Toshiko Kobayashi, Shona Meyer and Mary Albi for technical assistance.

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