Effects of carprofen on renal function and results of serum biochemical and hematologic analyses in anesthetized dogs that had low blood pressure during anesthesia

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Objective—To investigate effects of IV administered carprofen on indices of renal function and results of serum biochemical and hematologic analyses in dogs anesthetized with acepromazine-thiopentone-isoflurane that had low blood pressure during anesthesia.

Animals—6 healthy Beagles.

Procedure—A randomized crossover study was conducted, using the following treatments: saline (0.9% NaCl solution)-saline, saline-carprofen, and carprofen-saline. Saline (0.08 ml/kg) and carprofen (4 mg/kg) were administered IV. The first treatment was administered 30 minutes before induction of anesthesia and immediately before administration of acepromazine (0.1 mg/kg, IM). Anesthesia was induced with thiopentone (25 mg/ml, IV) and maintained with inspired isoflurane (2% in oxygen). The second treatment was administered 30 minutes after onset of inhalation anesthesia. Blood gases, circulation, and ventilation were monitored. Renal function was assessed by glomerular filtration rate (GFR), using scintigraphy, serum biochemical analyses, and urinalysis. Hematologic analysis was performed. Statistical analysis was conducted, using ANOVA or Friedman ANOVA.

Results—Values did not differ significantly among the 3 treatments. For all treatments, sedation and anesthesia caused changes in results of serum biochemical and hematologic analyses, a decrease in mean arterial blood pressure to 65 mm Hg, an increase of 115 pmol/L in angiotensin II concentration, and an increase of 100 seconds in time required to reach maximum activity counts during scintigraphy.

Conclusions and Clinical Relevance—Carprofen administered IV before or during anesthesia did not cause detectable significant adverse effects on renal function or results of serum biochemical and hematologic analyses in healthy Beagles with low blood pressure during anesthesia. (*Am J Vet Res* 2002;63: 712–721)

Preemptive analgesia can reduce the requirement, quantity, and duration of postoperative analgesic administration by decreasing peripheral and central sensitization of affected nerves.[1,2] Although opioids mainly prevent central sensitization,[3] **nonsteroidal anti-inflammatory drugs (NSAID)**, which mainly act at the site of tissue damage,[4] should be better at preventing peripheral sensitization and, thereby, also central sensitization. There is a need for effective analgesic and anti-inflammatory substances for preemptive analgesia that act at the site of tissue damage but have little or no effect on respiration and circulation. The NSAID can fill this need, but dogs are sensitive to the adverse effects of NSAID on renal function during hypovolemia and hypotension, and careful monitoring is necessary. Opioids, which are commonly used effective analgesic substances, have adverse effects on the cardiopulmonary system.

Renal blood flow is maintained by a complex interaction between several factors, including the sympathetic nervous system, various hormones, and local internal renal control systems.[5] Although changes in arterial pressure have some influence on renal blood flow, **glomerular filtration rate (GFR)** and renal blood flow are maintained relatively constant (mean arterial pressure ranges between 80 and 170 mm Hg[6]) through a process termed autoregulation. When blood pressure decreases, angiotensin II maintains GFR by constricting arterioles in the kidneys.[7] Its effect is greater on efferent arterioles than afferent arterioles.[8] The systemic blood pressure also is affected, because angiotensin II acts on all arterioles in the body. Other hormones that have a role in maintaining systemic blood pressure are vasopressin and aldosterone.[9,10] Prostaglandins that have vasodilatory effects may dampen the vasoconstrictor effects of angiotensin II, especially effects on the afferent arterioles, helping to maintain the perfusion pressure in the glomeruli.[11]

The NSAID are believed to act by inhibiting **cyclooxygenase (COX)** activity in the biochemical cascade, thus preventing the synthesis of prostaglandins. Prostaglandins play an important role only in inflam-

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mation as well as in homeostatic mechanisms that help to prevent gastric ulcers and renal damage attributable to hypovolemia.[12] In a healthy euvolemic conscious animal, blood flow to the kidneys is not impaired by the NSAID-induced decrease in prostaglandin synthesis.[13] However, in anesthetized dogs that may have a decrease in blood pressure below the threshold necessary for autoregulation and, thus, a subsequent decrease in renal blood flow during anesthesia, the effect of a superimposed NSAID-induced decrease in prostaglandin synthesis on renal blood flow and subsequent renal function may lead to serious adverse effects. Acute renal damage and even death may result from renal failure in dogs undergoing surgical procedures with concurrent administration of NSAID (ie, flunixin meglumine).[14,15]

More than 1 form of COX enzyme exists in the body. Cyclooxygenase-1 is a form of the enzyme responsible for the production of prostaglandins involved in homeostatic mechanisms that protect the stomach, kidneys, and other tissues. In contrast, COX-2 is a form of the enzyme that is mainly involved in production of prostaglandins induced by the inflammatory process. Therefore, it has been hypothesized that the selective inhibition of COX-2 could increase the safety of a NSAID.[12]

Carprofen is 1 of the newer NSAID being used in veterinary medicine. It has a more favorable ratio of inhibition for COX-1:COX-2 than many other NSAID (eg, acetyl salicylic acid), as documented in several in vitro models that used cell cultures from various species.[a] In 1 study[16] that involved the use of cultured canine cells, carprofen was 1.75 times more selective for COX-2 than COX-1, and in another study,[17] carprofen was > 100 times more potent for canine COX-2 than COX-1. Therefore, carprofen may be less deleterious to the kidneys in a hypovolemic condition, compared with other NSAID. Clinically, it has been proven that carprofen is a potent analgesic with few of the adverse effects classically associated with NSAID[18]; however, its mode of action has not been fully clarified.[19]

The purpose of the study reported here was to investigate the effect of IV administration of carprofen on GFR and other indices of renal function as well as on results of hematologic and serum biochemical analyses in anesthetized dogs that have low blood pressure during anesthesia. Serum hormone concentrations were measured to help evaluate the effects of anesthesia on blood pressure.

Materials and Methods

Animals—Six healthy Beagle dogs (3 males and 3 females) were used in the study. Dogs ranged from 15 to 48 months of age (mean ± SD, 22 ± 13 months) and weighed between 11.6 and 18.4 kg (mean, 15.2 ± 2.5 kg). Dogs were obtained from the Department of Small Animal Sciences, Faculty of Veterinary Medicine at the Swedish University of Agricultural Sciences, and they were housed and cared for by the department throughout the study. Approval of the study was obtained from the local Ethical Committee on Animal Experiments.

Study design—A crossover study with treatments allocated randomly was conducted. We selected 2 times at which an injection of a NSAID would be administered in an effort to examine a clinical situation in which the need for additional analgesia is not apparent until a dog is anesthetized. Treatments consisted of carprofen (50 mg/ml) and physiologic saline (0.9% NaCl) solution, both of which were administered IV. Carprofen was administered at a rate of 0.08 ml/kg, which corresponded to 4 mg of carprofen/kg; an equivalent volume of saline solution was administered (ie, 0.08 ml/kg). The dose is the amount recommended for preemptive analgesia.[20] Carprofen or saline solution was administered as 2 separate injections during each anesthetic episode. Treatments were as follows: treatment 1, the first and second injections were both saline solution (S-S treatment); treatment 2, the first injection was saline solution, and the second injection was carprofen (S-C treatment); and treatment 3, the first injection was carprofen, and the second injection was saline solution (C-S treatment).

All dogs received each of the 3 treatments during the course of the study. Dogs were assigned to 3 groups, and all dogs in 1 group were treated at the same time. There was a 3-week washout period between subsequent treatments.

On the day of the anesthetic procedure, the dogs were not given food, and water was withheld for 2 hours prior to induction of anesthesia. Blood and urine samples were collected on the morning of the anesthetic procedure and used for serum biochemical analyses, determination of hormone concentrations, and urinalysis. An IV catheter was placed in the cephalic vein before collection of the preanesthetic blood sample. The GFR was measured by use of scintigraphy.

Following local administration of analgesia, a 20-gauge catheter[b] was inserted in the femoral artery, using the Seldinger technique.[21] The catheter was used for invasive measurement of arterial blood pressure and collection of blood samples for serum biochemical analyses, blood gas determinations, and assessment of acid-base balance during the anesthetic procedure. Blood gases and arterial blood pressure were measured before administration of carprofen or acepromazine. Baseline values for heart and respiratory rates and rectal temperature were obtained. A baseline ECG also was obtained.

Sedation and anesthesia—Acepromazine (0.1 mg/kg, IM) was administered in the right triceps brachii muscle to produce sedation, vasodilatation, and a lower blood pressure than would be caused by the other anesthetics alone. The first injection of the treatment regimen was administered IV immediately prior to acepromazine administration.

Thirty minutes after injection of acepromazine, anesthesia was induced with thiopentone (25 mg/ml) administered slowly IV as needed to enable endotracheal intubation (mean dosage, 9.5 ± 0.9 mg of thiopentone/kg). Anesthesia was maintained with isoflurane (measured inspired concentration of 2%) in oxygen (150 ml/kg/min) in a Bain coaxial breathing system. The time at which thiopentone was administered as well as the start and end of administration of isoflurane was recorded. The volume of thiopentone administered to each dog also was recorded. Each dog was anesthetized for 2.25 hours. Dogs were covered with a blanket during anesthesia, except during scintigraphy and insertion of a urinary catheter.

Heart and respiratory rates, arterial blood pressure, ECG variables, fraction of inspired oxygen, end-tidal CO_2, end-tidal and inhaled isoflurane concentration, and arterial oxygen saturation of hemoglobin were monitored continuously throughout anesthesia. Values were recorded 30, 90, and 120 minutes after induction of anesthesia. End-tidal CO_2, fraction of inspired oxygen, isoflurane concentrations, and arterial oxygen saturation of hemoglobin were measured by use of the gas monitor. Tidal volume was calculated from the respiratory rate and minute volume, which was measured with a Wright respirometer[c] connected to the endotracheal tube;

values for these variables were recorded 30, 90, and 120 minutes after induction of anesthesia. Rectal temperature was also measured at the same time points. The arterial catheter was flushed repeatedly with small amounts of saline solution. The volume used for each flush was recorded. Thirty minutes after extubation, a blood sample was collected for blood gas analysis, and arterial blood pressure, ECG variables, respiratory rate, and rectal temperature were recorded.

Thirty minutes after the start of maintenance of anesthesia by the administration of isoflurane, samples were obtained for serum biochemical analyses, urinalysis, determination of hormone concentrations, and measurement of blood gases. The GFR also was measured. After these samples and measurements were obtained, the second injection of the treatment regimen was administered IV. At 120 minutes after onset of isoflurane administration, another set of samples was obtained for serum biochemical analyses, urinalysis, determination of hormone concentrations, and measurement of blood gases. The GFR was measured again.

Thirty minutes after the end of the anesthetic period, blood samples and measurements were obtained again. The arterial catheter then was removed, and pressure was manually applied to the femoral artery for approximately 10 minutes to prevent hemorrhage attributable to removal of the catheter.

Twenty hours after the induction of anesthesia, blood and urine samples were collected and used to determine the state of the dogs following complete recovery from the anesthetic episode. Serum biochemical analyses, urinalysis, and measurement of GFR were conducted. Three weeks after the last anesthetic procedure, blood and urine samples were collected from each dog and used for comparison with baseline values (ie, the first values obtained in the study for each dog before administration of any drug).

Monitoring during anesthesia—Arterial blood samples for blood gas analysis and assessment of acid-base balance, including arterial pH, Pa_{CO_2}, and Pa_{O_2}, were obtained anaerobically from the femoral artery and stored in airtight syringes on ice until assayed by use of a standard electrode technique, using an electrode temperature of 37 C.[d] Arterial blood pressure was measured via a pressure transducer[e] positioned at the level of the sternum (considered to correspond to the right atrium of the heart when a dog is in lateral recumbency) and connected to the catheter in the femoral artery via a line filled with saline solution. Dogs were maintained in left lateral recumbency. Arterial blood pressure was monitored with a cardiovascular monitor[f] and recorded with an ink-jet recorder.[g] A lead-II ECG was monitored and recorded by the same ink-jet recorder. Heart rate was calculated from the ECG, and respiratory rate was measured by use of a gas monitor.[h] Rectal temperature was measured with a battery-powered thermometer.[i]

Hematologic examinations, serum biochemical analyses, and urinalysis—Blood samples were collected by venipuncture for the baseline sample and the sample obtained 20 hours after the end of the anesthetic episode, whereas all other samples were collected via the indwelling arterial catheter. Urine samples obtained before (baseline) and 20 hours after the end of the anesthetic episode were collected during natural voiding, when possible, to avoid the need for additional catheterizations and an increased risk of urinary tract infection. During anesthesia, urine was collected via a urinary catheter that was allowed to remain in place until the final sample was collected on that day. Urine specific gravity was estimated by use of refractometry, and urinary sediments were examined by use of light microscopy (400× magnification). Urine pH was determined by use of pH paper. Serum concentrations of potassium, sodium, inorganic phosphorus, calcium, albumin, and total protein; serum activity of **alanine transaminase (ALT)**; and serum and urinary concentrations of creatinine and activities of **alkaline phosphatase (ALP)** were determined on a selective analyzing system.[j] Creatinine, sodium, potassium, calcium, inorganic phosphorus, and protein concentrations were measured by use of standard reagent kits,[k-p] and ALP and ALT activity as well as albumin concentration also were measured by use of standard reagent kits.[q-s] A CBC was performed, using an automated hematology analyzer.[t]

Hormonal analysis—Immunoreactive angiotensin II and arginine-vasopressin were measured in plasma that had been extracted with acetone[u] and petroleum benzene[v] (boiling range, 40 to 60 C; recovery of 92%). Arginine-vasopressin then was analyzed by use of a vasopressin radioimmunoassay.[w] Angiotensin II was determined by use of an angiotensin-II radioimmunoassy.[x] Both radioimmunoassays are intended for use in human samples, but the amino-acid sequence of arginine-vasopressin and angiotensin II in dogs are identical to the sequences in humans, indicating complete cross-reactivity. Furthermore, serially diluted canine plasma samples and standards of human arginine-vasopressin and angiotensin II yielded parallel concentration curves, which validated the quantification of canine arginine-vasopressin and angiotensin II by use of these assays. Limits of detection for the methods and interassay **coefficient of variation (CV)** were 0.62 pmol/L and 13 to 19%, respectively, for the arginine-vasopressin assay and 2.0 pmol/L and 1 to 10%, respectively, for the angiotensin-II assay. The intra-assay CV was < 10% for the range of 1.3 to 59 pmol/L for the arginine-vasopressin assay and 6.3 to 300 pmol/L for the angiotensin-II assay. Immunoreactive aldosterone was determined in plasma, using a commercially available radioimmunoassay.[y] This assay has been evaluated for use on canine samples.[22,23] Limit of detection for this method is 32 pmol/L, and recovery ranged from 71 to 98%. The intra- and interassay CV were 8 and 10%, respectively.

Renal scintigraphy—Renal function was determined by measurement of GFR and by use of scintigraphic measurements, using the method of Krawiec et al,[24] with slight modifications to make the measurements more reproducible.[25] **Diethylene-triaminepentacetic acid (DTPA)** was used as a radiolabeled tracer; this compound is excreted only by glomerular filtration. An aliquot (70 MBq) of technetium^{99m}-labeled DTPA was injected in the cephalic vein as a bolus, followed by injection of 4 ml of saline solution. A dynamic acquisition was performed (3 frames/s during the first minute and then 1 frame/10 s for 5 minutes) with each dog positioned in left-lateral recumbency and the gamma camera[z] positioned against the dorsum of the dog to obtain a dorsal view. A 64 × 64 matrix was used. The first minute was reformatted to 1 frame/10 s. Motion during the acquisition was evaluated, using a movie program, and corrected when needed, using a special motion-correction program.[aa] The injected dose was measured by using the gamma camera to record the activity of the syringe before injection and subtracting that value from the activity of the syringe, tubing, and needle after injection and then correcting the difference for radioactive decay between the measurements. A 30-second static lateral view was made without repositioning the dog.

Frames from the second minute were summed to create a single image of the kidneys with sufficient counts to define the edges of the kidneys. **Regions of interest (ROI)** were drawn around each kidney by placing a rectangular ROI closely around the kidney to exclude everything except the kidney and surrounding background. A background-subtracted image of the kidney was calculated, using an interpo-

lation technique.[26] Because the edge of each kidney is not sharp, each kidney ROI was drawn automatically, using a predetermined threshold of 20% of the maximum pixel counts within the background-subtracted kidney. Circumferential ROI that were used to measure the extrarenal background were automatically drawn; these circumferential ROI were 1 pixel in width and located 1 pixel from the edge of each kidney ROI, and they were subtracted, using a mean activity-per-pixel basis, from the kidney ROI. When baseline kidney activity was evident 30 or 120 minutes after a preceding injection, it was subtracted by setting a horizontal cursor line at the offset from zero of the first data point of the uncorrected renal time-activity curve. The distance from the middle of each kidney to the surface of the skin was measured on the lateral view, using computer calipers calibrated to pixel size. Each kidney's activity was corrected for absorption attributable to depth, using the attenuation coefficient for soft tissue (ie, 0.153/cm). Total net activity in counts accumulated in each kidney between 30 and 120 seconds after injection was adjusted on the basis of the injected dose. Counts were then converted to a value of milliliters per minute per kilogram, using a regression equation.[25] The equation relates GFR measured by plasma clearance of technetium^{99m}-labeled DTPA to the corrected value for uptake between 30 and 120 seconds. Total GFR was the sum of the GFR for each kidney.

Statistical analysis—Data were analyzed, using a repeated-measures ANOVA, with treatment and time as within-dog factors. Estimated values were substituted for missing values. Variance between paired differences was tested by use of the Mauchley sphericity test.[27] When the test resulted in a value of $P < 0.05$, the Greenhouse-Geisser correction[27] was used, and adjusted P values were reported. When the overall F-test of the ANOVA was significant, the Tukey honest post-hoc analysis was performed, unless the Mauchley sphericity test indicated significance or an interaction was observed. In those instances, a planned comparison test was performed. Comparisons were made for blood and serum variables at the time of entry into the study and after the final 3-week washout period, using a t-test for paired samples. Information reported as intervals (eg, results of examination of urine sediment) was translated to categoric data and was analyzed by use of the Friedman ANOVA. Determinations of mean corpuscular volume were analyzed, using a 1-way ANOVA. Statistical analysis was performed, using a commercial software program.[bb] Results were reported as mean ± SD. Significance was defined as values of $P < 0.05$ for all statistical analyses.

Estimated values for missing observations were calculated, using the following formula:

$$Bs_{ji} = \frac{n(\Sigma S_i) + k(\Sigma B_j) - \Sigma BS}{(n-1) \bullet (k-1)}$$

where n is the number of blocks, ΣS_i is the sum of remaining observations in the block that contains the missing observation, ΣB_j is the sum of remaining observations in the treatment that contains the missing observation, ΣBS is the sum of all available observations, and k is the number of types of treatment.[28]

Power analysis was performed for 1 variable (ie, GFR), using another commercial software program.[cc]

Results

Monitoring of anesthesia and hormone concentrations—Value for **mean arterial blood pressure (MAP)** was significantly ($P < 0.001$) lower in dogs during anesthesia than when the dogs were conscious (**Table 1**). The MAP before and 20 hours after the end of an anesthetic episode was (mean ± SD) 115 ± 8 mm Hg, whereas during anesthesia, the mean for all treatments was 65 ± 8 mm Hg. Heart rate did not change significantly over time. Rectal temperature decreased significantly ($P < 0.001$) during anesthesia. Rectal temperature decreased the most during the first 90 minutes after induction of anesthesia.

Table 1—Mean ± SD values for cardiovascular variables and rectal temperature measured in 6 dogs used in a randomized crossover design to study the effects of administration of carprofen (C) and saline (0.9% NaCl) solution (S) during anesthesia

Treatment*	Period†	MAP (mm Hg)	$Paco_2$ (mm Hg)	Heart rate (beats/min)	Respiratory rate (breaths/min)	Arterial pH	Rectal temperature (C)
S-S							
	Before	115 ± 11[bcd]	31.1 ± 1.3[bcd]	105 ± 22[e]	21 ± 4[bcd]	7.41 ± 0.01[bcd]	38.6 ± 0.2[bcde]
	During						
	30 min	65 ± 7[ae]	58.3 ± 8.0[ade]	117 ± 16[e]	5 ± 3[ae]	7.21 ± 0.04[ae]	37.2 ± 0.4[acde]
	90 min	66 ± 6[ae]	64.7 ± 7.2[ae]	113 ± 11[e]	7 ± 5[ae]	7.18 ± 0.04[ae]	36.1 ± 0.4[ab]
	120 min	66 ±11[ae]	69.2 ± 14.4[abe]	110 ± 12[e]	8 ± 5[ae]	7.17 ± 0.06[ae]	36.1 ± 0.9[ab]
	After	116 ± 9[bcd]	37.3 ± 3.8[bcd]	148 ± 32[abcd]	20 ± 7[bcd]	7.37 ± 0.02[bcd]	36.1 ± 0.8[ab]
S-C							
	Before	116 ± 6[bcd]	30.6 ± 1.1[bcd]	111 ± 29	22 ± 5[bcd]	7.41 ± 0.0[bcde]	38.3 ± 0.5[bcde]
	During						
	30 min	66 ± 10[ae]	61.0 ± 5.9[ae]	120 ± 17	4 ± 2[ae]	7.18 ± 0.02[ae]	37.2 ± 0.7[acde]
	90 min	63 ± 11[ae]	66.6 ± 9.6[ae]	110 ± 15	9 ± 5[ae]	7.16 ± 0.02[ae]	36.4 ± 1.1[ab]
	120 min	65 ± 12[ae]	67.9 ± 7.0[ae]	109 ± 16	8 ± 7[ae]	7.16 ± 0.04[ae]	36.1 ± 1.1[ab]
	After	118 ± 7[bcd]	36.5 ± 3.1[bcd]	131 ± 26	21 ± 8[bcd]	7.36 ± 0.01[abcd]	36.1 ± 0.8[ab]
C-S							
	Before	114 ± 8[bcd]	31.3 ± 2.8[bcd]	106 ± 30	21± 4[bcde]	7.41 ± 0.01[bcde]	38.7 ± 0.2[bcde]
	During						
	30 min	66 ± 5[ae]	57.6 ± 4.6[ae]	118 ± 13	4 ± 2[ae]	7.21 ± 0.03[ae]	37.4 ± 0.3[acde]
	90 min	62 ± 7[ae]	60.0 ± 6.4[ae]	110 ± 9	8 ± 3[ae]	7.19 ± 0.02[ae]	36.5 ± 0.5[ab]
	120 min	64 ± 6[ae]	62.4 ± 5.4[ae]	111 ± 7	7 ± 4[ae]	7.20 ± 0.02[ae]	36.3 ± 0.7[ab]
	After	111 ± 8[bcd]	36.9 ± 2.0[bcd]	135 ± 36	16 ± 3[abcd]	7.36 ± 0.02[abcd]	36.1 ± 1.0[ab]

*Treatments were administered as 2 injections (saline-saline [S-S], saline-carprofen [S-C], and carprofen-saline [C-S]), with the first and second injections administered 30 minutes before and 30 minutes after induction of anesthesia, respectively. †Values were obtained before anesthesia, during anesthesia (30, 90 and 120 minutes after induction), and 30 minutes after extubation at the end of the anesthetic procedure.

[a-e]Within a treatment, values within the same column differ significantly ($P < 0.05$) from values for other periods ([a]before, [b]30 minutes, [c]90 minutes, [d]120 minutes, [e]after).

Respiratory rate decreased significantly ($P < 0.001$) during anesthesia. End-tidal isoflurane concentration was 1.3 ± 0.1% at 30 minutes after induction of anesthesia and 1.6 ± 0.1% at 90 and 120 minutes after induction of anesthesia. Tidal volume decreased significantly ($P = 0.01$) during anesthesia, from a mean of 0.23 ± 0.07 L/breath at 30 minutes after induction of anesthesia to 0.18 ± 0.07 L/breath at 120 minutes after induction of anesthesia. The Pa_{CO_2} increased significantly ($P < 0.001$) during anesthesia. End-tidal CO_2 correspondingly increased significantly ($P = 0.01$) during anesthesia. Arterial pH decreased significantly ($P < 0.001$) during anesthesia, whereas Pa_{O_2} increased significantly ($P = 0.01$) during anesthesia. Values of Pa_{O_2} before and during anesthesia were 91 to 109 and 532 to 567 mm Hg, respectively.

Concentration of angiotensin II was significantly ($P < 0.001$) increased 30 minutes after induction of anesthesia, and a further increase was measured 120 minutes after induction (**Table 2**). Vasopressin concentration also increased significantly ($P = 0.01$) during anesthesia. Aldosterone concentration did not differ from baseline values 30 minutes after induction of anesthesia but increased significantly ($P < 0.001$) 120 minutes after induction (**Table 3**).

Serum biochemical analyses and urinalysis—Serum creatinine concentration decreased significantly

Table 2—Mean ± SD values for renal variables and hormones measured in 6 dogs used in a randomized crossover design to study the effects of administration of carprofen and saline solution during anesthesia

Treatment*	Period	GFR (ml/min/kg)	Time to peak (s)	Angiotensin (pmol/L)	Vasopressin (pmol/L)	Creatinine (pmol/L)
S-S						
	Before	3.5 ± 0.6	183 ± 33[b]	7 ± 2[bd]	0.1 ± 0[bd]	76.2 ± 6.8[bd]
	During					
	30 min	4.0 ± 0.5	266 ± 74[ae]	76 ± 28[ade]	13.8 ± 8[ae]	68.8 ± 2.9[a]
	120 min	3.9 ± 0.6	218 ± 81[e]	136 ± 40[abe]	16.6 ± 11[ae]	66.2 ± 3.8[ae]
	20 h after	3.9 ± 0.4	140 ± 24[bd]	7 ± 2[bd]	0.1 ± 0[bd]	75.5 ± 6.8[d]
S-C						
	Before	3.6 ± 0.2	147 ± 26[b]	6 ± 1[bd]	0.1 ± 0[bd]	74.0 ± 6.9[b]
	During					
	30 min	3.9 ± 0.8	249 ± 99[ae]	96 ± 29[ae]	21.1 ± 13[ae]	67.3 ± 4.8[a]
	120 min	3.7 ± 0.7	234 ± 106[e]	124 ± 32[ae]	17.2 ± 12[ae]	68.5 ± 5.5
	20 h after	23.7 ± 0.6	139 ± 16[bd]	8 ± 3[bd]	0.3 ± 0[bd]	72.7 ± 3.7
C-S						
	Before	3.6 ± 0.7	169 ± 27[b]	8 ± 2[bd]	0.1 ± 0[bd]	73.3 ± 4.6[bd]
	During					
	30 min	3.8 ± 0.4	289 ± 61[ae]	73 ± 15[ade]	6.7 ± 4[ae]	68.2 ± 5.2[ae]
	120 min	3.8 ± 0.7	229 ± 85[e]	112 ± 6[abe]	9.8 ± 5[ae]	67.3 ± 1.5[ae]
	20 h after	3.6 ± 0.3	154 ± 39[bd]	7 ± 2[bd]	0.2 ± 0[bd]	72.8 ± 3.1[bd]

See Table 1 for key.

Table 3—Mean ± SD values for hematologic and serum biochemical analyses measured in 6 dogs used in a randomized crossover design to study the effects of administration of carprofen and saline solution during anesthesia

Treatment*	Period	Hematocrit (%)	WBC (X 10^3 cells/L)	Total protein (g/L)	Aldosterone (pmol/L)	Potassium (mmol/L)	Inorganic phosphorus (mmol/L)
All							
	Baseline†	46 ± 6	9.6 ± 1.5	66 ± 4	184 ± 94	4.3 ± 0.1	1.2 ± 0.2
	End of study†	52 ± 3*	10.4 ± 3.4	67 ± 4	173 ± 75	4.4 ± 0.3	1.1 ± 0.1
S-S							
	Before	46 ± 6[bd]	10.1 ± 2.3[bde]	65 ± 4[bd]	219 ± 100[d]	4.3 ± 0.1[bd]	1.1 ± 0.2[bd]
	During						
	30 min	34 ± 8[ae]	8.3 ± 1.8[ade]	55 ± 4[ae]	433 ± 160[d]	3.8 ± 0.3[ade]	1.9 ± 0.3[ade]
	120 min	33 ± 8[ae]	6.6 ± 1.8[abe]	54 ± 4[ae]	1,651±1,051[abe]	4.7 ± 0.4[abe]	2.5 ± 0.2[abe]
	20 h after	44 ± 8[bd]	12.4 ± 2.5[abd]	64 ± 3[bd]	342 ± 252[d]	4.2 ± 0.1[bd]	1.3 ± 0.3[bd]
S-C							
	Before	46 ± 4[bd]	9.4 ± 2.3[de]	66 ± 4[bde]	828 ± 771	4.4 ± 0.3[b]	1.1 ± 0.2[bd]
	During						
	30 min	32 ± 6[ae]	7.4 ± 2.7[e]	56 ± 3[ae]	547 ± 194	3.8 ± 0.2[ad]	1.9 ± 0.3[ade]
	120 min	33 ± 4[ae]	6.6 ± 2.4[ae]	56 ± 4[ae]	1,205 ± 465[e]	4.7 ± 0.4[be]	2.7 ± 0.3[abe]
	20 h after	43 ± 4[bd]	11.6 ± 2.4[abd]	62 ± 3[abd]	312 ± 220[d]	4.1 ± 0.2[d]	1.2 ± 0.2[bd]
C-S							
	Before	46 ± 8[bd]	10.8 ± 3.4[de]	64 ± 3[bd]	412 ± 394[d]	4.4 ± 0.3[d]	1.2 ± 0.2[bd]
	During						
	30 min	34 ± 9[ae]	8.8 ± 2.0[e]	56 ± 3[ae]	367 ± 213[d]	4.0 ± 0.3[d]	1.9 ± 0.3[ade]
	120 min	35 ± 8[ae]	7.1 ± 1.6[ae]	56 ± 2[ae]	905 ± 433[abe]	5.1 ± 0.7[abe]	2.4 ± 0.3[abe]
	20 h after	44 ± 6[bd]	14.4 ± 4.6[abd]	64 ± 2[bd]	243 ± 179[d]	4.2 ± 0.3[d]	1.3 ± 0.4[bd]

*Value is significantly ($P < 0.05$) different from baseline value. †Baseline refers to values measured at time of entry into the study. End of study refers to values measured 3 weeks after the final anesthetic procedure.
See Table 1 for key.

(P = 0.01) during anesthesia (Table 2). The urinary ALP-to-creatinine ratio did not differ among treatments or over time; however, changes were seen in specific dogs. In 2 male dogs, a slight increase in the ratio was seen during or 20 hours after end of an anesthetic episode. In 1 of these dogs, a value greater than the reference value of < 0.1 was detected 20 hours after end of the anesthetic procedure for the S-S treatment and also during anesthesia for the S-C treatment. This dog had a ratio of 0.1 before anesthesia for the S-S treatment. The other dog had a value of 0.1 during anesthesia for the S-C treatment. In both dogs, the ratio was < 0.1 by 20 hours after the end of the anesthetic procedure for the S-C treatment **(Fig 1)**.

Urine pH increased significantly during anesthesia. The pH increased significantly 30 minutes after induction of anesthesia (mean, 7.7 ± 1.0), compared with other time points (mean, 6.8 ± 1.0). Specific gravity and numbers of cylinders, crystals, and epithelial cells did not differ significantly among treatments and over time. Number of leukocytes detected during sediment examination increased significantly 20 hours after the anesthetic procedure for the S-S and C-S treatments. Number of RBC increased significantly during anesthesia for the C-S treatment.

Hematologic analysis and measurement of serum proteins, enzymes, and electrolytes—Hemoglobin concentration and hematocrit decreased significantly (P < 0.001) during anesthesia. Values for both variables were higher 3 weeks after the last anesthetic procedure. Hemoglobin concentration was 163 ± 21 g/L before the start of the study and 185 ± 8 g/L 3 weeks after the final anesthetic procedure. Mean corpuscular volume did not change during the study. Number of circulating WBC decreased significantly (P < 0.001) during anesthesia and increased 20 hours after the end of the anesthetic procedure, compared with values before onset of anesthesia (Table 3).

Albumin and total protein concentrations decreased significantly (P < 0.001) during anesthesia. Albumin concentration increased significantly 3 weeks after the last anesthetic procedure, compared with values before the start of the study. Total protein concentration had an interaction between treatments and time. For the S-S treatment, total protein concentration decreased 120 minutes after induction of anesthesia, whereas for the S-C and C-S treatments, concentrations remained the same 30 and 120 minutes after induction of anesthesia.

Serum activity of ALT and ALP did not differ during anesthesia or among treatments; however, there were changes among dogs. In 1 male dog, there was a transient increase in ALT and ALP activity during the final anesthetic procedure for the S-C treatment. The high ALT value was seen before administration of carprofen. The value before anesthesia was 29 U/L, whereas 30 and 120 minutes after induction of anesthesia, ALT activity was 294 and 306 U/L, respectively. Twenty hours after the end of the anesthetic procedure, ALT activity was 253 U/L. High ALP activity was seen later than the high ALT activity (before anesthesia, 71 U/L; 30 minutes after induction of anesthesia, 106 U/L; 120 minutes after induction of anesthesia, 124 U/L; 20 hours after end of the anesthetic procedure, 341 U/L). During the follow-up examination 3 weeks after the last anesthetic procedure, values for ALT and ALP were similar to baseline values. At that time, the same male dog had hemoglobin and hematocrit values (125 g/L and 35%, respectively) that were lower than for the other dogs at the onset of the study.

Serum potassium concentration changed significantly (P < 0.001) over time (Table 3). It was lower 30 minutes after induction of anesthesia, compared with values before and after an anesthetic procedure. At 120 minutes after onset of anesthesia, serum potassium concentration was increased, compared with values before and after the anesthetic procedure. Serum sodium concentrations did not differ among treatments or during anesthesia.

Inorganic phosphate concentration increased significantly (P < 0.001) over time, with a maximum value 120 minutes after induction of anesthesia. Serum calcium concentration also changed significantly during anesthesia, with lower concentrations 120 minutes after induction of anesthesia, compared with values for other time points. Serum calcium concentration also increased significantly at the end of the study, compared with values at the onset of the study.

Renal scintigraphy and GFR—Values for GFR did not differ significantly among the 3 treatment groups or over time (Table 2). Result of the power

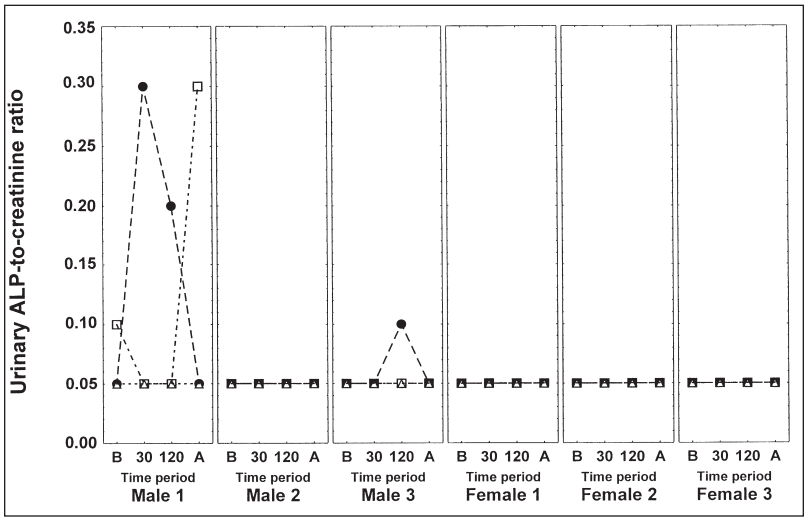

Figure 1—Values for urinary alkaline phosphatase (ALP)-to-creatinine ratio for 6 dogs used in a randomized crossover design of effects of administration of carprofen and saline (0.9% NaCl) solution during anesthesia. Ratios were obtained before anesthesia (B), during anesthesia (30 and 120 minutes after induction), and 20 hours after end of the anesthetic procedure (A). Treatments were administered as 2 injections (saline-saline, open square; saline-carprofen, solid circle; carprofen-saline, open triangle), with the first and second injections administered 30 minutes before and 30 minutes after induction of anesthesia, respectively. Notice the unique results for Male 1.

analysis was approximately 70%. None of the dogs had a GFR before, during, or after the anesthetic procedures that was less than the reference range of 2.45 to 4.49 ml/min/kg established by our laboratory group. Time to reach maximum activity counts in the kidney (time to peak, mean value of both kidneys) during scintigraphy increased significantly ($P < 0.001$) during anesthesia, with the interval being the longest 30 minutes after induction of anesthesia.

Discussion

The anesthetic model reported here proved successful. The objective was to achieve deep anesthesia with low blood pressure, something that may commonly happen to dogs and that may affect renal function. A reproducible low blood pressure among and within dogs was achieved with simple means, using a routine sedative and anesthetic protocol that is commonly used in clinical practice. At least 1 study[29] has documented that the pressure limit in the renal artery for renal flow autoregulation is an approximate mean of 65 mm Hg (range, 61 to 71 mm Hg), and the limit for mean arterial blood pressure for GFR autoregulation is approximately 80 mm Hg (range, 72 to 88 mm Hg) in conscious dogs. The authors of that study suggested that anesthesia may increase these limits. In the study reported here, only 2 dogs had a mean arterial blood pressure of 80 to 82 mm Hg during anesthesia, and each of these was only during 1 experimental procedure in each dog (1 during S-S treatment and 1 during S-C treatment). All other dogs had values that were lower (47 to 76 mm Hg).

Angiotensin II, aldosterone, and vasopressin concentrations were significantly influenced by sedation and anesthesia, as indicated by increased plasma concentrations 120 minutes after induction of anesthesia; however, we did not detect significant differences among treatments. The high concentrations of vasopressin and angiotensin II were presumably aimed at increasing the systemic blood pressure through vasoconstriction and maintaining the GFR through constriction of efferent arterioles (angiotensin II).[5,7] Vasopressin is released from the neurohypophysis in response to increased extracellular osmotic pressure or decreased blood pressure.[9] Major effects of vasopressin include water retention in the kidneys and systemic vasoconstriction.[30] The vasoconstrictive effect of vasopressin requires plasma concentrations similar to those reported here, whereas the antidiuretic effect is evident at considerably lower plasma concentrations.[31] However, the compensatory mechanisms of angiotensin II and vasopressin on systemic blood pressure were partly blocked by sedation and anesthesia, because blood pressure remained low throughout the study.

Aldosterone is not known to influence renal blood pressure directly, but it does help to increase systemic blood pressure by increasing the blood volume through reabsorption of sodium and water in exchange for potassium or hydrogen ions in urine, saliva, and gastric juice.[10] The stimuli for increased aldosterone secretion 120 minutes after induction may have been an increased extracellular potassium concentration and increased angiotensin-II concentration.[10] Increased secretion of ACTH may also have contributed to the increased aldosterone concentrations, but ACTH concentrations were not measured. It appears that the increased potassium concentration was the major stimulus for aldosterone secretion in this study, because the aldosterone concentration was not significantly increased until an increase in potassium concentration was measured 120 minutes after induction of anesthesia, whereas angiotensin-II concentration was already high 30 minutes after induction of anesthesia.

Measurements of respiratory rate, body temperature, and end-tidal isoflurane concentration indicated that a steady state of anesthesia had not been reached 30 minutes after induction; however, 90 and 120 minutes after induction, these values were stable. Respiratory rate and tidal volume decreased during anesthesia. This likely reflected the combined respiratory depressive effects of the anesthetics,[32,33] which resulted in hypoventilation and respiratory acidosis during spontaneous breathing. Despite the fact that surgery was not performed, rectal temperature decreased considerably in all dogs during anesthesia, probably as a result of central and peripheral effects of acepromazine.[34] The flow of oxygen in the nonrebreathing system also may have contributed to the low rectal temperature. Inhalation anesthetics can also contribute to hypothermia.[32,33]

Increased ALP activity in urine is considered to be an early indication of renal damage.[35] Although we did not detect significant differences among treatments or over time, changes in the urinary ALP-to-creatinine ratio were seen in 2 male dogs. The ratios were slightly increased (≤ 0.3) and returned to < 0.1 after each anesthetic procedure. In the study of Heiene et al,[35] dogs with acute renal failure had a mean ratio of 0.8 (range, 0.07 to 6.4), whereas healthy dogs had a mean ratio of < 0.1 (range, 0.01 to 0.2). The dogs in the study reported here did not have signs of renal damage. Only 1 of the dogs had an increase in the ratio (to a value of 0.1) after treatment with carprofen. If this were a true effect of carprofen treatment, it would be difficult to differentiate it from a chance occurrence or an effect of anesthesia alone. Secretions from the prostate gland may also be a possible source of ALP in urine,[36] and in view of the fact that only male dogs in the study reported here had a slight increase in the urinary ALP-to-creatinine ratio, it supports the hypothesis that this was the explanation for this finding. In a study of renal function in female dogs undergoing routine ovariohysterectomy, none had an increased urinary ALP-to-creatinine ratio.[37]

The decrease in serum creatinine concentration during anesthesia could have been an effect of acepromazine,[38] perhaps in combination with less-effective transport (perfusion) from the muscles during anesthesia. Possibly, the decrease in concentration was caused by a decreased rate of metabolism during anesthesia-induced hypothermia. Urinary pH increased during the first 30 minutes after induction of anesthesia but decreased toward the end of the anesthetic procedure. Because renal compensatory mechanisms that respond to acidosis are slow and may require 1 to 3

days to return to typical pH,[39] this did not explain the changes in urinary pH.

Increase in the number of leukocytes in urine 20 hours after the anesthetic procedure for 2 of the treatment groups (S-S and C-S treatments) was probably caused by the urinary catheter that was used during the anesthetic procedure. The number of RBC increased during the anesthetic procedure for the C-S treatment, probably also as an effect of the urinary catheter. We did not detect significant differences among treatment groups for these variables, suggesting that the changes were slight or existed to some degree in each treatment group.

Many of the observed changes are known to be effects of acepromazine such as decreases in hematocrit, hemoglobin concentration, circulating WBC counts, and albumin and total protein concentrations during anesthesia. The increase in hemoglobin concentration and hematocrit 3 weeks after the last anesthetic procedure, compared with initial values, may have been an effect of blood loss in connection with sample collection during the study that led to triggering of erythropoiesis. However, assuming this happened, it was not sufficient to cause an increase in mean corpuscular volume. Although we detected a difference between saline treatment and treatments that involved carprofen (C-S and S-C treatments) over time for concentrations of total protein, the clinical relevance of this finding is unknown.

Slight changes in activities of hepatic enzymes in 1 dog did not seem to be associated with carprofen administration. The same dog also had low hemoglobin and hematocrit values, compared with those of the other dogs, at the time of entrance into the study, and the dog may have been slightly less healthy than the others. All Beagles housed at our facility are dewormed at regular intervals (twice yearly), but this dog was treated with an extra dose of anthelmintic (pyrantel embonate) during the 3-week washout period between the second and third anesthetic procedures, and the hemoglobin concentration increased after that treatment. Results of other laboratory variables and physical examination did not indicate subclinical disease in this dog.

Effects of sedation and anesthesia were evident on serum electrolyte concentrations. Similar changes have been described in connection with anesthesia and respiratory acidosis.[40-44] However, significant differences were not observed among the treatments, indicating that carprofen administered before or during anesthesia did not affect results of serum biochemical and hematologic analyses in healthy Beagles.

Although use of plasma clearance is a more reproducible and accurate technique than scintigraphy for measurement of GFR, it was not suitable for the study reported here, because it requires a steady-state condition for up to 4 hours during the collection of blood samples. The tracer-uptake method, using a gamma camera, requires only 5 or 6 minutes; thus, it was the only method suited to the multiple measurements needed at short intervals. Variability was reduced as much as possible by motion correction and use of automatic methods of drawing ROI, which have been determined to yield the best correlation of uptake with known measurements of GFR determined by the use of plasma clearance.[25]

Carprofen can affect prostaglandin synthesis[16,17,a]; however, such effects on prostaglandin synthesis did not have an apparent negative effect on GFR in the study reported here. None of the dogs had a GFR value less than the reference range before, during, or after anesthesia. The reference range (2.45 to 4.48 ml/min/kg) has been determined by personnel in the Department of Clinical Radiology, using scintigraphy to determine GRF in 39 healthy Beagles of both sexes. Glomerular filtration rate did not change during anesthesia in our study despite the low blood pressure values. This may have been attributable in part to the compensatory mechanisms of vasoconstriction of efferent arterioles in the kidneys caused by the renin-angiotensin system responding to the low blood pressure.[7] A vasodilatory effect caused by acepromazine may result in increased renal blood flow, and together with the aforementioned augmentation of blood volume, this may have had a positive effect on GFR. In a study by Newell et al,[45] sedation with acepromazine and butorphanol did not cause a decrease in GFR despite a significant decrease in blood pressure when the dogs were sedated. In another study,[46] sedation with acepromazine increased maximum renal uptake, compared with that for conscious dogs and dogs anesthetized with thiopentone.

Anderson et al[47] reported that hypercapnic acidosis can decrease renal blood flow and GFR during the period when renal perfusion pressure decreases from 125 to 75 mm Hg. The amount of acidosis reached in that study (pH 7.03 ± 0.01) was more extreme than in the study reported here during anesthesia (pH 7.18 ± 0.04). Hypercapnic acidosis is a common finding during anesthesia with spontaneous breathing. In a study of conscious dogs, GFR decreased when renal arterial blood pressure decreased to less than a threshold value of 81 mm Hg.[29] Therefore, the dogs in the study reported here, which were subjected to hypercapnic acidosis and anesthetic agents and whose blood pressures were equal to or less than the lower limits for autoregulation for GFR, should have been at risk for low perfusion caused by COX-1 inhibition. If this had been the case, GFR should have decreased during anesthesia when the dogs were treated with carprofen. Because there was not a significant decrease in GFR for any treatment during or after anesthesia, it would suggest that carprofen does not adversely affect glomerular perfusion in healthy Beagles anesthetized with acepromazine-isoflurane.

The reason for an increase in the time to peak values in the renogram is uncertain. Acepromazine is an α_1-receptor antagonist, and the urinary tract contains α_1-receptors. In the study reported here, the ureters were visible on the scintigrams of several dogs. Acepromazine may have caused dilatation of the ureters by blocking α_1-receptors in smooth muscle. Furthermore, because acepromazine can decrease intraurethral pressures through relaxation of smooth muscle in the preprostatic and prostatic regions of the urethra in healthy anesthetized sexually intact male

cats,[48] it probably has a similar effect on the ureters. Dilatation of the renal pelvis and ureters attributable to the effects of acepromazine could prolong the measured transit time if the pelvis was included in the kidney ROI but not the background ROI. In a study of conscious human volunteers,[49] administration of the NSAID diclofenac affected peristalsis of the ureter and drainage from the kidneys and ureters with a major decrease in frequency of peristalsis, and the time to peak values increased significantly. In the study reported here, we did not detect significant differences in GFR or in time to peak values among the treatments, and an effect of carprofen can be excluded as the sole cause. However, the effects of sedation and anesthesia may have masked a slight effect of carprofen.

Our findings support results of other clinical reports and laboratory studies. Our results are similar to those of studies[50,51] in which renal function was evaluated after administration of carprofen to healthy anesthetized dogs with or without concomitant surgery. Clinically important negative effects were not found in those studies. Ko et al[50] did not find significant differences between carprofen-treated and control dogs in GFR determined by use of scintigraphy or in other measurements of renal function during anesthesia. Values for GFR in that study were lower (1.94 to 2.16 ml/kg/min) than those reported in another study[45] (sedated dogs, 2.80 to 3.13 ml/min/kg) and those for the study reported here (3.5 to 4.0 ml/min/kg). These values are considered to be typical.[52] The lower GFR values reported by Ko et al[50] may have been attributable to differences in anesthetic protocols and differences in methods of calculating GFR. However, those investigators did not measure GFR in conscious dogs, so the effects of anesthesia on GFR cannot be evaluated. Mean arterial blood pressures reached during anesthesia in the study by Ko et al,[50] despite the lack of sedation before anesthesia, may have been a result of the higher end-tidal isoflurane concentration (2%) together with impaired circulation caused by presumed use of positive-pressure ventilation. The method used for ventilation was not stated, but the high end-tidal isoflurane concentration coupled with the fact that the dogs were maintained at normocapnia indicates that positive-pressure ventilation was used. In the study reported here, low mean arterial blood pressures were achieved through the use of anesthesia and sedation. Together with spontaneous breathing, this may have resulted in a more favorable cardiac output in the dogs in our study, compared with the dogs in the study by Ko et al.[50] This may explain, in part, the higher GFR values during anesthesia in our study.

The dose of carprofen used in the study by Ko et al[50] (2.2 mg/kg, PO) was lower than that used in our study (4 mg/kg, IV). In comparison to IV administration, oral administration will cause greater variability in plasma concentrations of drugs as a result of differences among dogs in rate of gastric emptying, bioavailability, and metabolism. Our dose and route of administration, accurate measurement of low blood pressure, and standardized techniques for measurement of GFR provide a reliable assessment of the lack of effect of carprofen on renal function in healthy dogs during anesthesia induced by use of acepromazine-thiopentone-isoflurane.

[a]Akarasereenont P, Mitchell JA, Thiemermann C, et al. Relative potency of nonsteroid anti-inflammatory drugs as inhibitors of cyclooxygenase-1 or cyclooxygenase-2 (abstract). *Br J Pharmacol* 1994;122(suppl):183.
[b]Hydrocath, Ohmeda, Swindon, UK.
[c]Medishield RM121, Chest MI, Tokyo, Japan.
[d]ABL 5, Radiometer, Copenhagen, Denmark.
[e]Uniflow transducer, Baxter Medical AB, Eskilstuna, Sweden.
[f]Sirecust 730, Siemens-Elema, Solna, Sweden.
[g]Siredoc 220, Siemens-Elema, Solna, Sweden.
[h]Capnomac Ultima, Datex-Ohmeda, Helsinki, Finland.
[i]Terumo digital clinical thermometer, Terumo Corp, Tokyo, Japan.
[j]Cobas Mira, Hoffmann-La Roche, Basel, Switzerland.
[k]Unimate 7, Crea, Hoffmann-La Roche, Basel, Switzerland.
[l]ISE (Ion-selective electrode), Na, Hoffmann-La Roche, Basel, Switzerland.
[m]ISE (Ion-selective electrode), K, Hoffmann-La Roche, Basel, Switzerland.
[n]Uni-Kit II, Calcium MTB, Hoffmann-La Roche, Basel, Switzerland.
[o]Unimate 7, inorganic phosphate, Hoffmann-La Roche, Basel, Switzerland.
[p]Unimate 7, TP, Hoffmann-La Roche, Basel, Switzerland.
[q]Unimate 5, alkaline phosphatase, Boehringer Mannheim GmbH, Mannheim, Germany.
[r]Unimate 3, alanine aminotransferase, Boehringer Mannheim GmbH, Mannheim, Germany.
[s]ALB, MPR 3, Boehringer Mannheim GmbH, Mannheim, Germany.
[t]CELL-DYN 3500, Abbott Laboratories, Abbott Park, Ill.
[u]Petroleum benzine, Merck KG aA Darmstadt, Germany.
[v]Aceton, Merck KG aA, Darmstadt, Germany.
[w]RK-ARI, Bühlman Laboratories AG, Allswill, Switzerland.
[x]Catalogue No. RB 320, Eurodiagnostica AB, Malmö, Sweden.
[y]Coat-a-Count aldosterone RIA, Diagnostic Products Corp, Los Angeles, Calif.
[z]Picker SX300, Picker International Inc, Highland Heights, Ohio.
[aa]Hermes nuclear medicine programs, Nuclear Diagnostics, Stockholm, Sweden.
[bb]STATISTICA, 1998 ed, StatSoft, Tulsa, Okla.
[cc]nQuery Advisor, release 4.0, Statistical Solutions Ltd, Cork, Ireland.

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