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Am J Physiol Regulatory Integrative Comp Physiol 281:230-238, 2001.

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Small bowel motility and colonic transit are altered in dogs with moderate renal failure

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Lefebvre, Hervé P., Jean-Pierre Ferré, A. David J. Watson, Cathy A. Brown, Jean-Paul Serthelon, Valérie Laroute, Didier Concorde, and Pierre-Louis Toutain. Small bowel motility and colonic transit are altered in dogs with moderate renal failure. *Am J Physiol Regulatory Integrative Comp Physiol* 281: R230–R238, 2001.—Although gastrointestinal complications are common in patients with renal disease, the effects of renal dysfunction on bowel motility and gut transit times are not well known. We assessed gastrointestinal electromyographic activity, gastric emptying rate, orocolonic transit time, oroanal transit time, and xylose absorption before and after surgically inducing a 66% decrease in glomerular filtration rate in dogs. Moderate renal failure induced no gross or microscopic gastrointestinal lesions but caused a 16–42% increase in gastrointestinal motility indexes. We found a 24% decrease in the propagation velocity of the myoelectrical migrating complex in the duodenojejunal segment, a 30% decrease in phase I duration in duodenal and jejunal regions, a 20% increase in the total irregular electrical activity of the small intestine, and a 22% increase in duration of the meal response in the duodenum and jejunum. Renal failure did not change xylose absorption, gastric emptying rate, and orocolonic transit time but decreased colonic transit time by 38%. The mean weight of feces was increased. These results indicate that moderate renal failure alters duodenojejunal motility and decreases colonic transit time.

gastric emptying; migrating myoelectrical complex; salicylazosulfapyridine; acetaminophen; xylose

EACH YEAR, MORE THAN 60,000 people in the United States develop dialysis-dependent end-stage renal disease (ESRD) (16), with an annual mortality rate of 14% (1). Gastrointestinal complications (mainly nausea and vomiting) occur in 75% of these patients (16); these, together with fluid overload, represent the major causes of hospitalization in this population (1). The conservative medical management of such patients by treating gastrointestinal lesions and dysfunctions is therefore an important concern. Dysfunctions of the esophagus and stomach motility have been described

in uremic patients. Alterations in contraction amplitude, duration, and velocity of middle and distal parts of the esophagus were shown to be a frequent subclinical manifestation of chronic renal failure (RF; see Ref. 12). Uremic, undialyzed patients have normal or delayed transit times (25) and abnormal gastric myoelectrical activity (30).

The cause-effect relationship between lesion and dysfunction is not clear; gastrointestinal signs occur in 38% of patients on renal dialysis without detectable alimentary tract lesions, whereas 61% of patients with gastric or duodenal lesions are symptom free (36). The time course of gastrointestinal dysfunctions or lesions during progression of RF is unknown, and moderate RF, which is frequently observed in geriatric patients, could affect gastrointestinal motility.

We postulated that alterations in intestinal motility may occur in RF based on the following: 1) >25% of patients with ESRD exhibit enteritis (45); 2) diarrhea and constipation occur in 25 and 59% of patients with ESRD (16); 3) prevalence of colonic lesions is high (60%; see Ref. 45); 4) plasma concentrations of gastrointestinal hormones that may modify small bowel motility (e.g., gastrin, CCK, motilin) are increased in renal-impaired subjects (38); and 5) intestinal motility disorders may explain intestinal malabsorption observed in patients with ESRD (38).

The aim of this study was therefore to evaluate in dogs the effect of moderate experimental RF on gastrointestinal electrical activity and its consequences on gastrointestinal transit times. The approach enabled comparison of motility patterns in the same individuals before and after RF. The dog is considered one of the most appropriate models for comparative gastrointestinal pathophysiology studies. The animals studied were not receiving complex drug or dietary therapies and were free of concurrent diseases, unlike many human patients, enabling identification of the effects of RF itself on gastrointestinal functions. Such interfer-

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ing factors (pharmacological agents and nutrients) might contribute to the current lack of available information on intestinal motility in patients with RF. A moderate form of RF was examined in the present study to determine if functional gut alterations occur early in the time course of renal disease.

MATERIALS AND METHODS

Experimental Model of RF

All experiments were approved by the scientific and ethics committee of the National Veterinary School of Toulouse. Male adult Beagle dogs, purchased from Harlan (Gannat, France), were housed in individual cages. The dogs were fed 240 g of a commercial dog food (M25 maintenance; Royal Canin, Aimargues, France) and allowed free access to water.

Experimental RF was induced by decreasing functional renal mass, as described (14). Briefly, the 24 h-fasting dogs were premedicated with acepromazine maleate (0.1 mg/kg im) 30 min before induction of general anesthesia with sodium thiopental (15 mg/kg iv). After endotracheal intubation, anesthesia was maintained with isoflurane (2% vol/vol) in oxygen (1.5 l/min). Briefly, the right kidney was removed, and portions of the left renal cortex were then electrocoagulated by repeated 1-cm stabs for a duration of 1 s with a stainless steel probe connected to an electrocautery unit set at 90 W. The number of stabs per kidney to induce moderate RF was 120. Each dog received morphine hydrochloride (0.5 mg/kg iv) at induction and immediately after the end of surgery.

Glomerular filtration rate (GFR) was assessed by determining total plasma clearance of iothalamate (Contrix 28 Perfusion; Laboratoire Guerbet, Roissy-Charles-de-Gaulle, France) after bolus administration (60 mg/kg) through the right cephalic vein. Jugular blood (1 ml) was sampled before and after administration at 2, 5, 10, 20, 30, 60, and 90 min and 2, 3.5, 6 and 10 h. GFR was determined initially in control conditions and then again 1 wk after chronic implantation of electrodes on the gastrointestinal tract (*protocol 1*), 1 wk after induction of renal impairment, and just before death. Blood was sampled before each GFR assessment to determine plasma osmolality, phosphate, albumin, alanine aminotransferase, alkaline phosphatase, bilirubin, urea, and creatinine concentrations.

Protocol 1: Effect of RF on Gastrointestinal Myoelectrical Activity

As previously described (40), six dogs were each fitted with four pairs of electrodes on the stomach (6 cm before the pylorus), the duodenum (10 cm from the pylorus), the jejunum (25 cm beyond the ligament of Treitz), and the ileum (25 cm oral to the ileocolic junction). Recordings were performed before and 1 wk after induction of RF. The myoelectrical activity was registered with an electroencephalogram machine (mini VIII; Alvar, Paris, France) over 4 days for each period and continuously during 22 h each day (the dogs were released in an outside run from 0800 to 1000). The dogs were fed on *days 1* and *3* and fasted on *days 2* and *4*. The signal was amplified and filtered (high-pass filter 10 Hz). The output signal, band-limited by low-pass filtering (100 Hz), was digitized to a eight-bit analog-to-digital converter, with a sampling frequency of 200 Hz, by a microcomputer system. The values summed over 20 s varied from 0 to 100 arbitrary units. In addition, a motility index for each 60-min period (expressed in arbitrary units) was assessed by summing all

values at 20-s intervals. In the fasted dog, characteristics of the migrating myoelectrical complexes (MMCs) were assessed from the following integrated records: number, duration, velocity of propagation, and duration of the different phases (I, II, and III). The total duration of irregular activity during 22 h of recording was calculated. In the fed dog, the duration of the response to the meal was determined as the time to return of the first MMC. The slow wave frequency of the antrum was measured each day from a 10-min period, 1 h after the meal in the fed dog, and during *phase I* of the MMC in the fasted state.

Protocol 2: Effect of RF on Gastric Emptying, Gut Transit, and D-Xylose Absorption

D-Xylose absorption, gastric emptying rate, orocolonic transit time, and oroanal transit time were measured successively in six dogs before and after 12, 16, 22, and 27 days, respectively, after induction of RF.

Oroanal transit time, total weight, and dry content of feces. The mean transit time (MTT) was calculated by giving 20 plastic pellets of three different colors (1 color/day) in the meal for 3 days (43). The pellets were 3.5 mm in diameter (specific gravity: ~1.3). The oroanal transit time was the mean MTT of the three color series of pellets, with each MTT calculated as follows

$$MTT = \sum (x_j \times t_j) / \sum x_j$$

where x_j is number of pellets of a given color in the j th stool, t_j is the time interval from the ingestion of pellets until the j th stool, and j is the number of defecations from 1 to n , with n being the last defecation with pellets of the series. All feces were collected over 4 days. The number of defecations, fecal weight, and dry matter percentage in feces were determined.

Kinetic studies of gastrointestinal transit markers. All bolus intravenous injections (through the right cephalic vein) and oral administrations (via stomach tube) were performed after ingestion of a 240-g solid meal (acetaminophen, sulfapyridine, and salicylazosulfapyridine) or after fasting (xylose). The following solutions were prepared for intravenous administration with sterile distilled water: 10 mg/l acetaminophen, 150 g/l sulfapyridine, adjusted with 10 N NaOH to pH 12, and 100 g/l D-xylose. For oral administrations, commercially available formulations of acetaminophen (500 mg Doliprane; Théraplix-Rhône-Poulenc Rorer, Paris, France) and salicylazosulfapyridine (Salazopyrine comprimés; Pharmacia, Saint-Quentin-Yvelines, France) and a 500 g/l aqueous solution of D-xylose were used. The nominal doses were 10 mg/kg for intravenous and oral administrations of acetaminophen, 75 mg/kg for oral salicylazosulfapyridine, 50 mg/kg for intravenous sulfapyridine, and 100 (iv) and 500 (oral) mg/kg for D-xylose. Jugular blood samples (1 ml) were obtained at the following intervals: before and at 2, 5, 10, 20, 30 min and 1, 2, 4, 6, 8, 10, and 24 h after intravenous administrations of acetaminophen, xylose, and sulfapyridine; 15, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 h after oral administrations of acetaminophen and xylose; every hour up to 18 h and then 20, 24, 28, 32, and 48 h after salicylazosulfapyridine administration.

Each kinetic study was separated from the following one by a 2- to 4-day washout period.

Pathology. At the end of the experiment, animals were killed by an intravenous overdose administration of pentobarbital sodium. Specimens of kidney, stomach, duodenum, jejunum, ileum, and colon were fixed in 10% buffered formalin and stained with hematoxylin and eosin (all tissues) or hematoxylin and periodic acid-Schiff (kidney only) dyes for

histological examinations. The effect of decreased functioning renal mass on glomerular morphology was determined by examining the intervening viable tissue; 25 glomeruli in each kidney section were rated for the presence of mesangial matrix expansion with a scoring system (0 = normal, 1 = mild, 2 = moderate, and 3 = severe).

Assays

Plasma iothalamate, acetaminophen, and sulfapyridine concentrations were measured by described validated HPLC methods (24, 34). Plasma xylose concentrations were determined by spectrophotometry (33). Within- and between-day precisions for all assays were <13%, and limits of quantitation were 5.0, 0.1, 0.1, and 25 µg/ml for iothalamate, acetaminophen, sulfapyridine, and xylose, respectively. Plasma biochemical variables were measured by standard techniques.

Pharmacokinetic Analysis

Pharmacokinetic parameters were calculated by noncompartmental analysis using a statistical moment approach (21). Gastric emptying rate and orocolonic transit time were determined from the mean absorption time (MAT) of acetaminophen and sulfapyridine, respectively, with MAT determined as follows

$$\text{MAT} = \text{MRT}_{\text{oral}} - \text{MRT}_{\text{iv}}$$

where MRT_{oral} and MRT_{iv} are mean residence times after oral and intravenous administration, respectively.

Deconvolution was used to characterize the instantaneous absorption rate of sulfapyridine and to calculate times required for absorption of 25, 50, and 75% of the sulfapyridine administered orally in the form of salicylazosulfapyridine. Plasma sulfapyridine concentrations after intravenous administration were first fitted to a biexponential equation based on Akaike's information criterion, and then oral absorption of sulfapyridine was modeled using

$$C(t) = \int_0^t F(t - \tau) \times S(\tau) \times d\tau$$

where $C(t)$ is the measured plasma concentration of sulfapyridine at time t , $S(\tau)$ is the input rate of sulfapyridine to be calculated, $F(t)$ is the response function to a unit impulse, and τ is the integration variable. $F(t)$ was identified in a separate experiment solving the $C(t)$ equation for $S(\tau)$ given $Y(t)$ and $F(t)$. Raw data were smoothed using an unweighted least-square spline function, and a discretizing step of 20 min was selected to perform deconvolution (44).

Statistical Analysis

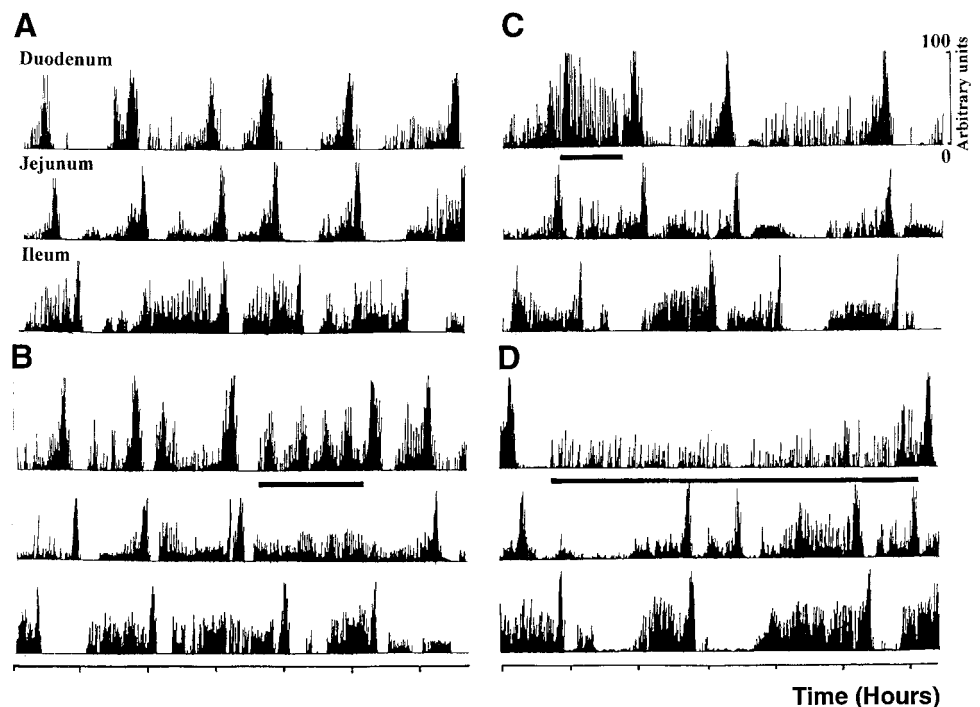
Results are expressed as means $\pm$ SD. Statistical analysis was performed using a general linear model to test status and dog effects. A similar model was used to compare data obtained from myoelectrical recordings during the day and the nighttime in both conditions. Data were considered significant at $P \leq 0.05$. Correlation between colonic transit time and water content in feces was evaluated using Pearson's correlation coefficients.

RESULTS

Model of Experimental RF

All dogs continued to eat during the study, and no signs other than polyuria-polydipsia were observed. Renal surgery induced a decrease in body weight [from 12.2 ± 1.14 kg before renal surgery to 11.3 ± 1.29 kg before death ($P < 0.001$)] but not after chronic implantation of electrodes (*protocol 1*). GFR values of dogs in *protocol 1* were increased after implantation of electrodes (4.8 ± 0.90 vs. 3.6 ± 0.47 ml·kg⁻¹·min⁻¹, $P < 0.01$). GFR decreased in all dogs after induction of RF (1.1 ± 0.53 vs. 3.4 ± 0.50 ml·kg⁻¹·min⁻¹, $P < 0.001$).

Fig. 1. Integrated myoelectrical activity of duodenum, jejunum, and ileum before (A) and after (B-D) renal failure (RF) in a representative fasted dog; the fasted pattern consists of migrating myoelectrical complexes (MMCs) with successive *phases I* (inactivity), *II* (irregular activity), and *III* (regular activity). Main alterations on recordings are indicated by black bars under the traces. After RF, the cyclic pattern was always present, but the amplitude of *phase II* was increased at the three sites of recording. B: the duodenal irregular activity was frequently more intense, grouped in periods lasting 10–20 min, and not systematically propagated. C: the record showed 1–3 periods/day when *phases II* consisted of intense short bursts of activity at intervals of 70–100 s. D: additionally, MMCs of abnormally long duration were observed in the duodenum. Summation of recorded values by the digital converter over 20 s was plotted on the y-axis of a potentiometric recorder.



but increased slightly at the end of the study (1.4 ± 0.51 vs. 1.1 ± 0.53 ml·kg⁻¹·min⁻¹, $P < 0.05$). Increases ($P < 0.001$) in plasma urea (11.6 ± 4.59 vs. 3.8 ± 0.95 mmol/l) and creatinine (180 ± 61.7 vs. 79 ± 15.2 μmol/l) concentrations and in plasma osmolality (311 ± 5.9 vs. 299 ± 3.7 mosmol/kgH₂O) were observed. Pathological examination of electrocoagulated areas of the left kidney revealed coagulative necrosis, papillary necrosis, multifocal mineralization, interstitial fibrosis, lymphocyte infiltration, tubular atrophy, and dilation. In the remnant kidney, there was very mild mesangial matrix expansion (mean score of 0.3). No macroscopic or microscopic lesions were observed in gastrointestinal specimens.

Protocol 1: Effect of RF on Gastrointestinal Myoelectrical Activity

Typical MMCs (Fig. 1A) were observed in both control and renal impaired conditions. In healthy conditions, nighttime was associated with significant changes in MMC durations; the durations of MMCs at the duodenal ($P < 0.05$) and jejunal ($P < 0.001$) levels were increased (from 97 ± 38.6 to 113 ± 44.4 min and from 92 ± 29.2 to 116 ± 48.5 min, respectively). The jejunal *phase I* (+17%, $P < 0.01$), the duodenal (+20%, $P < 0.05$) and jejunal (+27%, $P < 0.01$) *phase II*, and the duodenal *phase III* (+18%, $P < 0.01$) durations were increased during the night period.

RF frequently induced abnormal MMC patterns as follows: 1) frequent and intense irregular activity grouped in periods lasting 10–20 min (Fig. 1B); 2) intense short bursts of activity (Fig. 1C); 3) MMCs of abnormally long duration (>240 min) on the duodenum (Fig. 1D); and 4) MMCs with two consecutive *phase II*s at <30-min intervals. The percentage of abnormal MMCs among the total number was increased in RF conditions in the duodenum (from 9.7 to 42.0%, $P < 0.05$) and the jejunum (from 8.5 to 21.6%, $P < 0.01$) but not in the ileum (9.4 in control vs. 13.2% in RF conditions). In fasted dogs, RF did not significantly modify the number of MMCs over the 22-h period and the mean duration of MMCs. RF induced a decrease in *phase I* duration at duodenal (24 ± 18.9 vs. 34 ± 19.4 min, $P < 0.001$) and jejunal (31 ± 20.2 vs. 45 ± 17.9 min, $P < 0.001$) levels (Fig. 2). RF did not change the duration of *phase II* (73 ± 74.0 vs. 56 ± 42.9 min in the duodenum, 60 ± 54.6 vs. 51 ± 38.1 min in the jejunum, and 80 ± 56.3 vs. 66 ± 46.5 min in the ileum) but increased intraindividual variation in this parameter (intraindividual coefficient of variation ranges 61–85% and 75–137% for the duodenum before and after induction of RF, respectively). No biologically relevant effect was observed on *phase III* duration, although a small increase was observed for the ileum after RF induction (8.5 ± 1.68 vs. 7.4 ± 1.27 min, $P < 0.001$). According to the time (day vs. night) of the recording, more pronounced changes were observed between control and RF conditions. The duodenal and jejunal *phase I* durations during the day were reduced ($P < 0.001$) in renal-impaired dogs (from 33 ± 20.1 to

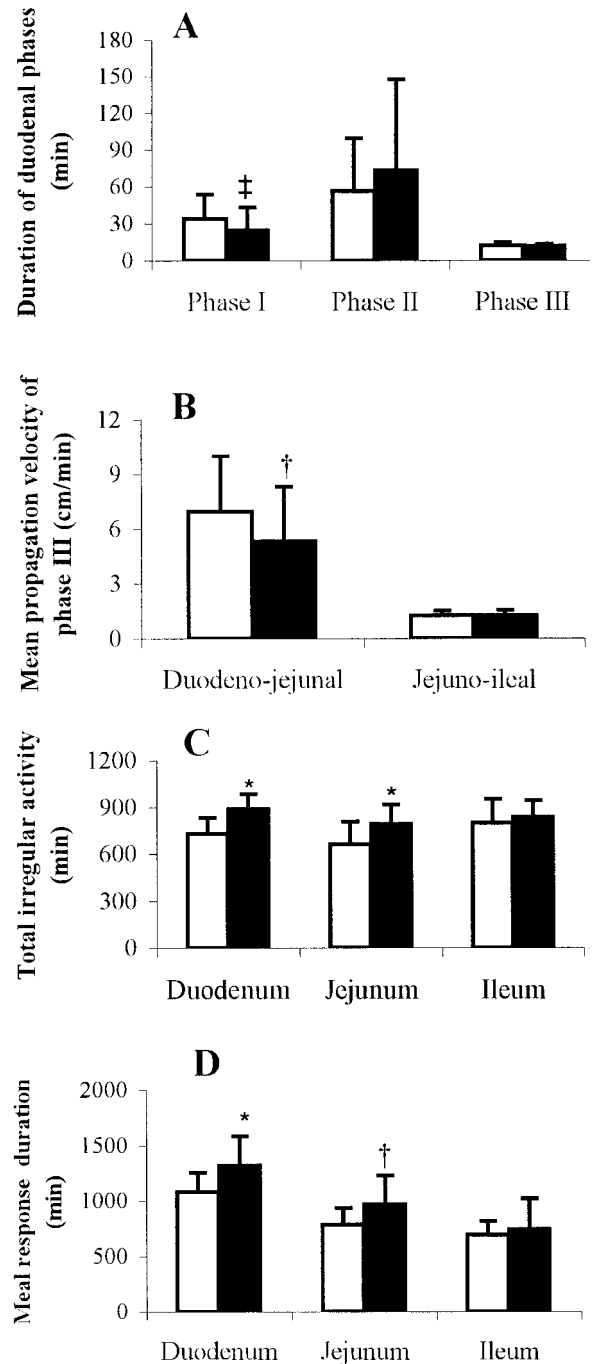


Fig. 2. Duration of the MMC phases in duodenum (A), mean propagation velocity of *phase III* (B), total irregular activity (C), and meal response duration (D) before (open bars) and after (filled bars) RF. Results are expressed as means $\pm$ SD of 6 dogs. * $P < 0.05$, † $P < 0.01$, and ‡ $P < 0.001$ compared with control conditions by ANOVA.

19 ± 13.5 min and from 41 ± 18.4 to 25 ± 16.5 min, respectively). RF induced a decrease, during the night, of the duodenal (from 34 ± 18.9 to 30 ± 21.8 min, $P < 0.05$) and jejunal (from 48 ± 16.8 to 38 ± 21.4 min, $P < 0.001$) *phase I* and duodenal (from 13 ± 2.7 to 11 ± 1.9 min, $P < 0.001$) *phase III* durations. No effect was observed for the ileum, except an increase in the duration of *phase III* (from 7.2 ± 1.1 to 8.6 ± 1.6 min, $P <$

0.001). The propagation velocity of *phase III* was decreased by RF on the duodenojejunal (5.3 ± 3.02 vs. 7.0 ± 3.55 cm/min, $P < 0.01$) but not the jejunoileal (1.2 ± 0.28 vs. 1.2 ± 0.26 , $P > 0.05$) segment (Fig. 2).

The total irregular electrical activity over a 22-h period of the small intestine increased by ~20% (Fig. 2). RF increased the duration of the meal response by 22% in the duodenum ($P < 0.05$) and jejunum ($P < 0.01$), but not ileum, and increased slightly the frequency of antral slow waves in fed dogs (4.5 ± 0.30 vs. 4.3 ± 0.15 , $P < 0.05$). In both fed and fasted states, gastrointestinal hourly indexes were increased by RF ($P < 0.001$); in the fasted state, the percentage of increase was 16, 38, 42, and 26 for stomach, duodenum, jejunum, and ileum, respectively.

Protocol 2: Effect of RF on Gastric Emptying, Gut Transit, and D-Xylose Absorption

The pharmacokinetic parameters of each marker are shown in Table 1.

The MAT of acetaminophen, i.e., the gastric emptying rate, was not modified by RF. The only effect of RF on acetaminophen kinetics was an increase in the MRT_{iv} and MRT_{oral} .

RF decreased the peak plasma concentration of sulfapyridine ($P < 0.05$). RF did not change the time-to-peak plasma concentration (from 8.0 ± 0.9 to 9.9 ± 2.0 h, $P = 0.069$) or MAT (from 8.9 ± 0.8 to 7.4 ± 2.3 h, $P = 0.066$). Deconvolution analysis revealed in all dogs two peaks of absorption rate (at 6.3 ± 0.8 and 12.1 ± 1.5 h) that were not modified in renal-impaired conditions (Fig. 3). The times required for absorption of 25, 50, and 75% of sulfapyridine (6.1 ± 0.8 , 8.0 ± 0.9 , and 11.8 ± 1.3 h, respectively) were not significantly

Table 1. Pharmacokinetic parameters (determined by noncompartmental analysis) of acetaminophen, xylose, and sulfapyridine in six dogs before and after induction of renal failure

Parameter	Status	Test Substances		
		Acetaminophen	Sulfapyridine	Xylose
Cl, ml·min ⁻¹ ·kg ⁻¹	Control	24.3 ± 6.7	5.9 ± 0.8	3.4 ± 0.5
	RF	21.9 ± 9.2	5.7 ± 0.8	1.7 ± 0.1‡
MRT_{iv} , min	Control	36 ± 9	142 ± 10	44 ± 11
	RF	55 ± 18*	153 ± 12	92 ± 12‡
C_{max} , µg/ml	Control	4.1 ± 1.17	7.3 ± 0.80*	935 ± 79
	RF	4.4 ± 1.08	5.9 ± 0.52	1,469 ± 285‡
T_{max} , min	Control	15 ± 0	480 ± 54	55 ± 8
	RF	15 ± 0	591 ± 117	50 ± 8
MRT_{oral} , min	Control	79 ± 21	677 ± 46	100 ± 13
	RF	101 ± 26‡	594 ± 146	150 ± 14‡
F, %	Control	58 ± 11	59 ± 6	79 ± 9
	RF	57 ± 10	49 ± 13	79 ± 11
MAT, min	Control	43 ± 24	534 ± 46	56 ± 8
	RF	47 ± 22	441 ± 135	58 ± 15

Values are means ± SD. Cl, total plasma clearance determined after intravenous administration; MRT_{iv} , mean residence time after intravenous administration; C_{max} , peak concentration after oral administration; T_{max} , time to C_{max} ; MRT_{oral} , mean residence time after oral administration; F, oral bioavailability; MAT, mean absorption time; RF, renal failure. Differences between control and RF statistically significant at * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

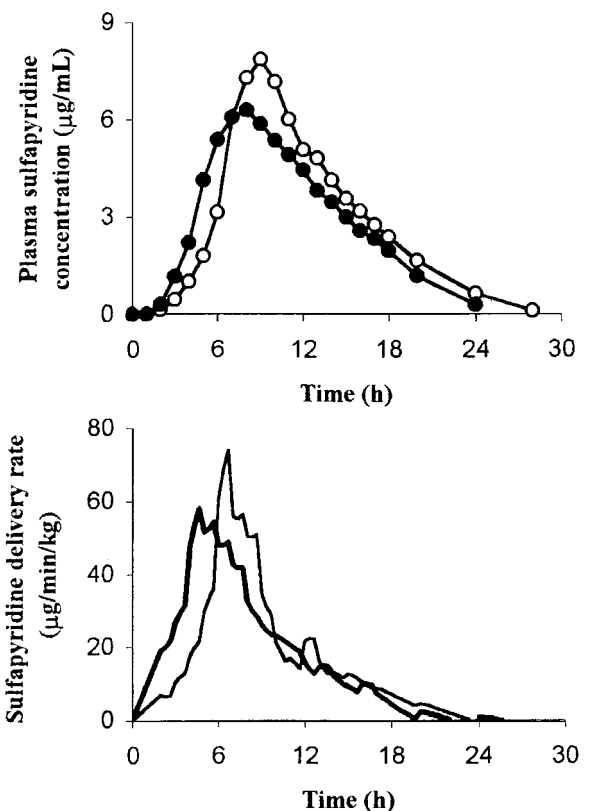


Fig. 3. Plasma profile (A) of sulfapyridine after oral administration of salicylazosulfapyridine and instantaneous sulfapyridine delivery rate (B) from colon into the circulation in a representative dog before (thin line and ○) and after (thick line and ●) RF.

changed by RF. The oroanal transit time was decreased in renal-impaired dogs (19.0 ± 5.8 vs. 25.5 ± 8.0 h, $P < 0.01$). RF induced a significant decrease (10.2 ± 3.3 vs. 17.5 ± 5.2 h, $P < 0.05$) in colonic transit time (estimated from the difference between total transit time and time for 50% absorption of sulfapyridine). The rate of defecation was unchanged (8 ± 1.2 vs. 7 ± 1.4 defecations over 4 days in renal-impaired and control conditions, respectively). The mean weight of each dog's feces (74 ± 19.4 vs. 61 ± 26.0 g, $P < 0.01$) was significantly increased, but the proportion of dry matter remained unchanged (32 ± 4.4 vs. $31 \pm 4.9\%$ in RF and control conditions, respectively). The total amount of water excreted in feces over 4 days was correlated with the colonic transit time (coefficient of correlation: -0.761 , $P = 0.004$; Fig. 4).

RF modified xylose disposition (Fig. 5 and Table 1). Plasma xylose clearance was decreased; MRT_{iv} , MRT_{oral} , and peak plasma concentration were increased, but oral bioavailability and MAT were not altered in renal-impaired dogs.

DISCUSSION

The noteworthy findings of this study are that moderate RF induces 1) alterations in gastrointestinal electrical activity, namely increases in stomach and small bowel indexes, irregular activity and meal responses, and reduced *phase I* MMC duration, 2) no changes in

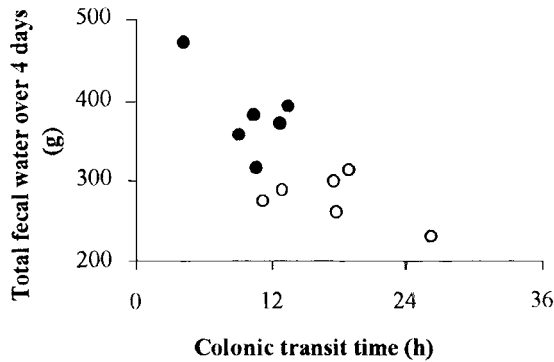


Fig. 4. Correlation between the total amount of water excreted in feces over 4 days and the colonic transit time (Pearson's correlation coefficient: -0.761 , $P = 0.004$). $\circ$ and $\bullet$, values before and after RF, respectively.

transit times of the proximal gut, 3) a decrease in oroanal transit time, which is largely explained by a decrease in colonic transit time, associated with increased water quantity in feces, and 4) no change in intestinal xylose absorption. It should be emphasized that these dysfunctions were not clinically detectable and not associated with apparent gastrointestinal lesions.

A canine model was used because fasted gastrointestinal motility patterns (13) and gastrointestinal signs in RF (vomiting, nausea, and diarrhea) are quite similar in dogs and humans. The main advantages of this surgical model were its specificity, the potential to induce various levels of renal dysfunction (14), and the stability of GFR values after induction of renal impairment (29). The increase in GFR after chronic implantation of electrodes is difficult to explain but was probably transitory. The extent of renal dysfunction induced in the present study corresponds to moderate RF, based on clinical signs, GFR assessment, and biochemical variables.

RF-induced myoelectrical activities of stomach and small bowel together have not been reported previously. Abnormal myoelectrical activity (such as tachygastrias) has been found in 48% of patients with unexplained nausea and vomiting (20). RF does not appear to alter gastric electrical activity in dogs, apart from a mild increase in frequency of antral slow waves. Electrogastrography in nondiabetic patients with RF revealed a 30% decrease in the mean percentage of normal slow waves compared with healthy controls (30). This discrepancy with our results may well be explained by the fact that human patients were symptomatic, unlike the dogs.

MMC patterns in control conditions were similar to those previously described in healthy dogs (9). RF induced an increase in total irregular activity in the fasted state, duration of meal response, and gastrointestinal motility indexes. The myoelectrical alterations were much more pronounced in the duodenojejunal than in the ileal parts, whatever the time of the day. The results demonstrated that these alterations decreased in frequency and intensity during the propa-

gation of the MMC from the duodenum to the ileum. RF multiplied the occurrence of abnormal MMCs by 4.3 for the duodenum and 2.5 for the jejunum. Therefore, the duodenum appeared much more sensitive to RF. Atypical MMC patterns have been described previously. A decrease in amplitude and disruption of the slow-wave pattern, an intense complex of spikes migrating in an aboral direction, and a disruption of the MMC have been observed, for example, in canine trichinosis (41). The fasted pattern was altered and similar to the fed pattern in uninfected dogs with the addition of migrating action potential complexes (MAPCs), i.e., action potential discharges of 2.5 s or longer and occurring at a minimum of three consecutive electrode sites (31). MAPCs, occurring concomitantly with vomiting and diarrhea, have been interpreted as a defense mechanism of the host to bacterial infection, under the control of the enteric nervous system, functioning to clear unwanted substances from the intestinal lumen (31, 41). However, in the dogs of the present study, clinical signs were not observed, and bursts of activity could not be interpreted as MAPCs because they were not propagated on the three electrode sites of the small bowel.

The second part of the study showed that RF-induced myoelectrical disturbances of the small intestine had no detectable effect on transit times through the stomach and small bowel. MAT of acetaminophen was used as an indicator of gastric emptying rate. Acetaminophen is a marker of the liquid phase of gastric emptying; therefore, our results are not extrapolatable to solids, because gastric residence time increases with increasing solid particle size, approaching a plateau value (~ 7.5 h and 1.5 h in the fed and fasted dog,

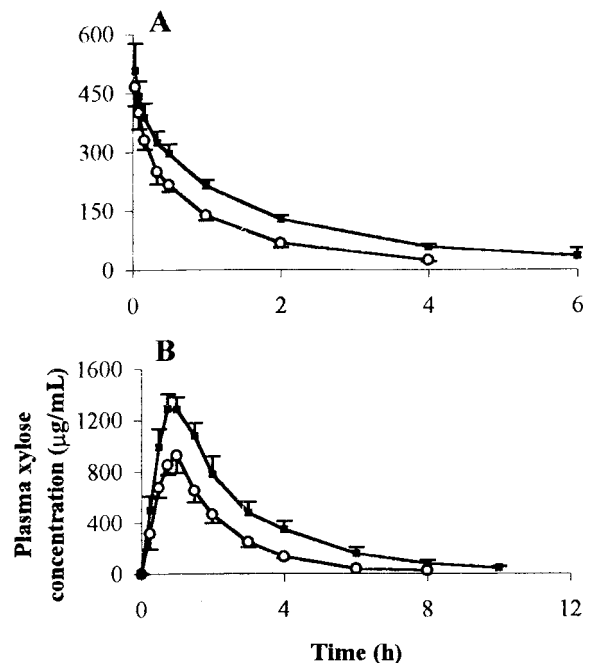


Fig. 5. Mean $\pm$ SD plasma profile of xylose after intravenous (A) and oral (B) administration of xylose in 6 dogs before (thin line and $\circ$) and after (thick line and $\bullet$) RF.

respectively) with particles >5 mm in diameter (23). Gastric emptying rate assessed by acetaminophen MAT was not modified by RF and was similar (~45 min) to that determined previously in dogs (34). In rats with experimental RF, gastric emptying rate of liquids was not changed but that of solids was decreased by 68% (39). In human patients with ESRD, results are conflicting; some investigators found no effect on gastric emptying (32), but more recent studies indicated that gastric emptying of solids (26), semisolids (15), and liquids (38) was delayed. A potential explanation for these discrepancies may be the categories of patients involved. Most studies of hemodialysis patients failed to demonstrate delayed gastric emptying, although such disturbances were frequently observed in patients on continuous ambulatory peritoneal dialysis (CAPD). Some authors concluded therefore that the addition of 2 liters of dialysate to the abdomen retards gastric emptying, possibly by mechanical or neurogenic (reflex) mechanisms (4).

The absence of an effect of RF on MAT and oral bioavailability of D-xylose, which is mainly absorbed from the duodenum in dogs (7), supports the finding that transit times in the gastroduodenal region were not modified in our study. D-Xylose was used here as 1) an indicator of the functional capacity of intestinal absorption because its disposition has been documented in patients with ESRD (47) and 2) a transit marker because absorption of D-xylose is affected by relatively minor changes in intestinal transit of digesta in dogs (8). Worwag et al. (47) found similarly that, in human patients with uncomplicated moderate to severe RF, D-xylose oral bioavailability was not modified ($77 \pm 14.8\%$ in patients vs. $69 \pm 13.6\%$ in normals). These results may suggest no major dysfunction in proximal intestinal absorption in early RF. The absence of effects on oral bioavailability of acetaminophen also supports this assumption, but the specific absorption test would be of interest to document this hypothesis.

Orocolonic transit time was assessed using salicylazosulfapyridine, as described previously in dogs (34) and humans (28). After oral administration, salicylazosulfapyridine reaches the colon intact, where its azo bond is hydrolyzed by bacterial enzymes, yielding sulfapyridine and 5-aminosalicylic acid (28). The first appearance of sulfapyridine in plasma, which is generally used to assess small bowel transit time, signals only the arrival of the front of a bolus in the large bowel. It does not indicate the average small intestine transit time. We preferred to use the time for 50% absorption of sulfapyridine to assess small bowel transit time, necessitating determination of intravenous kinetics of sulfapyridine. The sulfapyridine MAT (~7.4 h) and the lag time for absorption of sulfapyridine (~1.6 h) in control conditions were similar to those described previously (34). Absorption of sulfapyridine from the canine colon showed two peaks 5.8 h apart, with the first peak ~4.8 h after the first appearance of sulfapyridine in plasma. The two peaks probably result from two consecutive bolus arrivals of salicylazosulfapyridine in

the colon, because ~50% of a marker is propelled in the canine colon by the passage of a single MMC through the terminal ileum (42). The time required for 50% of the marker to enter the colon was similar in fed and fasted dogs (42). The absence of effects of RF on oral bioavailability and times to peak absorption rate of sulfapyridine indicate that bacterial hydrolysis and colonic absorption may not be altered in RF.

RF induced only a trend toward decreased orocolonic transit time, which contrasts with effects on small bowel electrical activity. In healthy fed dogs, the continuous irregular spiking activity is indeed associated with increased propulsion of digesta (6). We were surprised, therefore, that the increase in the meal response of the duodenojejunal electrical activity did not detectably shorten the transit time. This suggests that either the irregular activity observed does not propel the luminal contents as well in healthy animals or that measurement of orocolonic transit time did not allow detection of a transit change, as demonstrated previously (28, 34). This discrepancy may also be explained by ileal effects that may compensate for decreased transit time in the duodenum and jejunum. The effect of RF on the ileum was indeed much less pronounced, and *phase III* fronts migrate slowly through the canine terminal ileum (37).

One previous human study showed that gastric and small bowel transits were not altered in uremic nondiabetic patients with either ESRD, CAPD, or hemodialysis treatment (19). No effect was evident for colonic transit time, except for CAPD patients, where the orocolonic transit time was prolonged significantly (71 h) compared with that in healthy volunteers (40 h). These results are in contrast with ours, but 1) the measurement of orocolonic transit time appears relatively semiquantitative if performed by the patient himself; 2) the prolonged transit in patients with CAPD may result from peritoneal adhesions and strictures, complications of CAPD, or compression of the intestine by the dialysate infused into the abdomen several times a day; and 3) only patients with advanced RF were examined.

The most striking effects of moderate RF on gastrointestinal transit in dogs were the 38% decrease in colonic transit time and the 24% decrease in oroanal transit time. The colonic transit time was determined from the difference between the oroanal transit time and the time required for 50% absorption of sulfapyridine, but a similar effect was demonstrable using the 25 and 75% absorption times. The colonic transit time determined here in control conditions was similar to that determined radiographically in normal dogs (5) and represented 70 and 55% of the oroanal transit times before and after induction of RF, respectively. The decrease in colonic transit time was correlated to higher fecal water quantity. Because increased water excretion in the colon does not affect colonic motor activity in dogs (27), the increased fecal water may result from reduced water reabsorption because of the quicker colonic transit.

The underlying causes of the RF-induced alterations of gastrointestinal motility were not determined and are probably multifactorial. Three distinct nonexclusive phenomena may be hypothesized. Effects of gastrointestinal hormones should probably be considered one major hypothesis. The kidney plays a major role for the plasma clearance and inactivation of many gastrointestinal hormones, and especially gastrin and CCK. About 30% of endogenous canine gastrin is extracted from the renal artery plasma in a single pass through the kidney (11). No data are available for dogs, but rats with bilateral nephrectomy exhibited an almost eight-fold increase in serum gastrin activity (10). Gastrin and CCK are able to induce a pattern of spike activity resembling that of the fed state in the small bowel (35, 46) and are also able to stimulate motility of the colon (3). The minor effects of RF on gastric motility in the present study may result from the opposite effects of gastrin and CCK on gastric emptying.

Another explanation for motility disorders would be autonomic dysfunction, based on what has been described or hypothesized in renal-impaired human patients with delayed gastric emptying. This so-called uremic gastroparesis has been attributed to an advanced autonomic neuropathy (15). Such mechanism cannot be considered here because of the minor effect of RF on canine gastric motility. Nevertheless, it cannot be excluded as an explanation for RF-induced effects on colonic transit. Dysfunction of sympathetic adrenergic inhibitory innervation (by mesenteric ganglia ablation) of the canine colon was indeed shown to shorten colonic transit time considerably (up to 6-fold) without alteration in small bowel transit (5). In such conditions, colonic storage capacity is decreased without diarrhea, which could also explain RF-associated colonic transit disturbances. After ganglionectomy, defecation rate was increased, and the dry matter content of the feces was decreased, unlike in the present study. Moreover, such sympathetic dysfunction cannot be invoked to explain small bowel myoelectrical alterations, as the effect of total sympathectomy on the canine small bowel is minor (22).

The third hypothesis is based on the fact that the amount of feces increased in RF conditions, which indicates an overall quantitative malassimilation process. In other words, alterations in motility patterns would be the consequence of a decrease in digestibility. In a recent study, life-threatening undernutrition was shown in about one-third of 7,123 hemodialysis patients (2). In our study, only a moderate 7% decrease in body weight was observed in renal-impaired dogs, but the postoperative period was too short to adequately disclose undernutrition. Impaired pancreatic, but not biliary, secretion has been involved in patients with chronic RF (16, 38) because histological evidence of pancreatitis was found in varying proportions of patients, but no study to our knowledge has documented the efficiency of digestion in RF. Whatever the cause of maldigestion, the increased intraluminal volume after induction of RF, as suggested by the increase in fecal weight with constant food intake, may induce a longer

meal response and shorter colonic transit time in RF (17). In dogs, it is not the composition but the volume of the luminal contents that determines the changes in the postprandial colonic motility (18). Moreover, indigestible particles added to canned food were shown to decrease the mean residence time of digesta from 28 to 17–20 h in dogs (8).

Perspectives

This study provides the first evidence that moderate RF alters small bowel motility in the absence of gastrointestinal signs or gut lesions. The orocolonic transit time is unaffected, but colonic transit is quicker, and fecal water and dry weight increase. These results suggest that subclinical dysfunction appears before lesions and should therefore be assessed early in the time course of the renal disease. The duodenojejunal myoelectrical response to RF appears more pronounced than that of the stomach and the distal parts of the small bowel but apparently was not able to change the orocolonic transit time. The reduced colonic transit time appears to be one of the major alterations. The underlying mechanisms of RF-induced gastrointestinal dysfunction remain unknown and may involve various neurohormonal and luminal factors. It is not clear whether these findings are transferable from dogs to human patients. However, because gastrointestinal complications are the major cause of hospitalization for patients with ESRD, the present study should encourage further assessment of gastrointestinal function in these patients, especially by longitudinal clinical studies.

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