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Time-Restricted Feeding Schedules Modify Temporal Variation of Gentamicin Experimental Nephrotoxicity

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The effect of timing of gentamicin dosing relative to food access periods was evaluated in experimental animals. Female Sprague-Dawley rats were treated for 4 and 10 days with gentamicin (40 mg/kg of body weight/day) intraperitoneally at either 0700, 1300, 1900, or 0100 h according to three food presentation schedules: food was available from 0800 to 1600 h in the first group, from 1600 to 0000 h in the second group, and from 0000 to 0800 h in the last group. Animals were thus subjected to a restricted feeding period. Results indicate that time-restricted feeding schedules displace the peak and the trough of gentamicin-induced renal toxicity, as evaluated by changes in the inhibition of sphingomyelinase activity, cellular regeneration (incorporation of [^{3}H]thymidine into DNA of renal cortex), and blood urea nitrogen and serum creatinine levels, as well as histopathological lesions observed after 10 days of treatment. In fact, the toxicity was minimal when gentamicin was injected during the feeding period, while the maximal toxicity was found when gentamicin was administered during the fasting period. It is concluded that the feeding period can modulate aminoglycoside nephrotoxicity. The time of dosing of gentamicin relative to the time of feeding seems to be a more important modulator of gentamicin nephrotoxicity than the light-dark cycle.

Gentamicin is an antibiotic belonging to the aminoglycoside family, and it is used for the treatment of severe gram-negative bacterial infections including those caused by *Pseudomonas aeruginosa*. As with all other members of this antibiotic family, nephrotoxicity is an important factor limiting the clinical use of gentamicin. The mechanisms by which aminoglycosides induce nephrotoxicity are not completely elucidated. Following glomerular filtration, gentamicin accumulates in renal proximal tubular cells, where it induces a lysosomal phospholipidosis (2, 14). Discharge of lysosomal and brush border membrane enzymes in tubular lumina, cellular necrosis, and postnecrotic cellular regeneration are other manifestations observed following treatment with aminoglycosides (10, 16).

Time of administration is one of many factors that can modulate gentamicin-induced renal toxicity. Nakano and Ogawa (21) were the first to report that gentamicin killed more mice when the drug was injected in the middle of the rest period than during the middle of the activity period. Pariat et al. (24) observed that urinary excretion of *N*-acetyl-β-D-glucosaminidase and γ-glutamyltransferase in rats was higher when gentamicin was administered at 2000 h than at 0800 h. Yoshiyama et al. (29) showed that gentamicin injected in the middle of the rest period induced a higher renal toxicity than gentamicin injected in the middle of the activity period. The results of studies done in our laboratory concurred with the results of those studies by demonstrating that tobramycin nephrotoxicity was maximal when rats were injected in the middle of the rest period and minimal when they were injected in the middle of the activity period (18).

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Because the minimal toxicity was found during the period of maximal food intake, we previously evaluated the effect of fasting on the temporal variation in the nephrotoxicity of aminoglycosides. This study demonstrated that fasted rats are more susceptible to the renal toxicity of gentamicin and that fasting modified temporal variations in the nephrotoxicity of gentamicin (1). These data suggest that food intake may be responsible in part for the temporal variations in the nephrotoxicity of aminoglycosides. Since it is well acknowledged that periodic access to food synchronizes several circadian rhythms (5), the present study sought to verify the influence of time-restricted feeding schedules on temporal variation in the nephrotoxicity of gentamicin in rats.

MATERIALS AND METHODS

Animals and treatment. Female Sprague-Dawley rats weighing 160 to 200 g were used throughout this study. They were maintained on a 14-h light (rest period) and a 10-h dark (activity period) schedule, with the light on at 0600 h. The animals were divided into three groups of 96 rats each according to the feeding schedule. The first group had access to food (Rat Chow; Charles River Breeding Laboratories, Montréal, Québec, Canada) only between 0800 and 1600 h, whereas food was available to the second group at between 1600 and 0000 h and to the third group at between 0000 and 0800 h. Rats were acclimatized to these conditions 10 days prior to the beginning of treatment. Tap water was available ad libitum for all groups. Animals were treated for 4 and 10 days with gentamicin (40 mg/kg of body weight/day) given intraperitoneally (i.p.) at either 0700, 1300, 1900, or 0100 h. For each treated group (n = 6 rats), a corresponding control group (n = 6 rats) received saline (NaCl, 0.9%) i.p. Rats were killed by decapitation on day 5 or 11 of the experiment (18 to 24 h after the last injection). One hour before sacrifice, each rat received an i.p. injection of 200 μCi of [^{3}H]thymidine. At sacrifice, blood was collected and centrifuged, and the serum was immediately frozen (−20°C) for subsequent determination of creatinine and blood urea nitrogen (BUN) levels. The kidneys were removed, and the renal cortex was dissected out and snap frozen on dry ice for further measurement of the cortical concentration of gentamicin, the incorporation of [^{3}H]thymidine into cortical DNA, and sphingomyelinase activity. A piece of renal cortex was put in a drop of buffered glutaraldehyde (2%) and was cut into small cubes of 1 mm^3. These cubes were incubated overnight at 4°C in the same fixative.

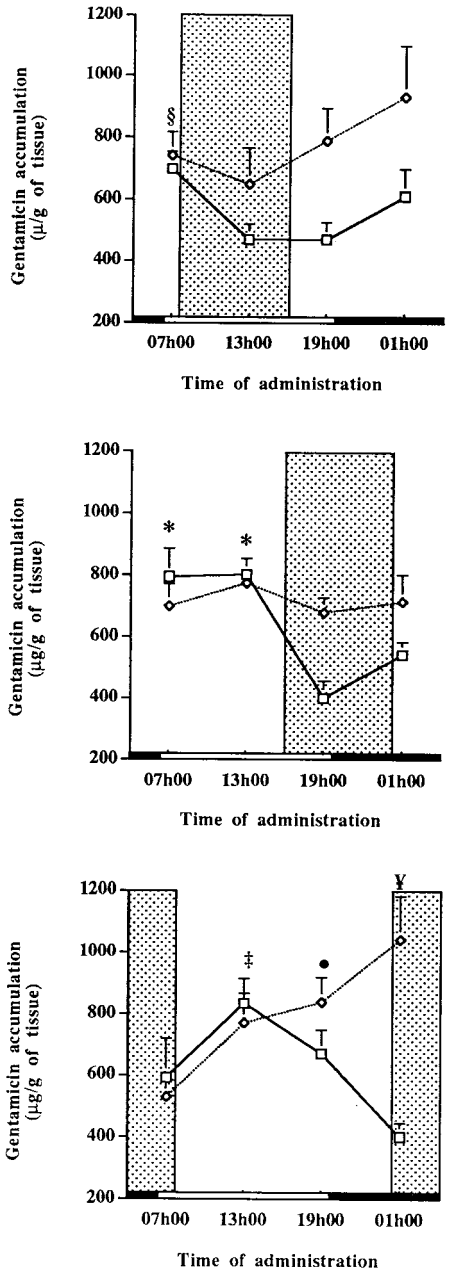

FIG. 1. Effects of time-restricted feeding schedule on the renal cortical accumulation of gentamicin (mean ± SEM). Rats were treated with gentamicin (40 mg/kg/24 h) for 4 and 10 days at either 0700, 1300, 1900, or 0100 h and were fed from either 0800 to 1600, 1600 to 0000, or 0000 to 0800 h. §, significantly different from animals treated at 1300 and 1900 (4 days; $P < 0.01$); *, significantly different from animals treated at 1900 h (4 days; $P < 0.01$); ¥, significantly different from animals treated at 0700 and 1300 (10 days; $P < 0.05$); ●, significantly different from animals treated at 0700 h (10 days; $P < 0.05$); ‡, significantly different from animals treated at 0100 h (4 days; $P < 0.05$). Shade boxes, food access period; open bars, light period; closed bars, dark period; □, day 4; ◇, day 10.

Gentamicin levels in the renal cortex. Gentamicin accumulation in the renal cortex was measured by a fluorescence polarization immunoassay (TDX system; Abbott Diagnostics, Mississauga, Ontario, Canada). Frozen samples of renal cortex were homogenized in cold water with a Tissue-Tearor. Homogenates were sonicated and diluted in TDX buffer to obtain concentrations of between 0 and 10 μg/ml. The lower limit of sensitivity of this assay was of 3 μg/g of tissue. The interday coefficients of variation were 3.44% at 1 μg/ml and 2.72% at 8 μg/ml.

Biochemical analysis. Sphingomyelinase activity in the renal cortex was measured by a previously published method (15). The DNA synthesis rate in the renal cortex (an index of cellular necrosis) was measured by the method of Laurent et al. (16). Serum creatinine and BUN levels were measured by an automated enzymatic method (with a Hitachi 737 analyzer).

Histology. Cubes of 1 mm^3 taken from the cortex were left overnight in the same fixative at 4°C and were washed with phosphate buffer (0.1 M; pH 7.4). The cubes were further fixed in 1% osmium tetroxide for 60 min, dehydrated in ascending grades of alcohol, and embedded in Araldite 502 epoxy resin. Thick sections (1 μm) were cut with an Ultracut S ultramicrotome (Leica Canada Inc., Québec, Québec, Canada), stained with hot toluidine blue, and observed by using a blinded code to identify gross lesions.

Microscopic renal lesions were scored on plastic sections at a magnification of ×400. Each slide was coded so that identification of the groups was not possible for the observer (L.G.). Slices came from three different pieces of renal cortex for each rat, and only four rats per group were selected at random. The following lesions in the renal cortex were scored: isolated cell necrosis, tubular necrosis (proximal tubule with more than 50% necrotic cells), tubular desquamation (proximal tubule with 100% necrotic cells), and metachromatic materials in the tubular lumina. The number of interstitial cells (no specification of cell type was made) and the total number of proximal tubules on each slice were also measured. The number of isolated necrotic cells, the number of necrotic tubules, the number of desquamated tubules, and the number of proximal tubules with metachromatic materials in the tubular lumina were recorded as percentages of the total number of proximal tubules on each respective slice and were assigned a score as follows: 0 to 9%, 1; 10 to 19%, 2; 20 to 29%, 3; etc. The score for the interstitial cells was obtained by dividing the total number of interstitial cells by the total number of proximal tubules on each respective slice. The lesion scores were summed to produce a single toxicity score for each animal.

Statistical analysis. Data are presented as means ± standard errors of the mean (SEMs). Statistical analysis of the data was performed by using SuperANOVA Software (Abacus Concepts Inc., Berkeley, Calif.). Groups were compared by an analysis of variance (ANOVA) method. When the Fisher F test was significant ($P < 0.05$), multiple comparisons were done by the Tukey-Kramer method. Multivariate ANOVA was also performed in order to determine the relative importance of the feeding state and the activity status on gentamicin nephrotoxicity. The Wilk's Lambda test was performed, and a P value of <0.05 was considered significant.

Materials. Rats were purchased from Charles River Breeding Laboratories (Montréal, Québec, Canada). Gentamicin was kindly provided by Schering Canada Inc. (Pointe-Claire, Québec, Canada). [*N-methyl*-^{14}C]sphingomyelinase (58 mCi/mmol) and [*methyl*-^{3}H]thymidine (47 Ci/mmol) were bought from Amersham Canada Ltd. (Oakville, Ontario, Canada). Sphingomyelinase (from bovine brain) was purchased from Sigma Chemical Co. (St. Louis, Mo.). All other products used were of analytical grade and came from Fisher Scientific Ltd. (Québec, Québec, Canada) and from Sigma Chemical Co.

RESULTS

The intracortical accumulation of gentamicin measured after 4 and 10 days of treatment is illustrated in Fig. 1. In animals fed from 0800 to 1600 h and treated with gentamicin for 4 days, the levels of gentamicin in the renal cortex were significantly higher in rats treated at 0700 h than in those treated at 1300 and 1900 h ($P < 0.01$). In animals fed from 1600 to 0000 h, significantly higher levels of gentamicin were measured in rats injected at 0700 and 1300 h than in those injected at 1900 and 0100 h ($P < 0.01$). Significantly higher levels of gentamicin were observed in the renal cortexes of rats treated at 1300 and fed from 0000 to 0800 h than in those treated at 0100 h ($P < 0.05$). After 10 days of treatment, the peak and the trough gentamicin accumulation were observed when gentamicin was injected at 0100 and 1300 h, respectively, in animals fed from 0800 to 1600 h and at 1300 and 1900, respectively, in animals fed from 1600 to 0000 h, although these data are not significantly different from those for the other groups (Fig. 1). In animals fed from 0000 to 0800 h, gentamicin accumulation was significantly higher in animals injected at 0100 than in animals injected at 1300 and 0700 h ($P < 0.05$). The accumulation of gentamicin was also significantly higher in animals injected at 1900 h than in those injected at 0700 h (Fig. 1).

The effects of timing of gentamicin dosing relative to food access periods on the inhibition of sphingomyelinase activity, cellular regeneration and BUN and serum creatinine levels are illustrated in Fig. 2 to 5. No significant difference in any of the parameters evaluated was found among the groups after 4 days of treatment (data not shown). The sphingomyelinase activity

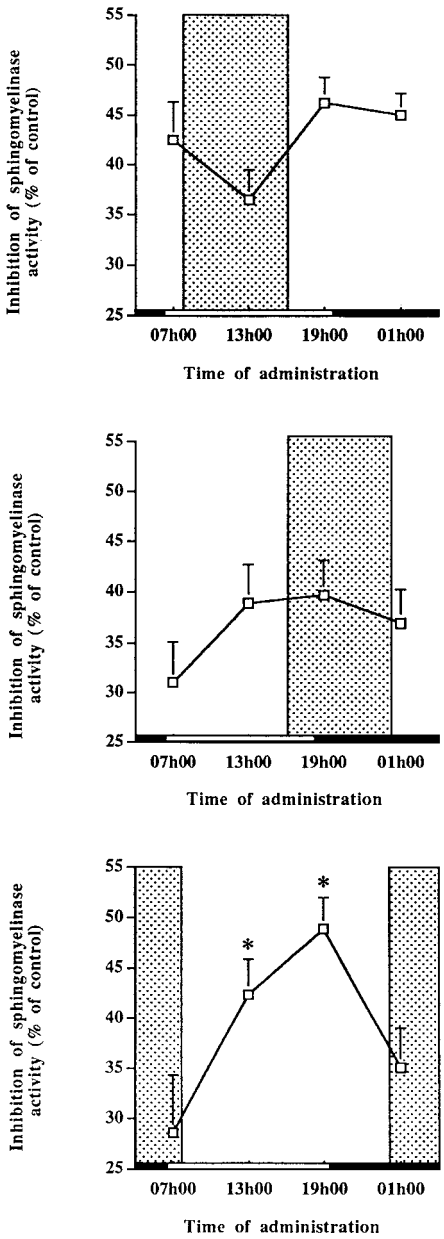

FIG. 2. Effects of time-restricted feeding schedule on gentamicin-induced inhibition of sphingomyelinase activity (mean ± SEM). Rats were treated with saline (NaCl; 0.9%) or gentamicin (40 mg/kg/24 h) for 10 days at either 0700, 1300, 1900, or 0100 h and were fed from either 0800 to 1600, 1600 to 0000, or 0000 to 0800 h. *, significantly different from animals treated at 0700 and 0100 h ($P < 0.05$). Data for all treated groups are significantly different from those for the respective time-matched control groups ($P < 0.05$). Shaded boxes, food access period; open bars, light period; closed bars, dark period; □, gentamicin.

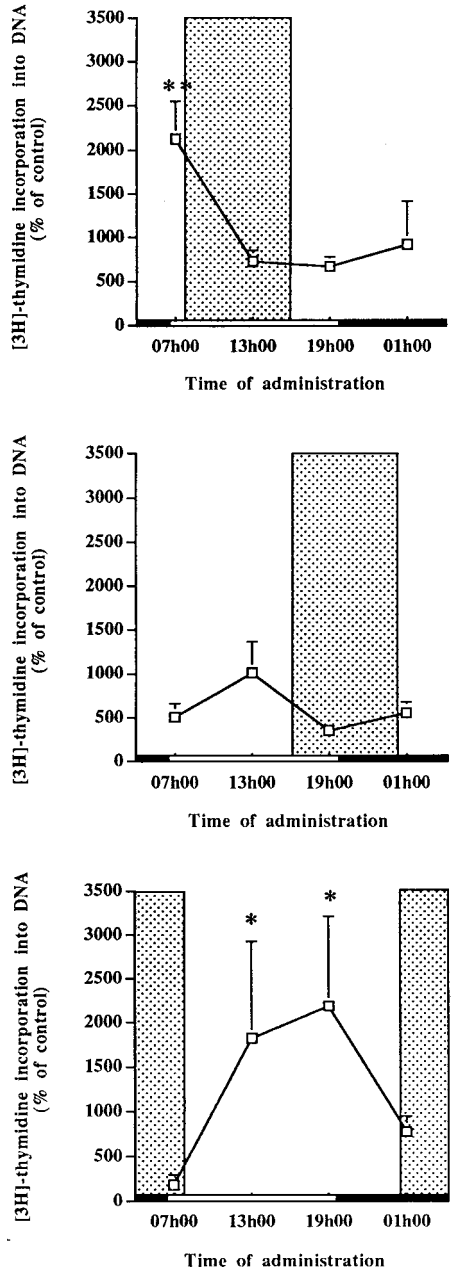

FIG. 3. Effects of time-restricted feeding schedule on gentamicin-induced increase in cellular regeneration (mean ± SEM). Rats were treated with saline (NaCl; 0.9%) or gentamicin (40 mg/kg/24 h) for 10 days at either 0700, 1300, 1900, or 0100 h and were fed from either 0800 to 1600, 1600 to 0000, or 0000 to 0800 h, **, significantly different from all other groups ($P < 0.05$); *, significantly different from the time-matched control group and from animals treated at 0700 and 0100 ($P < 0.05$). Shaded boxes, food access period; open bars, light period; closed bars, dark period; □, gentamicin.

was significantly lower in all gentamicin-treated animals ($P < 0.05$) than in the time-matched control groups, independent of the feeding schedules (Fig. 2). In animals fed from 0800 to 1600 h and from 1600 to 0000 h, no significant difference was observed in the inhibition of sphingomyelinase activity among the different times of injection. In animals fed from 0000 to 0800 h, the inhibition of sphingomyelinase activity was significantly higher in animals injected at 1300 and 1900 h than in animals receiving the aminoglycoside at 0700 and 0100 h ($P < 0.05$) (Fig. 2).

In animals fed from 0800 to 1600 h, the cellular regeneration was significantly higher ($P < 0.05$) in animals injected at 0700 h than in rats receiving gentamicin at 1300, 1900, and 0100 h (Fig. 3). No significant difference in cellular regeneration was observed among the rats injected with gentamicin at different times and fed from 1600 to 0000 h. In animals fed from 0000 to 0800 h, the cellular regeneration was significantly higher in animals injected at 1300 and 1900 h than in animals treated with gentamicin at 0700 and 0100 h ($P < 0.05$) (Fig. 3).

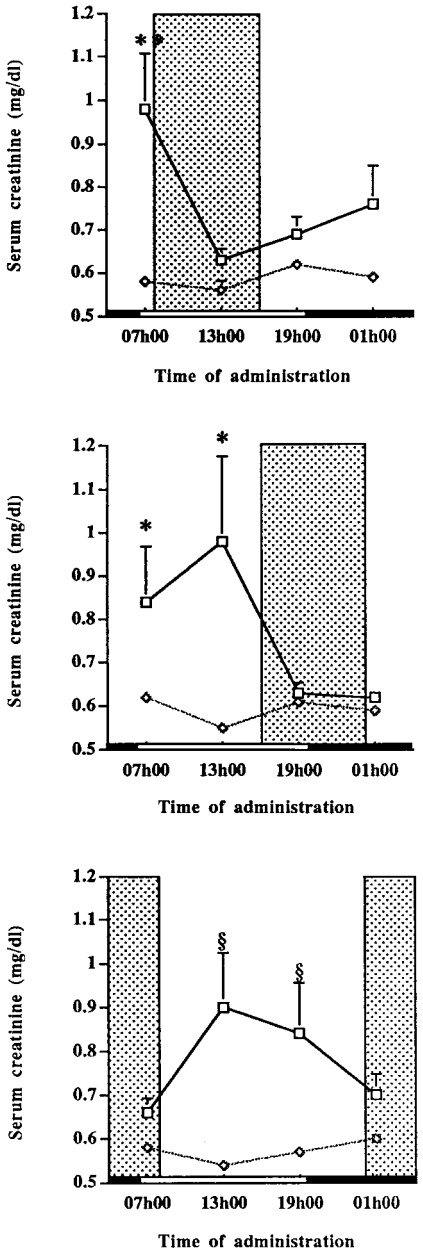

FIG. 4. Effects of time-restricted feeding schedule on gentamicin-induced increase in serum creatinine level (mean ± SEM percentage of control). Rats were treated with saline (NaCl; 0.9%) or gentamicin (40 mg/kg/24 h) for 10 days at either 0700, 1300, 1900, or 0100 h and were fed from either 0800 to 1600, 1600 to 0000, or 0000 to 0800 h. **, significantly different from other treated groups ($P < 0.05$); *, significantly different from animals treated at 1900 and 0100 h ($P < 0.05$); §, significantly different from the time-matched control group and from animals treated at 0700 and 0100 h ($P < 0.05$). Shaded boxes, food access period; open bars, light period; closed bars; dark period; □, gentamicin; ◇, saline.

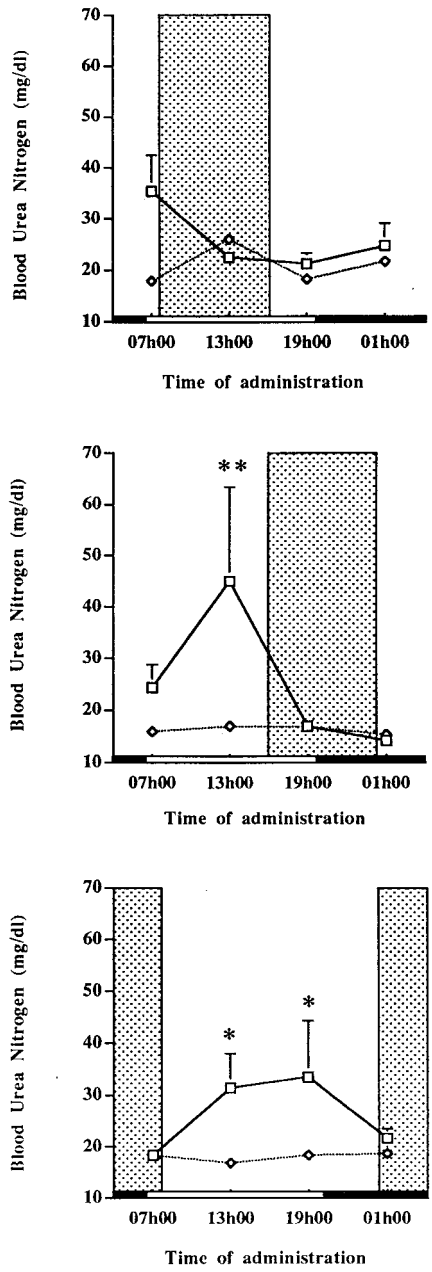

FIG. 5. Effects of time-restricted feeding schedule on gentamicin-induced increase in BUN levels (mean ± SEM percentage of control). Rats were treated with saline (NaCl; 0.9%) or gentamicin (40 mg/kg/24 h) for 10 days at either 0700, 1300, 1900, or 0100 h and were fed from either 0800 to 1600, 1600 to 0000, or 0000 to 0800 h. **, significantly different from the other treated groups ($P < 0.05$); *, significantly different from the time-matched control group and from animals treated at 0700 and 0100 h ($P < 0.05$). Shaded boxes, food access period; open bars, light period; closed bars, dark period; □, gentamicin; ◇, saline.

Significantly higher serum creatinine levels ($P < 0.05$) were measured in animals injected at 0700 h than in rats receiving gentamicin at 1300, 1900, and 0100 h for animals fed from 0800 to 1600 h (Fig. 4). In animals fed from 1600 to 0000 h, the creatinine levels in serum were significantly higher in animals injected at 0700 and 1300 h than in animals injected at other times of the day ($P < 0.05$) (Fig. 4). In animals fed from 0000 to 0800 h, the creatinine levels in serum were significantly higher in animals injected at 1300 and 1900 h than in animals treated with gentamicin at 0700 and 0100 h ($P < 0.05$) (Fig. 4).

The BUN levels were significantly higher in rats treated at 1300 h than in animals treated at other time of day for animals fed from 1600 to 0000 h ($P < 0.05$) (Fig. 5). In animals fed from 0000 to 0800 h, the BUN levels were significantly higher in animals injected at 1300 and 1900 h than in animals given the same injection of gentamicin at 0700 and 0100 h ($P < 0.05$) (Fig. 5).

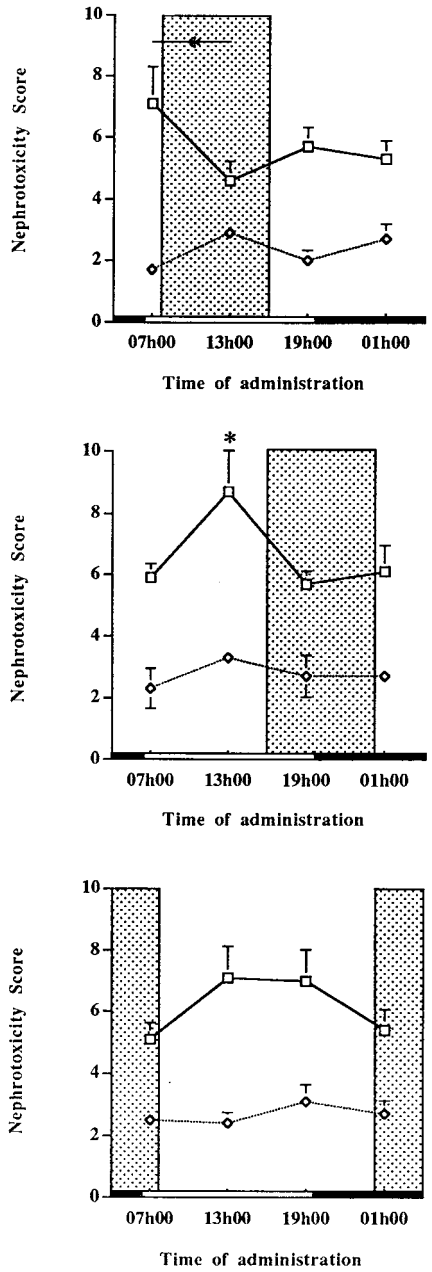

FIG. 6. Effects of time-restricted feeding schedule on gentamicin-induced histopathological lesions. Animals were treated for 10 days with saline (NaCl; 0.9%) or gentamicin at 40 mg/kg/24 h at 0700, 1300, 1900, or 0100 h and were fed either from 0800 to 1600, 1600 to 0000, or 0000 to 0800 h, —∗—, groups at the ends of the lines are significantly different ($P < 0.05$); ∗, significantly different from other treated groups ($P < 0.05$). Data for all treated groups are significantly different from those for the respective time-matched control group ($P < 0.05$). Shaded boxes, food access period; open bars, light period; closed bars, dark period; □, gentamicin; ◇, saline.

Histopathological observations of the renal cortex showed typical signs of aminoglycoside nephrotoxicity. Indeed, large lysosomes containing myeloid bodies were seen in proximal tubular cells. The severities of the lesions in the different groups of animals were analyzed quantitatively by using different criteria of toxicity, as defined in the Materials and Methods section. Figure 6 shows the effects of time-restricted feeding schedule on the total nephrotoxicity scores calculated for all groups of rats. All the nephrotoxicity scores obtained for the gentamicin-treated groups are significantly higher than those for their respective time-matched control groups, independently of the feeding period. In animals fed from 0800 to 1600 h, histopathological lesions were significantly more severe when gentamicin was injected at 0700 h than when it was injected at 1300 h ($P < 0.05$). In rats fed from 1600 to 0000 h, the histopathological score was significantly higher in animals treated with gentamicin at 1300 h (fasted group) than in rats treated at any other time of the day ($P < 0.05$). In animals fed from 0000 to 0800 h, the lowest nephrotoxicity scores were found when gentamicin was injected at 0700 and 0100 h, although these results were not significantly different from those for animals treated at 1300 and 1900 h.

A multivariate statistical ANOVA of the effects of feeding state and activity status on gentamicin nephrotoxicity is presented in Table 1. For the feeding state analysis, individual data measured after 10 days of treatment were separated into three groups, independently of the time of gentamicin injection, as follows: fed group, results for each parameter measured in animals injected during the food intake period; intermediary group, results for each parameter measured in animals injected within 9 h after the end of the period of food intake; and fasted groups, results for all parameters measured in animals injected at least 8 h after the end of the period of food intake. For example, data for animals fed from 0800 to 1600 h and injected at 0700 h were included in the fasted group, data for animals injected at 1300 h were included in the fed group, and data for animals injected at 1900 and 0100 h were included in the intermediary group. The same pattern of distribution was applied for data for animals fed from 1600 to 0000 h and from 0000 to 0800 h. For the activity status analysis, the light-dark cycle was used as a reference. In fact, the activity period corresponds to the dark period and the rest period corresponds to the light period. This multivariate analysis shows that gentamicin-induced inhibition of sphingomyelinase activity, increased BUN and creatinine levels in serum, and histopathological alterations (two-factor ANOVA) were significantly dependent on the feeding state but independent of the activity status. By contrast, gentamicin accumulation was independent of the feeding state but dependent on the activity status.

TABLE 1. Multivariate analysis of variance of feeding schedule and of rest and activity period on aminoglycoside nephrotoxicity[a]

Parameters evaluated	*P* value		
	Feeding state	Activity status	Food/activity
Gentamicin accumulation (μg/g)	0.1999	0.0006	0.0421
Sphingomyelinase activity (% of control)	0.0195	0.7686	0.7017
Cellular regeneration (% of control)[b]	0.0539	0.7402	0.7887
Serum creatinine (mg/dl)	0.0079	0.6400	0.2264
BUN concn (mg/dl)	0.0108	0.6995	0.3835
Histopathological scores[b]	0.0054	0.7887	0.5252

[a] The data for the animals were separated into fed, intermediary, or fasted groups according to the feeding schedule and into active or rest groups according to the activity status. Data for all animals were separated independently of the time of gentamicin injection.

[b] The results obtained for cellular regeneration and histopathological scores were not included in the multivariate analysis of variance due to missing values. A two-factor ANOVA was performed for these two parameters.

DISCUSSION

This study indicates that a time-restricted feeding schedule induced a shift in the peak and the trough of gentamicin nephrotoxicity in animals injected at different times of the day. It was done with sensitive and specific parameters of aminoglycoside nephrotoxicity such as sphingomyelinase activity, cellular regeneration, and histopathological changes in the renal cortex and with less sensitive parameters of renal function such as BUN and serum creatinine levels. Our previous data for animals fed ad libitum indicated that the peak of tobramycin toxicity was found when the drug was given in the middle of the rest period (at 1400 h), while the trough of the toxicity was observed when the drug was injected in the middle of the activity period (at 0200 h) (1, 18). In rodents, it is well known that the activity period corresponds to the period of maximal food intake, while the rest period corresponds to the period of minimal food intake (17).

The mechanisms associated with the temporal variations in the nephrotoxicity of aminoglycosides are still unknown. Many investigators suggested that changes in the serum pharmacokinetics (12, 22, 25, 29) and cortical accumulation (23, 29, 30) of aminoglycosides might be responsible for temporal variations in the nephrotoxicities of these agents. We also found a significant increase in total clearance from serum and a decrease in the tobramycin area under the curve for the serum of rats given a single intravenous injection at 0200 h compared with the values for those treated at 1400 h (20). The multivariate analysis of the data (Table 1) indicates that in contrast to the other parameters of toxicity that were evaluated, gentamicin accumulation is dependent on the activity period but not on the feeding state. Thus, changes in the pharmacokinetics and/or cortical accumulation of the antibiotic observed in the present study cannot explain time-dependent variations in the renal toxicity of aminoglycosides relative to the food access period. Other experiments done previously in our laboratory showed that the 24-h variation in the serum corticosterone levels also did not explain the chrononephrotoxicity of aminoglycosides (3).

The role of fasting on the temporal variations in the nephrotoxicity of gentamicin was also investigated. A recent study done in our laboratory indicated that fasting abolished the 24-h variations in the nephrotoxicity of the drug: the low level of renal toxicity of gentamicin observed previously in the middle of the activity period of fed rats (i.e., at 0100 h) was replaced by a level of toxicity which was equivalent to the highest renal damage which was found at 1300 h, i.e., in the middle of the rest period (1). Compared with normally fed animals, fasting was also associated with higher levels of tobramycin in the serum and cortex 60 to 240 min following a single injection of 40 mg of tobramycin per kg given at 0200 h (19). The data presented in this report strengthen the working hypothesis that food can modulate the time-dependent variations in the nephrotoxicities of aminoglycosides.

Many circadian rhythms are under the influence of food ingestion. Sulzman et al. (28) demonstrated in squirrel monkeys that time-restricted feeding schedule modified the circadian rhythms of many parameters, including drinking, body temperature, and urinary and water excretion. The period of activity of these monkeys was also modified by periodic feeding (28). It has also been demonstrated in rodents that circadian activity cycles are influenced by periodic access to food (9, 11, 26, 27). Indeed, rats anticipated the period of food access by increasing their activity. More precisely, there was an increase in the locomotor activity (movement, agitation, running, etc.), as indicated by an increase in the mean number of wheel revolutions per hour prior to food presentation (11). This experiment measuring running activity on a wheel also demonstrated that modification in the feeding schedule is as much susceptible to dictating rats' behavior as the light signal (9). This was also demonstrated in rabbits, in which the period of food restriction took over most of the circadian rhythms (13). Many other daily biological rhythms of rodents are synchronized by periodic food intake, such as oxygen consumption, mitosis, corticosterone levels, blood glucose levels, and amino acids (5). However, the present study was not designed to answer the question as to whether temporal variations in the nephrotoxicities of aminoglycosides are due to changes in the locomotor activities of the animals induced by a time-restricted feeding schedule.

Furthermore, Dallman et al. (7) demonstrated that the composition of the diet and modification in the feeding schedule induced a circadian pattern of DNA synthesis in female Sprague-Dawley rats. More precisely, the incorporation of [^{3}H]thymidine in liver nuclear DNA is highly susceptible to the time of day, the moment of food intake, and the nature of the diet (7). Burns et al. (6) demonstrated in healthy mice that the incorporation of tritiated thymidine by kidneys is maximal at 0100 h and minimal at 0900 h. If such circadian rhythms are affected by a time-restricted feeding schedule, it can be assumed that parameters assessing renal toxicity might be subjected to the same phenomenon. However, in the present study, this phenomenon is largely controlled by the use of time-matched saline-injected controls.

The temporal variations in the nephrotoxicities of aminoglycosides, as observed in the present study, might be related to the protein portion of the diet (8%). It has been demonstrated that the glomerular filtration rate is higher during the period of food intake and that this increase is related to a protein load (8). In fact, this increase was present in healthy human subjects ingesting a regular protein diet and absent from healthy human subjects ingesting a vegeterian diet (4). An increase in the glomerular filtration rate that was induced when animals had access to food might explain the higher tobramycin clearance observed in our previous studies (20) and, consequently, the lower accumulation of gentamicin and the lower nephrotoxicity observed when gentamicin was injected during the feeding period compared with those observed for gentamicin injected during the fasting period. Competition for brush border membrane receptors between proteins and gentamicin might also explain the decrease in nephrotoxicity observed when rats are injected during the food access period. If such competition occurs, less gentamicin will be reabsorbed by the proximal tubules, resulting in a less severe renal toxicity. The mechanisms by which food intake modulates aminoglycoside nephrotoxicity remain to be elucidated.

In conclusion, the present study strongly suggests that food ingestion can affect the temporal variations in the nephrotoxicity of aminoglycosides. Further studies must be undertaken to identify the specific nutrient(s) associated with these changes.

ACKNOWLEDGMENT

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