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Characterization of Fluoroquinolone-Induced Achilles Tendon Toxicity in Rats: Comparison of Toxicities of 10 Fluoroquinolones and Effects of Anti-Inflammatory Compounds

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Fluoroquinolone antibacterial agents have been reported to induce tendon lesions in juvenile rats. In the present study, we characterized fluoroquinolone-induced Achilles tendon lesions by comparing the effects of 10 fluoroquinolones and examining the potential of one of these antimicrobial agents, pefloxacin, to induce tendon lesions when coadministered with one of nine anti-inflammatory compounds. Among the 10 fluoroquinolones tested, fleroxacin and pefloxacin were the most toxic, inducing lesions at a dose of 100 mg/kg of body weight or more, while lomefloxacin, levofloxacin, and ofloxacin or sparfloxacin and enoxacin induced lesions at 300 mg/kg or more and 900 mg/kg, respectively. In contrast, norfloxacin, ciprofloxacin, and tosufloxacin had no effect even at the high dose of 900 mg/kg. The severity of the Achilles tendon lesions appeared to correlate with the structure of the substituent at the seventh position. Furthermore, pefloxacin-induced tendon lesions were inhibited by coadministration with dexamethasone and *N*-nitro-L-arginine methyl ester. Phenidone (1-phenyl-3-pyrazolidinone) and 2-(12-hydroxydodeca-5,10-diynyl)3,5,6-trimethyl-1,4-benzoquinone (AA861) also decreased the incidence of tendon lesions. In contrast, catalase, dimethyl sulfoxide, indomethacin, pyrilamine, and cimetidine did not modify these tendon lesions. These results suggest that nitric oxide and 5-lipoxigenase products partly mediate fluoroquinolone-induced tendon lesions.

Fluoroquinolone antibacterial agents are widely used in the clinical field because of their excellent antibacterial activity, wide spectrum, and high bioavailability. However, these compounds have been reported to induce adverse effects on the musculoskeletal system, but the incidence is low (1% or less) (38). These effects consisted mainly of myalgia and arthralgia. Furthermore, Achilles tendon disorders probably related to treatment with the drugs have also been reported recently (2, 11, 19, 33, 43), with more than 400 cases of fluoroquinolone-induced tendon disorders reported in France, The Netherlands, and other countries (18, 19, 29, 32, 33, 40) since Bailey et al. (2) first described norfloxacin-induced tendinitis in patients in 1983. These Achilles tendon disorders were characterized by bilateral sharp pain upon walking, which occurred a few hours after receiving an initial dose of fluoroquinolones in some patients, and tender swelling on palpation. Some patients complained of an abrupt inability to walk due to bilateral rupture of the Achilles tendon. We have previously demonstrated that the administration of a single oral dose of fluoroquinolones could induce lesions in the tendon and synovial membrane in juvenile rats, but these lesions recovered, with fibrotic appearance after 2 weeks of repeated administration (12). Although the pathophysiologic mechanism remains obscure, this animal model is thought to be useful for helping to provide an understanding of the fluoroquinolone-induced tendon disorders.

In the present study, we examined the toxic potentials of 10 fluoroquinolones on the Achilles tendon in this animal model. Furthermore, we also investigated the effects of nine compounds with different anti-inflammatory actions on pefloxacin-induced Achilles tendon lesions, because the incidence of lesions induced by this drug was very high (12).

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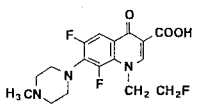
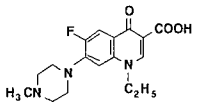
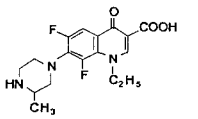
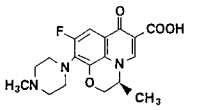
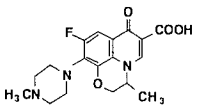
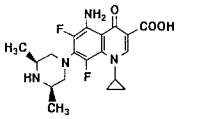
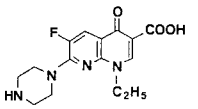
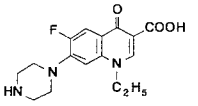
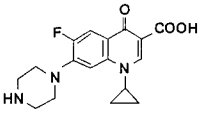
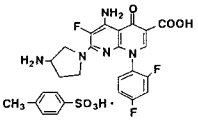
MATERIALS AND METHODS

Animals. Two hundred forty-two male Sprague-Dawley (Crj:CD) rats (age, 4 weeks) purchased from Charles River Japan Inc. were used in all experiments. Animals were housed at two or three per wire-mesh cages in an air-conditioned room (temperature, 23 ± 2°C; humidity, 55% ± 15%; lighting cycle, 12 h/day).

Chemicals. Fleroxacin (Megalocin) and pefloxacin (pefloxacin; Péflacin) were purchased from Kyorin Pharmaceutical Co. Ltd. (Tokyo, Japan) and Bellon (Neuilly sur Seine, France), respectively. Lomefloxacin, levofloxacin, ofloxacin, sparfloxacin, enoxacin, norfloxacin, ciprofloxacin, and tosufloxacin were synthesized at Daiichi Pharmaceutical Co., Ltd. (Tokyo, Japan). Pefloxacin and fleroxacin tablets were ground before use. Catalase (CAT), dimethyl sulfoxide (DMSO), dexamethasone (DM), indomethacin (IM), pyrilamine (PY), cimetidine (CM), and *N*-nitro-L-arginine methyl ester (L-NAME) were purchased from Sigma Chemical Co. (St. Louis, Mo.); and phenidone (PD) and 2-(12-hydroxydodeca-5,10-diynyl)-3,5,6-trimethyl-1,4-benzoquinone (1-phenyl-3-pyrazolidinone) (AA861; AA) were from Aldrich Chemical Co. (Milwaukee, Wis.) and Wako Pure Chemical Industries Ltd. (Osaka, Japan), respectively.

Comparison of Achilles tendon toxicity among fluoroquinolones. Each fluoroquinolone was suspended in a 0.5% sodium carboxymethylcellulose (CMC) solution, 1% methylcellulose solution, or distilled water and was orally administered to animals once at a dose of 100, 300, or 900 mg/kg of body weight in a fixed volume of 10 ml/kg. The group receiving norfloxacin at 900 mg/kg, however, was dosed with a volume of 30 ml/kg due to its high viscosity. Doses of 300 and 900 mg/kg were selected according to our previous study, in which pefloxacin or ofloxacin induced lesions at 300 and 900 mg/kg or 900 mg/kg, respectively (12). When a dose of 300 mg/kg induced tendon lesions, a group of rats receiving 100 mg/kg was added to the study. The fluoroquinolones tested have been used at clinically similar dosages of 300 to 600 mg/person/day; pefloxacin and fleroxacin, however, have been used at dosages of 800 and 200 to 300 mg/person/day. Although the bioavailabilities of the drugs are different, we used the fixed doses because accurate bioavailability data are unavailable, particularly for juvenile rats. Experiments were conducted with five rats/group, and some fluoroquinolones were repeatedly examined so that their effects could be compared with those of the other fluoroquinolones, causing different group sizes. Group compositions and the chemical structures of fluoroquinolones used are presented in Table 1. At approximately 24 h after drug administration, the animals were killed by bleeding under ether anesthesia. Use of this time point for examination was based on previously reported data indicating that almost all fluoroquinolones are excreted within 24 h after the administration of a single oral dose (1, 21–28, 41) and on the basis of data from our preliminary study showing that at 16, 24, and

TABLE 1. Incidence of Achilles tendon lesions in rats receiving single oral doses of fluoroquinolones

Fluoroquinolone	Chemical Structure	Dose (mg/kg)	No. of animals	Incidence of lesions	TD_{50} (mg/kg) (95% confidence limit)
Fleroxacin		100	5	1/9[a] (11%)	176 (112 - 285)
		300	5	7/8 (88%)	
		900	5	10/10 (100%)	
Pefloxacin		100	5	2/9 (22%)	212 (77 - 397)
		300	5	6/9 (67%)	
		900	5	9/10 (90%)	
Lomefloxacin		100	5	0/10 (0%)	NC[b]
		300	5	5/8 (63%)	
		900	5	7/7 (100%)	
Levofloxacin		100	5	0/8 (0%)	419 (268 - 849)
		300	10	7/17 (41%)	
		900	5	6/8 (75%)	
Ofloxacin		100	10	0/19 (0%)	616 (455 - 1177)
		300	20	5/33 (15%)	
		900	5	7/10 (70%)	
Sparfloxacin		300	5	0/9 (0%)	-
		900	5	3/7 (43%)	
Enoxacin		300	5	0/10 (0%)	-
		900	10	7/18 (39%)	
Norfloxacin		300	5	0/10 (0%)	-
		900	10	0/17 (0%)	
Ciprofloxacin		300	5	0/10 (0%)	-
		900	10	0/18 (0%)	
Tosufloxacin		300	5	0/9 (0%)	-
		900	5	0/9 (0%)	

[a] Values are number of lesions/total number of ankles examined.
[b] NC, values could not be calculated because of an insufficient dose setting.

48 h after drug administration the lesions were similar in severity and that their incidence was similar (unpublished data). The right and left ankles were removed from all rats, fixed in 10% buffered formalin, and decalcified with formic acid. These ankles were trimmed sagittally, embedded in paraffin wax, sectioned, stained with hematoxylin and eosin, and examined microscopically. Sections not including an appropriate portion of the Achilles tendon were excluded from the evaluation. The incidence of lesions in the tendon was calculated by dividing the total number of sections showing lesions by the number of sections examined. For each fluoroquinolone of which at least three doses were available, the 50% toxic dose (TD_{50}) was determined by the probit method to compare the toxic potentials of the drugs.

Effects of anti-inflammatory compounds on pefloxacin-induced tendon toxicity. CAT, DMSO, IM, PD, PY, CM, and L-NAME were dissolved in or diluted with physiological saline (acidic or alkaline conditions were used if necessary), while DM and AA were dissolved in 50% ethanol for continuous subcutaneous administration through osmotic pumps. For intraperitoneal injection, CAT, DMSO, PY, and L-NAME were dissolved in physiological saline and DM, IM, PD, AA, and CM were suspended in 0.5% CMC solution. Pefloxacin was suspended in 0.5% CMC solution for oral administration.

The test compounds were administered by the method of Shimoda et al. (36), who previously demonstrated their effects on skin lesions induced by phototoxicity. Alzet model 2ML2 and model 1007D osmotic pumps (Alza Co., Palo Alto,

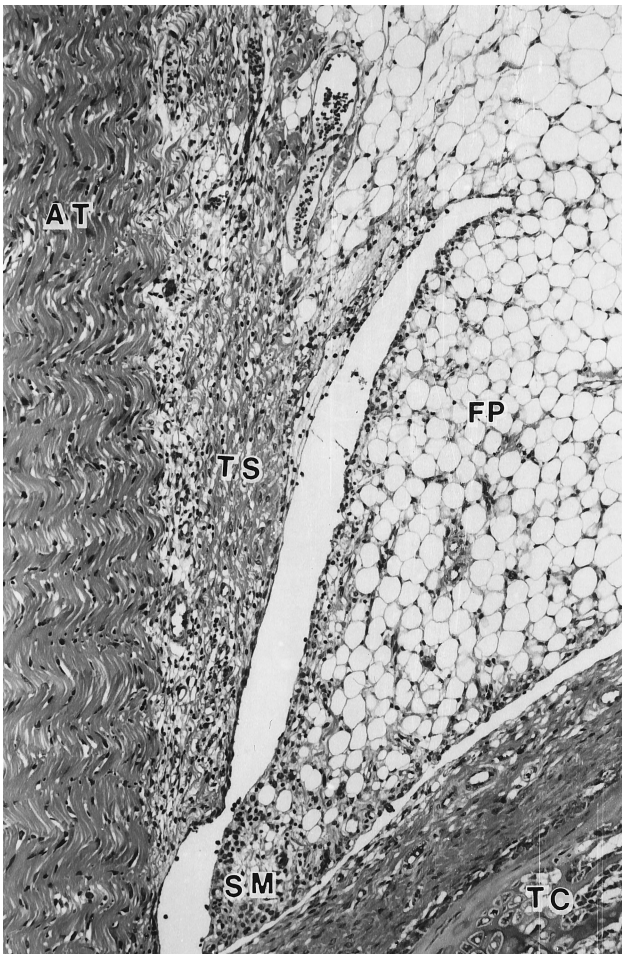


FIG. 1. Achilles tendon from a pefloxacin-treated rat. Edema with increased numbers of mononuclear cells in the tendon sheath and synovial membrane is seen. AT, Achilles tendon; TS, tendon sheath; TC, tuber calcanei; SM, synovial membrane; FP, fat pad. Magnification, ×97.

Calif.) containing 2.5% CAT, 50% DMSO, 0.25% DM, 0.5% IM, 2.5% PD, 2.5% PY, 0.9% CM, or 2.5% L-NAME and 1% AA, respectively, were subcutaneously implanted into the animals under ether anesthesia. The animals were fasted overnight and were additionally given a single intraperitoneal dose of 640 mg of CAT per kg, 5 mg of DMSO per kg, 1 mg of DM per kg, 5 mg of IM per kg, 100 mg of PD per kg, 50 mg of AA per kg, 10 mg of PY per kg, 20 mg of CM per kg, or 10 mg of L-NAME per kg. The subcutaneous and intraperitoneal doses of these anti-inflammatory compounds were determined on the basis of reference data (31, 36). Two hours after the intraperitoneal injection of these compounds, pefloxacin was orally administered once at 900 mg/kg. Control animals underwent subcutaneous implantation of an osmotic pump containing saline or 50% ethanol, intraperitoneal injection of 0.5% CMC, and oral administration of 900 mg of pefloxacin per kg. All animals were killed by bleeding, and the right and left ankles were removed and processed for histopathological examination as described above. The incidence of Achilles tendon lesions was calculated, and significant differences between the test and corresponding vehicle groups were determined by the chi-square test.

RESULTS

Comparison of Achilles tendon toxicity among fluoroquinolones. The changes to the Achilles tendon were as described previously (12). Briefly, edema with an increased number of mononuclear cells was often observed in the Achilles tendon sheath at the portion proximal to the tuber calcanei (Fig. 1). In some cases, the lesions were more severe and extensive, involving the surface of the tendon tissue. In the synovial membrane adjacent to the lesions above, mild edema and an increased number of mononuclear cells were observed; with the latter associated tissue debris was also sometimes seen in the joint space. Dilation of blood vessels was found in association with edema in both the tendon sheath and the synovial membrane, but diapedesis of erythrocytes was not observed. Lesion incidence and estimated TD_{50}s are presented in Table 1. These tendon lesions were induced by 7 of the 10 fluoroquinolones tested. After the administration of single doses, fleroxacin and pefloxacin at 100 mg/kg or more induced Achilles tendon lesions; lomefloxacin, levofloxacin, and ofloxacin at 300 mg/kg or more induced lesions. Compared to the toxic potentials of these fluoroquinolones according to their TD_{50}s, fleroxacin was most toxic, with a TD_{50} of 176 mg/kg, followed by pefloxacin (212 mg/kg), levofloxacin (419 mg/kg), and ofloxacin (616 mg/kg), in decreasing order. The TD_{50} of lomefloxacin, however, could not be determined because of an insufficient dose setting. Sparfloxacin and enoxacin at 900 mg/kg induced lesions. The incidence of lesions showed a dose-dependent trend for all these fluoroquinolones. In contrast, norfloxacin, ciprofloxacin, and tosufloxacin induced no lesions in the Achilles tendon.

Effects of anti-inflammatory compounds on pefloxacin-induced tendon toxicity. The incidence of lesions is summarized in Table 2. All (100%) and 11 of 13 (84.6%) ankles showed lesions in the groups receiving pefloxacin plus saline and pefloxacin plus 50% ethanol (control groups), respectively. Among the nine anti-inflammatory compounds examined, DM completely inhibited the pefloxacin-induced Achilles tendon lesions and L-NAME reduced the incidence of lesions to 36.4%, with statistical significance by the chi-square test. Furthermore, PD and AA also reduced the incidence to 54.5%, while the inhibition of lesions by AA for lesions caused by pefloxacin plus ethanol showed no statistical significance.

DISCUSSION

The toxic potentials of 10 fluoroquinolones on the Achilles tendon were compared in juvenile rats. Toxic potential was clearly differentiated: fleroxacin and pefloxacin were the most toxic, with the lowest toxic dose being 100 mg/kg; lomefloxacin, levofloxacin, and ofloxacin were the second most toxic, with the toxic dose being 300 mg/kg; sparfloxacin and enoxacin were the third most toxic, at 900 mg/kg, while norfloxacin, ciprofloxacin,

TABLE 2. Incidence of Achilles tendon lesions in juvenile rats given pefloxacin at 900 mg/kg alone or in combination with an anti-inflammatory compound

Treatment	Dose of pharmacological agents		Incidence of lesions[a]
	Osmotic pump (μg/h)	Intraperitoneal (mg/kg)	
PFLX[b] + saline	0	0	14/14 (100)
PFLX + 50% ethanol	0	0	11/13 (85)
PFLX + CAT	125	640	10/12 (83)
PFLX + DMSO	2,500	5.8	7/10 (70)
PFLX + DM	12.5	1	0/12** (0)
PFLX + IM	25	5	8/11 (73)
PFLX + PD	125	100	6/11* (55)
PFLX + AA	5	50	6/11 (55)
PFLX + PY	125	10	7/11 (64)
PFLX + CM	45	20	9/12 (75)
PFLX + L-NAME	125	10	4/11** (36)

[a] Values are number of lesions/total number of ankles examined (percent). *, $P < 0.05$; **, $P < 0.01$ versus corresponding vehicle control by the chi-square test.

[b] PFLX, pefloxacin.

and tosufloxacin showed no toxicity, even at the high dose of 900 mg/kg. The order of the first five drugs listed above was shown to be the decreasing order of the toxic potentials of the fluoroquinolones by estimation of TD_{50}s; for lomefloxacin, however, the calculation could not be done because of an insufficient dose setting.

With regard to the relationship between toxic potential and the chemical structure of fluoroquinolones, fleroxacin, pefloxacin, levofloxacin, and ofloxacin, which induced lesions at a higher incidence, commonly share a methylpiperadinyl substituent at the seventh position of the fluoroquinolone core structure. In contrast, enoxacin, norfloxacin, and ciprofloxacin, with little or no toxic effect, have a piperadinyl substituent. Domagala (6) has pointed out that the substituent at the seventh position of fluoroquinolones greatly influences their efficacies and toxicities (6). For example, effects on the central nervous system and interactions with theophylline and nonsteroidal anti-inflammatory drugs were reported to be directly influenced by the substituent at the seventh position. In addition, the substituent at the seventh position was also reported to influence the pharmacokinetics of fluoroquinolones; after oral administration to rats, ratios of peak concentrations in plasma to the dosage for the more toxic compounds fleroxacin, pefloxacin, lomefloxacin, and levofloxacin were higher than those of the compounds enoxacin, norfloxacin, and tosufloxacin, which have little or no toxic activity (1, 21–28, 41). Taken together, these data suggest that Achilles tendon lesions induced by fluoroquinolones are caused by the toxic substituent at the seventh position of the core structure, higher concentrations of the drugs in serum, or both. However, there is a possibility that constituents at positions other than the seventh position could make the difference in the toxic potentials among fluoroquinolones tested by influencing their solubility, absorption, tissue distribution, etc.

A number of reports dealing with fluoroquinolone-associated tendon disorders in humans have appeared, particularly in France (2, 11, 19, 29, 33, 43). Meyboom et al. (19) have reviewed international data submitted to the World Health Organization Program for International Drug Monitoring (19). Of the total of 29,709 adverse reactions reported for ciprofloxacin, enoxacin, norfloxacin, ofloxacin, pefloxacin, and temafloxacin, tendon disorders represented 0.3%, with the pefloxacin group accounting for the disorder at the highest incidence of 2.7% (33 of 1,237). Pierfitte and Royer (29) recently conducted a similar investigation in France and suggested that the risk may be greater with pefloxacin and for patients over 60 years of age. In addition to the greater toxic potential of pefloxacin itself, its higher daily dosage (usually 800 mg per day) than those of the other fluoroquinolones (e.g., 400 mg per day for ofloxacin) may also contribute to the appearance of the symptom in humans.

We examined the effects of anti-inflammatory compounds on pefloxacin-induced Achilles tendon lesions. Pefloxacin plus saline- or pefloxacin plus 50% ethanol-induced lesions in all (100%) or 11 of 13 (84.6%) ankles, respectively. In our previous examinations, the incidence of tendon lesions in pefloxacin-treated animals was estimated to be 80 to 100%. The present results for the control group are reasonably consistent with this incidence; the lower incidence in the pefloxacin-plus-ethanol control group may be due to an effect of ethanol on the absorption of pefloxacin or circulation in the blood. Lesions were apparently inhibited by coadministration with DM, a steroidal anti-inflammatory drug, and L-NAME, a nitric oxide (NO) synthase inhibitor. PD, a dual cyclooxygenase (CO) and lipoxygenase (LO) inhibitor, and AA, a lipoxygenase inhibitor, moderately inhibited the pefloxacin-induced Achilles tendon lesion, although IM, a cyclooxygenase inhibitor, was not effective. The antioxidants CAT and DMSO and the histamine antagonists PY and CM also had no effect.

Fluoroquinolone-induced Achilles tendon lesions were characterized by edema with an increased number of mononuclear cells but no neutrophils, suggesting increased permeability of blood vessels. The present results show the major contribution of NO to pefloxacin-induced tendon lesions. Both L-NAME and DM, both of which significantly inhibited the lesions, are potent NO synthase inhibitors (20, 30, 31). NO, an inorganic and gaseous free radical, is released from a variety of cells including vascular endothelial cells, macrophages, hepatocytes, chondrocytes, and some neuronal cells and acts as a vasodilator (5, 8, 37, 39). Recent studies have suggested various other actions for NO, including a role in the regulation of platelet function, neurotransmission, and cytotoxicity (4, 8). Some researchers have demonstrated the involvement of NO in inflammatory lesions accompanied by edema (10, 15). Mirroring the significant inhibition of Achilles tendon lesions by L-NAME and DM in the present study, the lesions induced by fluoroquinolones included the dilation of blood vessels in the edematous area, which may also suggest the involvement of NO. Furthermore, the interactions between NO and arachidonic acid products have been reported to be very complex (14, 34, 39). NO itself is not thought to mediate hyperpermeability, but it may participate in fluoroquinolone-induced Achilles tendon lesions in combination with some other mediators. A number of mediators are involved in hyperpermeability of blood vessels: prostaglandin I_2 prostaglandin E_2, leukotrienes, histamine, serotonin, bradykinin, platelet activating factor, interleukin-1, and tumor necrosis factor (7, 9, 16, 17, 35, 42). Considering the inhibitory effect of AA on pefloxacin-induced tendon lesions in the present study, we suspect that leukotrienes, which are 5-LO products, play a role in the development of the lesion. Kotyuk et al. (13) reported that acid-induced ear edema in mice was prevented by treatment with dual CO-LO inhibitors, 5-LO inhibitors, and steroids but not with CO inhibitors. Similar effects by the LO or the CO inhibitor were demonstrated in brain edema in rats (3). However, the absence of neutrophil infiltration in the tendon lesions in the present study suggests that leukotriene B_4, a potent chemotactic agent for neutrophils, was not involved. It is, however, possible that other leukotrienes might induce vascular hyperpermeability in the Achilles tendon sheath with NO. Additional investigations are needed to determine the specific mechanisms of these inhibitory effects.

In the present study, we investigated the characteristics of fluoroquinolone-induced Achilles tendon lesions in juvenile rats. The toxic potential was the strongest for pefloxacin and fleroxacin, but no effect was seen for norfloxacin, ciprofloxacin, or tosufloxacin. Furthermore, pefloxacin-induced lesions were completely inhibited by coadministration with a steroidal anti-inflammatory drug (DM). In humans, patients ages 60 years or older and undergoing corticosteroid therapy showed a high incidence of fluoroquinolone-induced tendinitis or tendon rupture, suggesting a different pattern of Achilles tendon lesions between the present animal model and humans. Furthermore, adverse effects in humans seemed to be more severe with the lower dosage than that in the present rat model. This means that the altered kinetics of fluoroquinolones, which are caused by aging, underlying disease, period or timing of therapies with other drugs, etc., may contribute to the development of the tendon disorders in humans. It is impossible to clarify the very complicated behaviors of drugs in patients. However, humans and these rats share a number of common features, namely, a

high susceptibility to pefloxacin-induced lesions, abrupt onset of lesions after administration, and edema.

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