Diagnosis of Quinolone-induced Arthropathy in Juvenile Dogs by Use of Magnetic Resonance (MR) Imaging

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ABSTRACT. The present study was carried out to confirm whether arthropathy in juvenile dogs induced by ofloxacin, a new quinolone antibacterial agent, may be diagnosed by magnetic resonance (MR) imaging. Three-month-old male beagle dogs were orally administered ofloxacin at 20 mg/kg once daily for 7 consecutive days. On day 8, MR images were obtained with a 4.7-tesla (T) super-conductive high magnetic field strength unit. An irregular cartilage surface and dissecans changes in the distal femoral condyle were observed. These MR findings were essentially consistent with pathologic observation showing multifocal blisters on the articular cartilage with an increased amount of turbid synovial fluid in the joint. The results demonstrate that occurrence of ofloxacin arthropathy in juvenile dogs can be clearly diagnosed by use of MR imaging. — KEY WORDS: canine, MR imaging, quinolone arthropathy.

Arthropathy in immature animals brought about by new quinolone antibacterial agents (quinolones) is an unusual adverse reaction observed with all known quinolones [1–6, 10]. In particular, immature dogs among the experimental animals tested have shown the most susceptibility to cartilage lesions in the epiphyses constituting almost all diarthrodial joints [3, 10]. Recently, the use of MR imaging has become widespread in the diagnosis of brain, spinal and joint lesions. MR imaging enables to follow-up the sequential changes without the need to kill the animals, and much more information is also gained from a single animal [12–16]. In addition, there are few investigations dealing with the diagnosis of quinolone-induced arthropathy in juvenile dogs by MR imaging except for the toxicological review of ciprofloxacin [8]. The present study was, thus, designed to determine whether knee arthropathy evoked by a quinolone may be diagnosed by MR imaging.

Four healthy male beagle dogs, 3 months of age, weighing 6 to 7.5 kg, purchased from BMR Co. (Gifu, Japan) were used in the investigation. The animals were housed individually in stainless-steel cages in air-conditioned canine facilities (temperature: 23± 2°C, relative humidity: 60 ± 20%, light cycle: on 8:00 to 20:00) and maintained on a standard laboratory chow (DM-2; Funabashi Farm, Chiba, Japan) with tap water ad libitum. All dogs were treated with free access to water, unless otherwise stated. Ofloxacin was synthesized at our laboratory, and was administered by gavage to three dogs at 20 mg/kg in a sixteen-ounce gelatin capsule once daily for 7 consecutive days. The dosage level and administration period of the drug used in this study were selected on the basis of preliminary studies and previously published reports [10].

An additional dog given only the gelatin capsule served as a control. Clinical signs and body weight were recorded throughout the experiment, and laboratory tests were performed before treatment and on day 7 according to a routine procedure. Twenty-four hours after the last treatment (on day 8), the animals were sacrificed under anesthesia with a combination of ketamine (40 mg/kg) and xylazine (2 mg/kg) given by intravenous injection. MR images were obtained by a 4.7 T super-conductive high magnetic field strength unit (Biospec CSI 47/40, Bruker Japan, Tokyo, Japan) with a birdcage-typed radio frequency (RF) coil. MR image was scanned by spin echo pulse sequence [recovery time (TR): 1500 mseconds; echo time (TE): 18.9 mseconds], and had a 70 mm field of view (FOV) with a 512 × 512 matrix and a slice thickness of 1 mm. Following MR images, the femoral condyles were macroscopically observed in order to identify changes in the signal intensity obtained by MR imaging. The femoral specimens were then subjected to histopathological examination by a standard method.

All dogs receiving 20 mg/kg ofloxacin orally for 7 days displayed a decrease in locomotor activity and abnormal gait including limping from day 6 to 7. No other changes were apparent in any of the animals employed. Clinical laboratory items including white blood cell counts, hemogram, and calcium, inorganic phosphorus and magnesium values in sera were within normal ranges on day 7. Findings at MR imaging were clear, and an irregular cartilage surface and dissecans changes in the distal femoral condyle were seen (Fig. 1, left). The images obtained were almost identical with those of immature rabbits treated with PD 1177596, a fluoroquinolone derivative, that was stated by Gough et al. [2]. No abnormal findings of MR imaging were observed in the control animal (Fig. 1, right). At necropsy, all dogs given ofloxacin exhibited multifocal fluid-filled vesicles (2 × 2 mm to 5 × 12 mm, round- and oval-shaped blisters) with partial erosion between the patellar surface and medial condyles of the distal head of the femurs (Fig. 2), and elicited an increased amount of
Fig. 1. Sagittal magnetic resonance imaging (TR/TE=1500/18.9 msec) of the left knee joint of a 3-month-old beagle dog treated orally with ofloxacin at 20 mg/kg (left) or gelatin capsule alone (right: control) for 7 consecutive days. Arrows show an irregular cartilage and dissecans changes in the distal femoral condyle. a: femur, b: tibia, c: patella, d: accretion lines, e: corpus adiposum infrapatellare, f: patellar ligament, g: meniscus.

Fig. 2. Macroscopic observation of the cartilage surface of the left knee joint of a 3-month-old beagle dog treated orally with ofloxacin at 20 mg/kg for 7 consecutive days. Note multifocal fluid-filled vesicles with partial erosion between the patellar surface and medial condyles.

turbid synovial fluid. Meanwhile, no macroscopic changes in the control dog were noted. Microscopically, only in dogs receiving ofloxacin, cavity formation was noted in the middle zone of the articular cartilage with the matrix tending to lose its basophilia. The chondrocytes were shrunken and their numbers were reduced. Moreover, the chondrocyte clusters commonly aligned along the border of the cavity containing tissue debris (Fig. 3). These macro- and micro-pathological findings were in agreement with previous results of known quinolones in immature dogs [1, 3, 7, 11], and basically resembled those reported in multiple species such as rats [4], rabbits [2], non-human primates [9] and others [5, 6], although there were slight differences in the arthropathic dose among the quinolones. Unfortunately, the sensitivity of MR imaging for the detection of vesicular lesions in articular cartilage remains an unresolved issue, as Gough et al. [2] reported.

In the present study, though MR images were scanned immediately after sacrifice, the almost same images can be taken even under continued anesthesia (data not shown).

In conclusion, it is suggested that the occurrence of ofloxacin arthropathy in juvenile dogs can be clearly diagnosed by use of MR imaging.

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Fig. 3. Light microscopic observation of the articular cartilage of the left knee joint of a 3-month-old beagle dog treated orally with ofloxacin at 20 mg/kg for 7 consecutive days. Note the cavity formation (arrow) in the middle zone of the articular cartilage with the matrix tending to lose its basophilia (H-E stain, ×10).

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