Effect of Injected Versus Iontophoretic Corticosteroid on the Rabbit Tendon*

DAVID F. MARTIN, MD, CATHY S. CARLSON, DVM, PhD, JOEL BERRY, MS, BETH A. REBOUSSIN, PhD, E. STANLEY GORDON, BS, and BETH PATERSON SMITH, PhD, Winston-Salem, NC

ABSTRACT

Background. The etiologic role of corticosteroid therapy in tendon rupture is controversial. This study compared the effects of injected versus iontophoretically delivered corticosteroid on the normal rabbit Achilles tendon.

Methods. Rabbits were divided into three treatment groups: (1) corticosteroid injections, (2) iontophoretically delivered corticosteroid, and (3) no treatment. One tendon of each rabbit in the treatment groups was treated with either drug injection or iontophoresis; the tendon of the other leg served as a control. Some tendons were used for testing elastic modulus, ultimate load, and ultimate stress, while the remaining tendons were evaluated histologically.

Results. Injections of either corticosteroid or saline into the tendon sheath resulted in short-term changes in tendon biomechanical characteristics and somewhat higher histologic severity scores; however, iontophoretic delivery of corticosteroid or saline did not affect either significantly.

Conclusions. Iontophoresis using sterile water or corticosteroid resulted in minimal or no biochemical and histologic changes in the tendon compared with injection of either substance. The method of corticosteroid delivery may be as important as the actual drug effects on the biomechanical and histologic properties of tendons.

THE USE of hydrocortisone to reduce joint swelling and pain and to improve function of patients with rheumatoid arthritis was first reported in 1949.[1,2] Currently, hydrocortisone is used commonly in clinical practice to treat a variety of musculoskeletal conditions. However, intra-articular steroid therapy has been associated with severe side effects including osteoporosis, avascular necrosis, and degenerative joint changes.[2-4] Oral corticosteroid therapy and injections of corticosteroids in or around tendons also have been implicated in the degeneration of soft tissues, sometimes leading to rupture.[3] It is not clear whether these tendon ruptures are due to the corticosteroid or to the primary disease for which the steroid treatment was prescribed.[5] The adverse effects associated with corticosteroid therapy also may occur because the treatment masks symptoms of pain, allowing individuals to return prematurely to the physical activity that caused the initial tendon disease.[2,3] Since the method of corticosteroid delivery may be important, iontophoresis, a noninvasive technique for the administration of corticosteroids, has been suggested to diminish the inflammatory response without the concomitant interference with healing that may result from injection.[6]

The present study compared the effects of injected versus iontophoretically delivered corticosteroid on the biomechanical properties and histologic appearance of the normal rabbit Achilles tendon. Rabbits were used as the animal model because the rabbit Achilles tendon is anatomically and physiologically comparable to the human Achilles tendon[7] and is the largest and strongest tendon in the rabbit.[8]

MATERIALS AND METHODS

Animal Subjects

Male New Zealand white rabbits weighing 3.5 to 4.0 kg (Robinson Rabbitry, Winston-Salem, NC) were housed individually in the animal resources unit at Wake Forest Uni-

*Presented at the annual meeting of the American Academy of Sports Medicine, June 16-20, 1996, Lake Buena Vista, Fla.

From the Departments of Orthopaedic Surgery (Drs. Martin, Gordon, and Smith); Comparative Medicine (Dr. Carlson); Radiology (Mr. Berry); and Public Health Sciences (Dr. Reboussin); Wake Forest University School of Medicine, Winston-Salem, NC.

Supported by the Wake Forest University School of Medicine Venture Grant and the Forsyth County United Way. R. J. Reynolds Co provided access to the Instron Universal Testing Instrument.

Reprint requests to David F. Martin, MD, Wake Forest University School of Medicine, Department of Orthopaedic Surgery, Medical Center Blvd, Winston-Salem, NC 27157-1070.

versity School of Medicine, a facility approved by the Association for Assessment and Accreditation of Laboratory Animal Care.

Experimental Protocols

The experimental protocols were approved by the Animal Care and Use Committee of Wake Forest University School of Medicine. The animals were divided into three groups.

Group 1 (n = 27). Animals were treated with peritendinous injections of corticosteroid or saline. Eighteen rabbits were randomly designated for biomechanical testing studies, and 9 rabbits for histology studies. One Achilles tendon in each animal was injected once with dexamethasone, 0.5 mg/kg body weight, a dosage recommended for the treatment of inflammation in rabbits. This dose was higher than that used clinically in patients, which ranges from 0.4 to 1.0 mg for single doses injected into the tendon sheath.[9] No lidocaine was used for this injection since it was given under general anesthesia. The opposite Achilles tendon was injected once with an equivalent volume of saline to serve as a control. The leg treated with dexamethasone was alternated as rabbits were entered into the protocol.

The method of injecting the rabbit Achilles tendon with corticosteroid was developed using two rabbit cadavers. A 26-gauge needle was used to inject ink into the peritendinous sheath, and the ink was observed to infiltrate the area between the sheath and the tendon. For the experimental protocols, rabbits were anesthetized before corticosteroid injection with an intramuscular injection of ketamine HCl (30 mg/kg body weight) and zylazine (8 mg/kg body weight). A small (1.0 cm) incision was made over the distal portion of both Achilles tendons to allow visualization of the tendon and surrounding tendon sheath. A 26-gauge needle was introduced into the peritendinous sheath, and the dexamethasone or saline was injected into the sheath. After the injection, the incision was closed with tissue-compatible cyanoacrylate glue. This injection method insured consistent placement of the drug around the tendon. Of course, this injection method is not practical clinically, but for the purpose of a research study, the use of a controlled type of injection removed one source of experimental variability.

Group 2 (n = 27). Animals received dexamethasone administered to one Achilles tendon by iontophoresis; the other tendon was treated by iontophoresis with an equal volume of sterile water. Eighteen rabbits were randomly designated for biomechanical testing studies and 9 for histology studies.

The rabbits were placed in restrainers during iontophoresis. The animals were conditioned to the restrainer for 1 week before iontophoresis treatment was initiated by repeated restraint training of increasing duration. They were anesthetized for the first iontophoresis treatment using the same anesthesia protocol as was used for the corticosteroid injections. The animals' legs were shaved over the tendons to allow placement of the iontophoresis delivery electrode and over the flank to allow placement of the reference electrode. An adhesive backing was used to hold the delivery electrode firmly attached to the rabbit's skin over the tendon. Dexamethasone sodium phosphate was used in the iontophoresis delivery electrode (1.7 x 3.75 inch) at a concentration of 0.4%, the drug formulation commonly used by physical therapists for treatment of musculoskeletal inflammatory conditions. Sterile water was placed in the delivery electrode on the opposite leg to serve as a control. The return electrodes were placed over the rabbit's flank (a skin area approximately 10 cm from the Achilles tendon). The drug or sterile water was administered during five treatments (20 minutes at 2.0 mA; one dose = 40 mA/min) given every other day for 9 days to approximate the dosage of dexamethasone given by injection. Light sedation was used for the subsequent treatments to prevent animals from injuring themselves.

Group 3 (n = 9). Animals in this group served as controls and received no corticosteroid drug treatment, anesthesia, or skin incisions. Six of these animals were randomly designated for biomechanical testing studies and three for histology studies.

Collection of Tissue Samples

Rabbits from groups 1 and 2 were killed 7, 14, and 30 days after the end of the corticosteroid treatment. Nine rabbits were killed from each group at each of the three time intervals. Tendons from 6 of the 9 animals from each group were used for biomechanical testing, and tendons from the remaining 3 rabbits in each group were used for histologic evaluation. Control animals in group 3 were killed 7 days after arrival at the animal facility.

At necropsy, both Achilles tendons of each rabbit were surgically exposed and were removed by severing the attachment at the

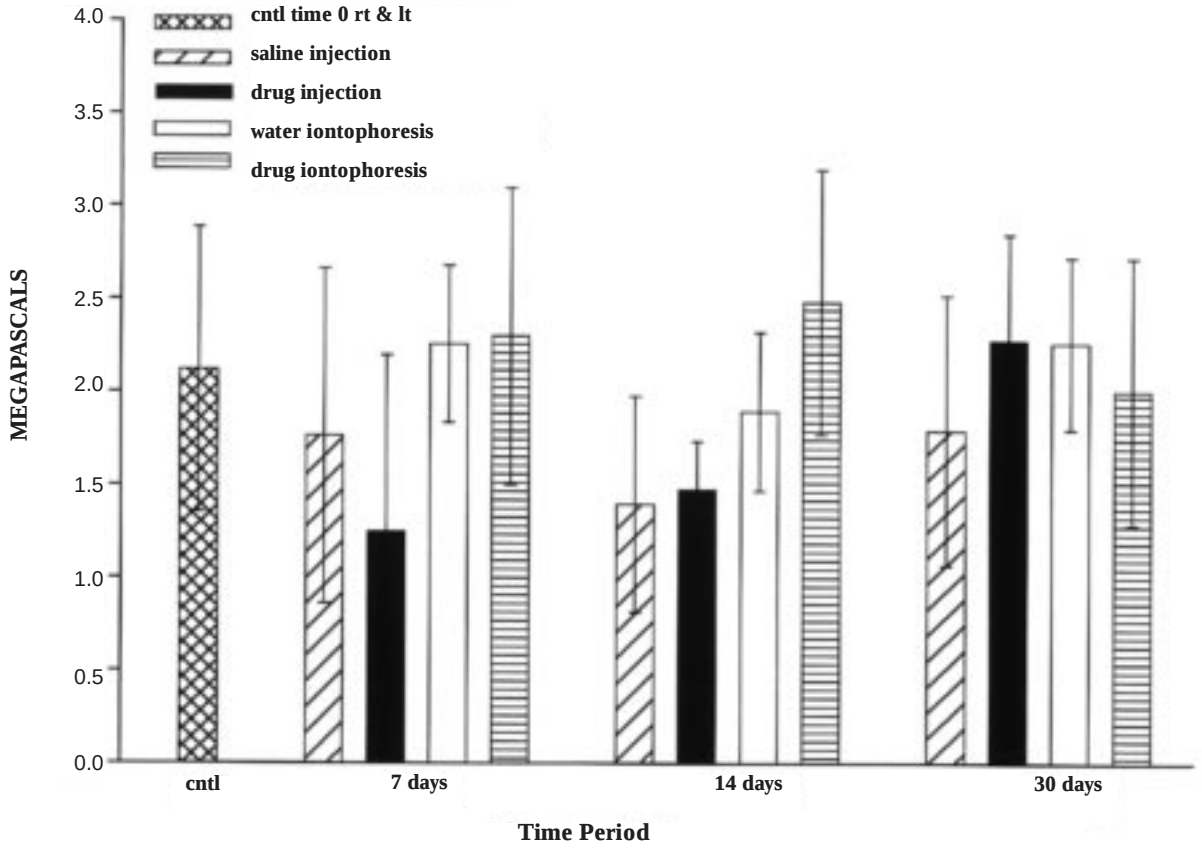

FIGURE 1. Ultimate stress of tendons. Tendons receiving four treatments were compared with each other and with control tendons that were not treated. Values are ± standard deviation.

muscle-tendon junction, as described by Kapetanos.[8] Tendons designated for biomechanical testing were placed in buffered saline and were tested within 4 hours of harvesting.

Tendons designated for histologic evaluation were fixed in 4% paraformaldehyde at 4°C for 24 hours and then were transferred to 70% ethanol. After fixation, each tendon was cut in half midlongitudinally. One half was embedded in paraffin with the cut side down; the remaining half was cut into three equidistant cross sections, each of which was embedded in methyl methacrylate. Two sections were cut from each block; one was stained with hematoxylin and eosin and one with trichrome. Paraffin sections were cut at 5 μm, and plastic sections were cut at 2 μm.

Biomechanical Testing Methods

The biomechanical properties of all tendon specimens were evaluated by experimental load-to-failure tests using an Instron Universal Testing Instrument (Model 4201, Instron Corp, Kenton, Ohio). Each individual tensile test produced an analog plot (strip chart recording) of pulling force versus specimen deformation. Ultimate stress, elastic modulus, and ultimate load were derived from each force-displacement curve.

Each tendon was clamped at each end; jaws secured the calcaneus at one end and the musculotendinous junction at the other to minimize the possibility of failure occurring at the musculotendinous junction or the clamping site. After the specimen was clamped, a small preload was applied to remove specimen laxity. Subsequently, the length of each tendon between the clamps was measured as the initial length. In addition, four diameter measurements were made at regularly spaced intervals along the length of the tendon. The specimen strain rate was normalized to its initial length and was 10% for all specimens. This strain rate was chosen in accordance with previous tendon studies to minimize any dynamic stiffening effects or creep recording.[10,11]

The force-displacement curve was converted to a stress-strain curve. The pulling force, F, throughout the linear region was divided by the average cross sectional area, A, and yielded an estimate of the material stress, or $F/A = \sigma$. The stress was then divided by specimen strain ($\ddot{\imath} = \Delta L/L$) across the elastic

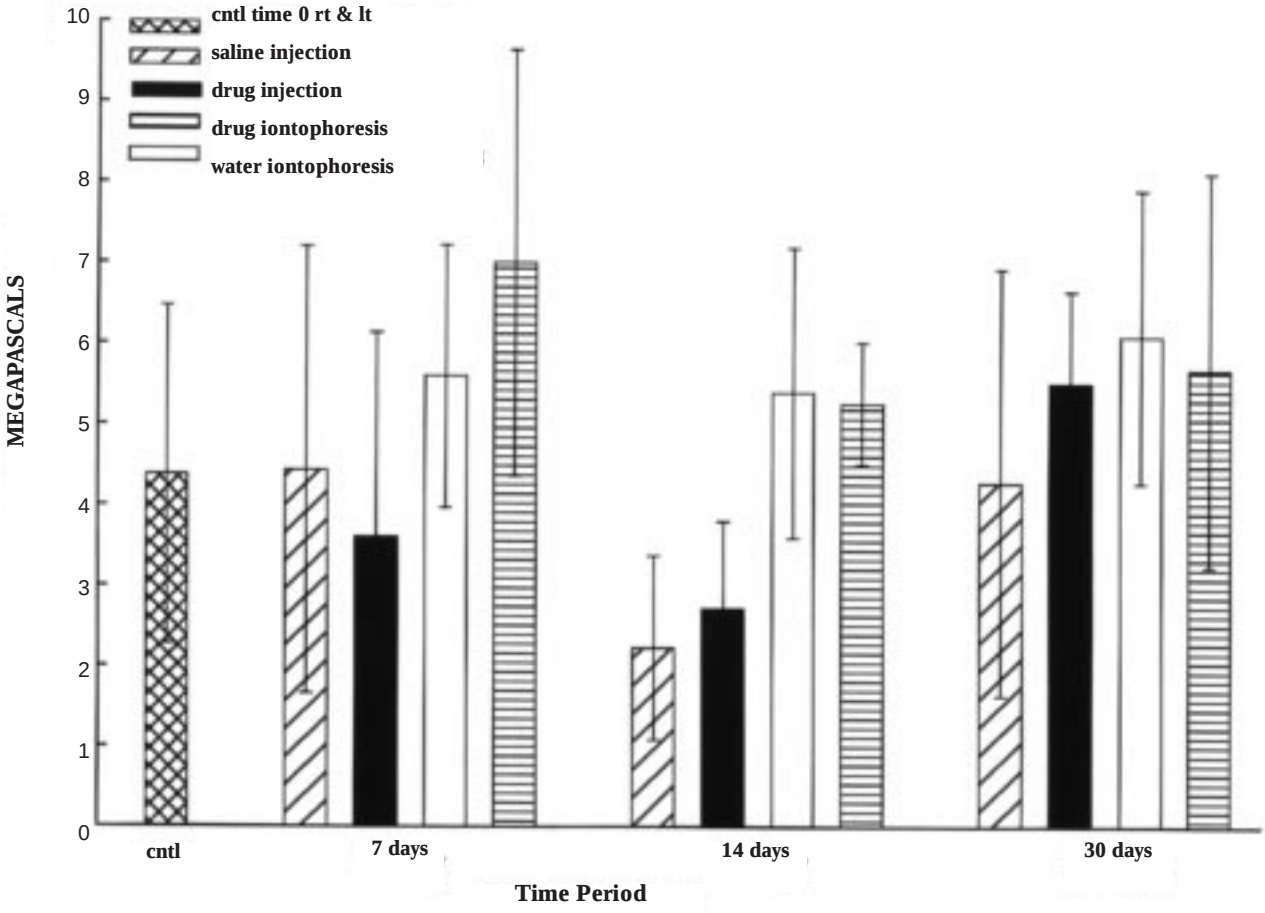

FIGURE 2. Elastic modulus of tendons. Tendons receiving four treatments were compared with each other and with control tendons that received no treatment. Values are ± standard deviation.

region for an estimate of elastic modulus, E. The peak of the stress-strain curve provided an estimate of ultimate stress. Percent elongation was expressed as $(L_f\text{-}L_i)/L_i$ where L_f was the final length and L_i was the initial length.

Histologic Evaluation of Tendons

All sections were evaluated histologically without knowledge of treatment group by a veterinary pathologist (C.S.C.) using routine light microscopy and cross-polarized light. The observed lesions were then summarized using the following grading scheme:

0 = no significant lesions;
1 = mild inflammation, focal thickening, or fibroblast infiltration of paratenon with normal appearance of tendon;
2 = focal adhesion of paratenon to tendon and/or moderate inflammation of paratenon, with or without thickening of paratenon, and normal appearance of tendon;
3 = multiple areas of adhesion or diffuse adhesion of paratenon to tendon and/or severe inflammation of paratenon and normal appearance of tendon;
4 = necrosis, fiber disruption, or fibroblast proliferation within the tendon itself.

Data Analysis

To determine the effect of dexamethasone compared with control solution on the normal Achilles tendon, comparisons in elastic modulus, ultimate load, and ultimate stress levels were made between (1) tendons treated with iontophoretically delivered dexamethasone and tendons treated with iontophoretically delivered control solution (water) and (2) tendons injected with dexamethasone and those injected with control solution (physiologic saline). For these comparisons, each rabbit served as its own control to reduce variability that might be introduced by unmeasured differences between rabbits.

Similarly, the effect of iontophoretically delivered treatment compared with injection treatment was evaluated by comparing elastic modulus, ultimate load, and ultimate stress levels of (1) tendons treated iontophoretically with dexamethasone and those injected with dexamethasone, and (2) tendons treated iontophoretically with control solution (water) with those injected with control solution

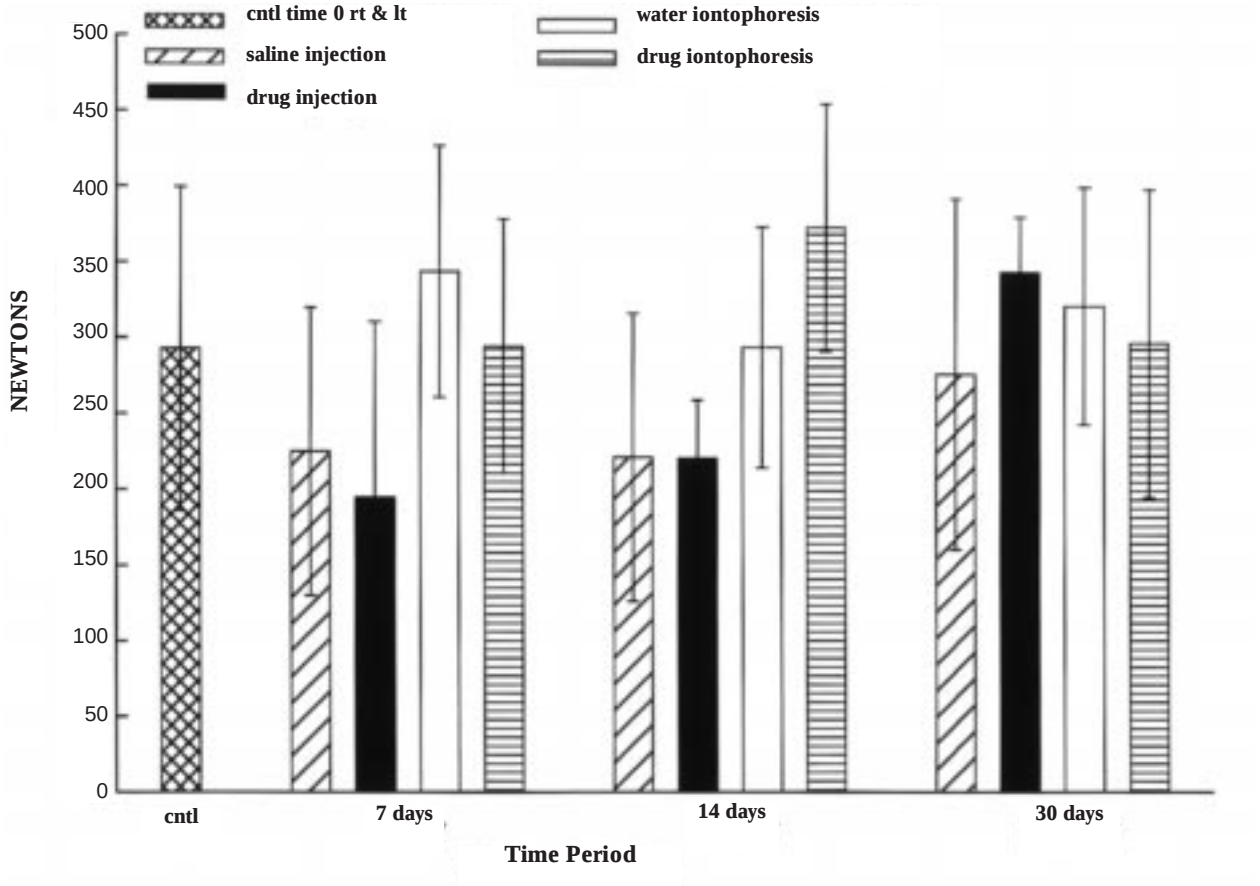

FIGURE 3. Ultimate load of tendons. Tendons receiving four treatments were compared with each other and with control tendons that received no treatment. Values are ± standard deviation.

(physiologic saline). Rabbits did not serve as their own control in this situation.

All comparisons were made at 7, 14, and 30 days after treatment. The empirical means, standard deviations, and medians of elastic modulus, ultimate load, and ultimate stress levels for the various comparison groups were calculated. Formal group comparisons were made using nonparametric statistical tests that do not require normally distributed data or variance homogeneity. The first set of comparisons determined the effect of dexamethasone using a Wilcoxon signed rank test for paired samples.[12] Comparisons of iontophoretically delivered solution with injected solution were made using the Wilcoxon Rank Sum test for two independent samples.[12] The null hypothesis for all nonparametric tests is that the medians for the groups being compared are equal. Statistical significance for all comparisons was based on a two-sided significance level of .05.

RESULTS

Biomechanical Testing

In the group 3 control animals, the following biomechanical testing results were determined and are expressed as the mean ± the standard error of the mean: elastic modulus 5.0 ± 3.1; ultimate load = 293.1 ± 106.8 newtons; and ultimate stress = 2.2 ± 0.8 megapascals.

In the experimental groups, there were no statistically significant differences in elastic modulus, ultimate load, or ultimate stress levels between (1) tendons treated iontophoretically with dexamethasone compared with water and (2) tendons injected with dexamethasone compared with saline at 7, 14, and 30 days after administration of the treatments (Figs 1, 2, and 3; Table 1).

Elastic modulus, ultimate load, and ultimate stress levels were higher at 7 and 14 days for tendons treated iontophoretically with dexamethasone or control solution than for tendons injected with the same solution. These differences were statistically significant for elastic modulus levels for tendons treated iontophoretically with dexamethasone versus injection at 7 days ($P = .04$) and for tendons treated iontophoretically with control solution compared with injection at 14 days ($P = .004$). Significantly higher levels of ultimate load were

TABLE 1. Elastic Modulus, Ultimate Load, and Ultimate Stress Levels by Route of Administration, Type of Solution, and Days Since Administration*

	Iontophoresis		*Injection*		*Dexamethasone*		*Water/Saline*	
	Water	*Dexamethasone*	*Saline*	*Dexamethasone*	*Iontophoresis*	*Injection*	*Iontophoresis*	*Injection*
Elastic Modulus								
Days since administration								
7 days	5.6	7.9 (.219)	4.1	2.7 (.688)	7.9	2.7 (.041)	5.6	4.1 (.378)
14 days	5.2	5.2 (.844)	2.3	2.6 (.563)	5.2	2.6 (.065)	5.2	2.3 (.004)
30 days	5.2	5.3 (.438)	4.0	5.7 (.438)	5.3	5.7 (.818)	5.2	4.0 (.378)
Ultimate Load								
Days since administration								
7 days	368.7	308.4 (.313)	236.3	152.5 (.438)	308.4	152.5 (.180)	368.7	236.3 (.026)
14 days	328.5	381.5 (.438)	201.0	228.1 (1.000)	381.5	228.1 (.004)	328.5	201.0 (.247)
30 days	294.2	313.8 (1.000)	322.1	332.4 (.563)	313.8	332.4 (.662)	294.2	322.1 (.937)
Ultimate Stress								
Days since administration								
7 days	2.3	2.3 (.844)	1.8	0.9 (.438)	2.3	0.9 (.108)	2.3	1.8 (.394)
14 days	1.8	2.6 (.221)	1.3	1.5 (.844)	2.6	1.5 (.002)	1.8	1.3 (.178)
30 days	2.2	2.2 (1.000)	1.9	2.1 (.248)	2.2	2.1 (.792)	2.2	1.9 (.336)

*Entries are medians with *P* values in parentheses from nonparametric tests.

also found at 7 days for tendons treated iontophoretically with water compared with those injected with saline ($P = .03$) and at 14 days for tendons treated iontophoretically versus those injected with dexamethasone ($P = .004$). Ultimate stress levels were significantly higher for tendons treated iontophoretically with dexamethasone compared with injection at 14 days after administration ($P = .002$). By 30 days after the treatments, there were no significant differences in any of the biomechanical properties measured in tendons treated by iontophoresis versus injection with either dexamethasone or the control solutions.

Histologic Evaluation

Minimal histologic changes were seen in the tendons treated with iontophoresis. In fact, all tendons treated with iontophoresis, either with dexamethasone or distilled water, received histologic scores of 0 or 1; the average scores for each of these groups were identical (0.22, Table 2). Scores for untreated control tendons or tendons injected with saline ranged from 0 to 2; the average scores for these groups were similar (0.5 for untreated controls and 0.67 for saline-injected controls) (Fig 4). Scores for the dexamethasone-injected tendons ranged from 0 to 4, with an average score of 1.56. Although more than half of the tendons in this group were histologically normal, 3 of 9 had proliferation of fibroblasts within the tendon and received a histologic score of 4 (Fig 5). The number of posttreatment days had no effect on the histologic appearance of the tendons.

TABLE 2. Histologic Grading Scores for Rabbit Tendons

	Control	*Iontophoresis, Sterile Water*	*Injection, Saline*	*Iontophoresis, Dexamethasone*	*Injection, Dexamethasone*
	0	0	0	0	0
	0	0	0	0	2
	2	0	0	1	4
	1	1	2	0	0
	0	0	2	0	4
	0	0	0	0	0
		1	0	1	0
		0	0	0	0
		0	2	0	4
Average	0.5	0.22	0.67	0.22	1.56

DISCUSSION

A review of the literature reveals a lack of consensus regarding the etiologic role of corticosteroid therapy in tendon rupture. The clinical literature is difficult to interpret because it consists mainly of case reports and contains few controlled clinical studies. Animal studies have had mixed results. In 1933, McMaster[13] pulled rabbit gastrocnemius muscle-tendon units to failure and found that under his experimental conditions, normal tendons did not rupture. Instead, the failure always occurred at the junction of the muscle and tendon or in the muscle belly itself. Therefore, spontaneous rupture of normal tendons is probably an unusual occurrence. The changes in tendons induced by corticosteroid administration are dependent on (1) the dose and duration of treatment and (2) the type of corticosteroid administered.[4] Long-term corticosteroid therapy is reported to result in reduced tendon dry weights, while tendon strength is unchanged[4]; however, other studies have shown that synthesis of collagen is reduced by corticosteroids, resulting in thinning and weakening of the tendons.[14] Corticosteroid injections also are reported to inhibit fibroblast proliferation.[6]

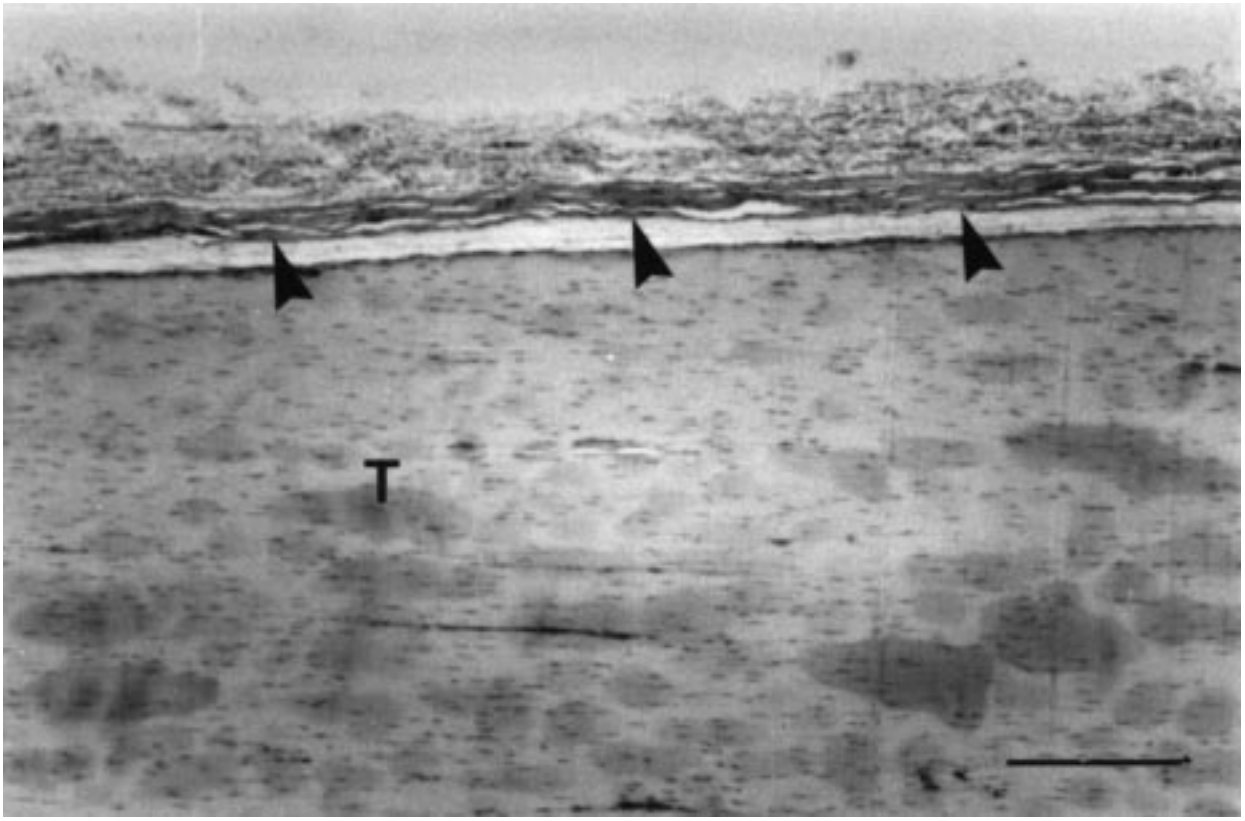

FIGURE 4. Longitudinal section of normal tendon (T) and paratenon (arrowheads) from a rabbit in control group. (Hematoxylin-eosin stain, Bar = 400 μm)

FIGURE 5. Longitudinal section of tendon and paratenon 30 days after peritendinous injection of dexamethasone. Paratenon is markedly thickened by fibroblast proliferation, which extends into tendon (arrowhead). (Hematoxylin-eosin stain, Bar = 400 μm)

It appears that differences in conclusions from experimental studies on the effects of corticosteroids on tendons have been largely due to differences in the experimental models used.[15] A dog model of tendon healing showed that daily cortisone injections inhibited excessive peritendinous fibrous tissue and did not prevent end-to-end healing in severed tendons.[16] The majority of the experimental work in this area, however, has been done in rabbits, and the results are mixed. In studies examining the effects of corticosteroid injections on transected tendons that have been surgically repaired, two showed decreases in tensile strength, impaired healing, and/or decreased weight in the treated tendons.[8,17] One study showed no effect of large doses of cortisone on the histology or tensile strength of sutured tendons,[18] and another showed improved function in tendons treated with injections of triamcinolone.[19] In studies on the effects of injected corticosteroids on normal tendons, two showed no deleterious biomechanical changes,[20,21] but one of these showed a decrease in tendon weight in the steroid-injected tendons.[20] Three other studies showed detrimental effects of steroid injections including decreased tensile strength biomechanically and collagenolysis histologically[22]; collagenolysis and subsequent incomplete repair, often complicated by dystrophic calcification[23]; or swelling, hemorrhage, and deposition of steroid in the tendon, accompanied by a decreased modulus of elasticity and tendency to rupture.[2]

Iontophoresis, also called common iontransfer or electro-osmosis,[24] has been used for more than 70 years.[25] With iontophoresis, selected ions are transported electrically through biologic membranes by passing a direct electrical current through both the drug solution and the patient.[26] Iontophoresis has several advantages: (1) it is noninvasive, (2) it reduces trauma, (3) it produces a locally high concentration of drug and a low systemic drug concentration, (4) it permits regulation of the amount of drug delivered, and (5) it allows drug dosages to be adjusted to meet the individual needs of patients.[27] The disadvantages associated with its use, possible electrical shock, skin irritation at the treatment site, and skin burns at the treatment site, have been reduced with recent technologic improvements.[27] Iontophoresis of tritium-labeled dexamethasone sodium phosphate and hydrocortisone sodium succinate at levels sufficient to be clinically effective has been shown in Rhesus monkey tendon and cartilage.[28,29] However, the tendons were not analyzed histologically or biomechanically to determine the drug effect on the treated tendons.

In our study, there was no evidence that dexamethasone itself, whether administered iontophoretically or by injection, had a detrimental effect on the biomechanical properties of normal rabbit Achilles tendons. There was some evidence, however, of a short-term (<30 days) detrimental effect of the injection procedure, whether dexamethasone or saline was administered. Although the results of the histologic studies were less clear, the trends were similar, and indicate that delivery of dexamethasone by iontophoresis does not adversely affect the histologic appearance of the rabbit Achilles tendon. The lowest histologic scores (fewest histologic changes) were observed in the tendons treated by iontophoresis with either dexamethasone or distilled water, and the highest scores were observed in the group treated with dexamethasone by injection. Although the majority of the tendons treated with dexamethasone by injection were histologically normal, there appears to be a potential for harmful effects of the injected steroid on the tendon. Tendons in the dexamethasone-injected group were the only ones receiving a histologic grade of 4, indicating that the histologic changes were not limited to the paratenon but involved the tendon itself. The injection of saline appeared to produce more histologic changes than no treatment, probably because the injection procedure involved an incision over the tendon and potential trauma to the tendon sheath. Although the biomechanical changes seen in this study were absent by day 30 after injection, the number of days after treatment had no effect on the histologic changes. This is puzzling but may be due to the small sample sizes for the histologic studies.

Our study showed agreement in the biomechanical and histologic results in that corticosteroid itself did not appear to have deleterious effects, but there was evidence for detrimental effects of injection of drug versus delivery by iontophoresis.

CONCLUSIONS

Injection of either saline or corticosteroid into the rabbit Achilles tendon sheath appears to cause short-term changes in tendon biomechanical and histologic characteristics. Iontophoresis using sterile water or cortico-

steroid resulted in minimal or no biomechanical and histologic changes in the tendon compared with injection of either substance. The method of corticosteroid delivery to soft tissues may be as important as the actual drug effects on the biomechanical and histologic properties of those tissues.

References

1. Hench PS, Kendall EC, Slocumb CH: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocortisone; compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. preliminary report. *Mayo Clin Proc* 1949; 24:181-197
2. Unverferth LJ, Olix ML: The effect of local steroid injections on tendon. *J Sports Med* 1973; 1:31-32
3. McWhorter JW, Francis RS, Heckman RA: Influence of local steroid injections on traumatized tendon properties. *Am J Sports Med* 1991; 19:435-439
4. Oxlund H: Changes in connective tissues during corticotrophin and corticosteroid treatment. *Danish Med Bull* 1984; 31:187-206
5. Halpern AA, Horowitz BG, Nagel DA: Tendon ruptures associated with corticosteroid therapy. *West J Med* 1977; 127:378-382
6. Lark MR, Gangarosa LP: Iontophoresis: an effective modality for the treatment of inflammatory disorders of the temporomandibular joint and myofascial pain. *Craniomandibular Pract* 1990; 8:108-119
7. Nesbit NW: Anatomy of the calcaneal tendon on the rabbit. *J Bone Joint Surg Br* 1960; 142:360-366
8. Kapetanos G: The effect of the local corticosteroids on the healing and biomechanical properties of the partially injured tendon. *Clin Orthop* 1982; 163:170-179
9. *Physician's Desk Reference.* Montvale, NJ, Medical Economics Co Inc, 52nd Ed, 1998, p 1638
10. Flahiff CM, Brooks AT, Hollis JM, et al: Biomechanical analysis of patellar tendon allografts as a function of donor age. *Am J Sports Med* 1995; 23:354-358
11. Noyes FR, Butler DL, Grood ES, et al: Biomechanical analysis of human ligament grafts used in knee-ligament repairs and reconstructions. *J Bone Joint Surg Am* 1984; 66:344-352
12. Wilcoxon R: Individual comparisons by ranking methods. *Biometrics Bull* 1945; 1:80-83
13. McMaster PE: Tendon and muscle ruptures. clinical and experimental studies on the causes and location of subcutaneous ruptures. *J Bone Joint Surg* 1933; 15:705-722
14. Oxlund H, Manthorpe R: The biomechanical properties of tendon and skin as influenced by long term glucocorticoid treatment and food restriction. *Biorheology* 1982; 19:631-646
15. Leadbetter WB: Corticosteroid injection therapy in sports injuries. *Sports Induced Inflammation*. Park Ridge, Ill, American Academy of Orthopaedic Surgeons, 1990, pp 527-545
16. Wrenn RN, Goldner JL, Markee JL: An experimental study of the effect of cortisone on the healing process and tensile strength of tendons. *J Bone Joint Surg Am* 1954; 36:588-601
17. Wiggins ME, Fadale PD, Ehrlich MG, et al: Effects of local injection of corticosteroids on the healing of ligaments. *J Bone Joint Surg Am* 1995; 77:1682-1691
18. Berkin CR: Effects of cortisone on the healing of tendons in rabbits. *Proc R Soc Med* 1955; 48:610-613
19. Ketchum LD: Effects of triamcinolone on tendon healing and function. *Plast Reconstr Surg* 1971; 47:471-482
20. Mackie JW, Golden B, Foss ML, et al: Mechanical properties of rabbit tendons after repeated anti-inflammatory steroid injections. *Med Sci Sports* 1974; 5:198-202
21. Matthews LS, Sonstegard DA, Phelps DB: A biomechanical study of rabbit patellar tendon: effects of steroid injection. *J Sports Med* 1975; 2:349-357
22. Kennedy JC, Willis RB: The effects of local steroid injections on tendons: a biomechanical and microscopic correlative study. *Am J Sports Med* 1976; 4:11-21
23. Balasubramaniam P, Prathap K: The effect of injection of hydrocortisone into rabbit calcaneal tendons. *J Bone Joint Surg Br* 1972; 54:729-734
24. Lekas MD: Iontophoresis treatment. *Otolaryngol Head Neck Surg* 1979; 87:292-298
25. Harris PR: Iontophoresis: clinical research in musculoskeletal inflammatory conditions. *J Orthop Sports Phys Ther* 1982; 4:109-112
26. Hasson SM, English SE, Daniels JC, et al: Effect of iontophoretically delivered dexamethasone on muscle performance in a rheumatoid arthritic joint. *Arthritis Care Res* 1988; 1:177-182
27. Banga AK, Chien YW: Iontophoretic delivery of drugs: fundamentals, developments and biomedical applications. *J Controlled Release* 1988; 7:1-24
28. Bertolucci LE: Introduction of anti-inflammatory drugs by iontophoresis: double blind study. *J Orthop Sports Phys Ther* 1982; 4:102-108
29. Glass JM, Stephen RL, Jacobson SC: The quantity and distribution of radiolabeled dexamethasone delivered to tissue by iontophoresis. *Int J Dermatol* 1980; 19:519-525