Initial Long-Term Results of Horses with Superficial Digital Flexor Tendinitis Treated with Intralesional β-Aminopropionitrile Fumarate

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The administration of 7–8 mg of β-aminopropionitrile fumarate (βAPN-F) intralesionally results in a statistically significant decreased tendon cross-sectional area and an improved fiber alignment score compared with placebo treated tendons. The use of βAPN-F 1–3 months postinjury results in better quality tendon repair with improved chances of the horse's returning successfully to racing. Authors' addresses: Dept. of Clinical Studies, New Bolton Center, University of Pennsylvania, 382 W. Street Rd., Kennett Square, PA 19348 (Reef); Randall Veterinary Clinic, 20600 Miles Pkwy, Warrensville Heights, OH 44128 (Genovese); and Alaco, Inc., 1500 N. Wilmot #290, Tucson, AZ 85712 (Davis). © 1997 AAEP.

1. Introduction

β-aminopropionitrile (βAPN) is the active nitrile found in the seeds of the wild sweet pea, Lathyrus odoratus. Seeds containing βAPN can cause connective tissue disorders, such as bony deformities and aortic aneurysms, when eaten over an extended period of time by young rapidly growing animals. Timed applications of βAPN (during peak production of lysyl oxidase) can temporarily alter newly formed scar tensile strength by specifically inhibiting the enzyme lysyl oxidase. Lysyl oxidase is needed for lysine deamination, an important first step in scar formation, specifically strong covalent collagen cross-linking.1–5 By blocking lysyl oxidase with βAPN, lysine deamination is also blocked, thus blocking collagen cross-linking. Brief interruption of collagen cross-linking in early scar formation creates a window of opportunity for physiologically beneficial scar remodeling, which can enhance function. Systemic toxicity is avoided by low-dose local application of βAPN.4

Early studies using βAPN fumarate (βAPN-F) in horses with recently bowed tendons showed a significant improvement in the clinical parameters, indicating tendon healing.3,6 A dose ranging trial (DRT) was designed to determine the optimal dose of βAPN-F for the efficacious treatment of acute bowed tendons in performance horses. A dose confirmation trial (DCT) was designed to confirm the efficacy of the 7-mg dose of βAPN-F chosen as a result of the DRT. The supplementary trial (ST) was designed to confirm the efficacy of the 7-mg dose of βAPN-F in a larger number of horses when administered 1–3 months postinjury.

2. Materials and Methods

Horses (N = 99) with a recent injury (1–4 months) to the superficial digital flexor tendon in one foreleg (DRT, DCT) or in one or both forelegs (ST) that were...
treated with the 7- or 8-mg dose of intralesional \( \beta \)APN-F (84 horses) or placebo (15 horses) and that the owners tried to return to racing were included in this study. Horses were not included in the study if the injury to the superficial digital flexor tendon at the worst injury zone involved less than 18% of the tendon’s cross-sectional area or if the cross-sectional area of the injured tendon was less than 1.5 cm\(^2\) or was not at least 50% larger at the worst injury zone than the contralateral normal tendon at the same zone. If the horse had bilateral superficial digital flexor tendon injuries, only the most severely affected tendon had to meet the above criteria. All horses included in this study were initially treated at least 2.5 years or more prior to January 1, 1997 or met the criteria for success, partial success, or failure prior to that time.

A horse was classified as a success (group 1) if the horse had returned to racing and had completed at least five races within the 2.5 years following treatment. If these five races occurred without clinical or sonographic reinjury, the horse was classified as 1A; if clinical or sonographic reinjury occurred, the horse was classified as 1B. The horse was classified as a partial success (group 2) if the horse returned to racing (EL-7) within 2.5 years following treatment of a tendon injury but raced fewer than five times. The partial success group was divided into horses that were only partially successful because of nontendon failure (2A), clinical or sonographic injury to the treated leg (2B), no clinical but sonographic reinjury to the treated leg (2C), and clinical or sonographic injury to the contralateral forelimb (2D). The failure group (group 3) never returned to racing (EL-7) within the 2.5 years following intralesional \( \beta \)APN-F treatment of the bowed tendon. The horses failed for nontendon reasons (3A), with clinical or sonographic injury to the treated leg (3B) or with clinical or sonographic injury to the contralateral forelimb (3C). Racing records from the respective racing associations were obtained and used to determine if the treatment was a success, partial success, or failure.

All horses were race horses between 2 and 15 years of age with no other significant lameness. A baseline ultrasound examination was performed in both forelegs immediately prior to treatment. Both legs were scanned with a 7.5- to 10.0-MHz transducer containing a built-in fluid offset or by using a hand-held standoff pad from the carpus to the fetlock in all seven zones (1A, 1B, 2A, 2B, 3A, 3B, and 3C). The length of the tendon injury was measured and the number of affected zones was determined. Tendon and lesion cross-sectional areas were measured\(^7\)–\(^9\) at each zone.

The worst injury zone was selected based on the site of the largest percentage of tendon damage. The cross-sectional area of the lesion and tendon at each of the seven zones was then summed to calculate the total injury area and total tendon area, respectively, for each horse. The percent injury of the total tendon was calculated from the total injury area divided by the total tendon area. Fiber alignment (Table 1) and echogenicity (Table 2) were graded at each zone (0–3) and the average score for the tendon was calculated. These initial sonographic findings were used to compare with the sonographic results following treatment with intralesional \( \beta \)APN-F at 8, 12, and 16 weeks after treatment and prior to each change in exercise level. An analysis of variance for repeated measures was used to compare the initial sonographic findings with those obtained at 16 weeks after treatment with a significance level of \( p < 0.05 \).\(^8\)

Prior to treatment the horses were evaluated for lameness and the tendon was palpated for heat, swelling, and sensitivity. Horses were randomly administered intralesional \( \beta \)APN-F or placebo in the DRT and DCT in a random, blinded fashion while a known 7-mg dose of \( \beta \)APN-F was administered to the horses in the ST. Horses were sedated and a sterile preparation of the affected limb was performed. Multiple injections of 0.2 ml of \( \beta \)APN-F or the blinded drug were made throughout the injured area of the superficial digital flexor tendon with a 25- or 27-gauge 3/4 in. to 1 1/4 in. (\( \sim \)1.9–3.2 cm) needle. The injections were repeated every other day for a total of five treatments. The DRT and DCT studies were double-blind placebo-controlled trials in which one of three doses (3.5, 7.0, or 8.0 mg) of \( \beta \)APN-F (DRT), the 7-mg dose of \( \beta \)APN-F (DCT), or a placebo (saline; DRT and CRT) were injected intralesionally in the affected tendon. The owners of all horses receiving the placebo were offered the option of having the drug injected into the healing tendon at the end of the double-blind phase of the trial (4 months after the initial treatment). In the ST, all horses received the 7-mg dose of \( \beta \)APN-F intralesionally in the affected tendon(s). Horses were then placed in a rigorous low-level controlled exercise program (Table 3) in which each increase in exercise level was based on sonographic improvement, evidence of tendon healing, and remodeling. No horses

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### Table 1. Scoring Lesion Echogenicity

<table>
<thead>
<tr>
<th>Echo Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>tendon has normal echogenicity, no lesion detected</td>
</tr>
<tr>
<td>1</td>
<td>lesion is mostly echogenic</td>
</tr>
<tr>
<td>2</td>
<td>lesion is 50% echogenic, 50% anechoic</td>
</tr>
<tr>
<td>3</td>
<td>lesion is mostly anechoic</td>
</tr>
</tbody>
</table>

### Table 2. Fiber Alignment Grading

<table>
<thead>
<tr>
<th>Fiber Alignment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>( \geq 75% ) of fibers in lesion are parallel</td>
</tr>
<tr>
<td>1</td>
<td>50–75% of fibers in lesion are parallel</td>
</tr>
<tr>
<td>2</td>
<td>25–50% of fibers in lesion are parallel</td>
</tr>
<tr>
<td>3</td>
<td>0–25% of fibers in lesion are parallel</td>
</tr>
</tbody>
</table>
began galloping or its equivalent exercise (Standardbred racehorses) prior to 6 months following treatment with intralesional βAPN-F.

3. Results

There were 99 horses that owners tried to return to racing or to their prior competition that received either the 7- or 8-mg dose of intralesional βAPN-F or the placebo. Eighty-four of these horses were treated initially with the 7- or 8-mg dose of βAPN-F and 15 horses received the placebo. Three of the 15 placebo-treated horses received the 7- or 8-mg dose of intralesional βAPN-F when the code for the double-blind study was revealed (4 months after the initial treatment), an option elected by the owners of these horses in hopes of increasing their success. Twelve placebo-treated horses never received intralesional βAPN-F. The owners of these horses did not select this option because tendon healing was progressing favorably, both clinically and sonographically, at the end of the double-blind phase of the trial.

Of the horses that initially received the 7- or 8-mg dose of intralesional βAPN-F, 42 were group 1 horses with 44 bowed tendons, 14 were group 2 horses with 17 bowed tendons, and 28 were group 3 horses with 31 bowed tendons. Two of the 28 group 3 horses were treated twice, 1 year apart, for a recurrent injury to the superficial digital flexor tendon in the same limb. Each of these treatments was counted as a separate horse. Of the horses receiving the placebo only, there were four group 1 horses, three group 2 horses, and five group 3 horses. Each of the placebo-treated horses had only one bowed tendon.

The severity of the initial tendon injury was similar in the group of 84 horses initially receiving βAPN-F and in those 12 horses receiving only the placebo. The total tendon cross-sectional area in the horses initially receiving 7 or 8 mg of βAPN-F ranged 6.3–31.0 cm² with a mean of 11.4 cm²; their total percent injury ranged 4.6–81.2% with a mean of 31.7%. The mean maximal injury zone cross-sectional area was 1.8 cm² in group 1 horses, 2.6 cm² in group 2 horses, and 2.2 cm² in group 3 horses. The mean percent damage at the maximal injury zone was 40.4% in group 1 horses, 53.0% in group 2 horses, and 47.7% in group 3 horses. Mean total fiber scores were also similar among groups (2.36 in group 1 horses, 2.24 in group 2 horses, and 1.97 in group 3 horses).

In the three horses treated initially with the placebo and subsequently treated with 7 or 8 mg of intralesional βAPN-F, the severity of the initial injury was similar to the injury severity in the horses initially treated with βAPN-F. The total affected tendon cross-sectional area in these horses ranged from 9.35 cm² to 12.3 cm² (mean = 10.3 cm²), and their total percent tendon injury ranged from 29.3% to 72.2% (mean = 44.7%). The mean tendon cross-sectional area at the maximal injury zone was 1.8 cm² and the mean percent damage at the worst injury zone was 47.6%.

There was a difference between the severity of the initial injury in the successful (group 1), partially successful (group 2), and failure (group 3) horses that received only the placebo (n = 12 horses). The successful placebo-treated horses (groups 1A, n = 2 and 1B, n = 2) had relatively mild injuries to the superficial digital flexor tendon with a total tendon area that ranged between 7.7 cm² and 12 cm² (mean = 9.5 cm²) and a total percent tendon injury that ranged between 7% and 16.5% (mean = 13%). The three placebo horses that reached EL-7 but were only partially successful (group 2B) had a moderate tendon injury with a total injury area that ranged between 9.6 cm² and 14.25 cm² (mean = 11.8 cm²) and a total percent tendon injury that ranged between 17% and 46% (mean = 29.3%). Overall both group 1 and group 2 placebo-treated horses had less severe initial injuries than the group 3 horses. The five placebo-treated horses that failed (group 3) had a total tendon cross-sectional area that ranged between 8.3 cm² and 21.2 cm² (mean = 12.8 cm²) and a total percent tendon injury that ranged between 29% and 63% (mean = 48.6%).

Most horses treated with βAPN-F rapidly became sound and the sensitivity of the affected tendon...
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disappeared. Although some swelling was seen in most horses following the series of intralesional tendon injections, this gradually decreased in all horses. The original core lesion was usually no longer detectable in βAPN-F treated horses 2 months following the injury but was detectable in nearly all the placebo-treated horses. Tendon cross-sectional area was significantly decreased at 16 weeks after treatment (p < 0.05) in the total injury zone area and the maximal injury zone in horses treated with the 7- or 8-mg doses of βAPN-F compared with the placebo-treated control horses and the horses receiving the 3.5-mg dose of βAPN-F. Fiber alignment was also significantly (p < 0.05) improved at 16 weeks in the horses treated with the 7- or 8-mg doses of βAPN-F when compared with the placebo controls and the low-dose βAPN-F treated horses. There was a clinical impression among all investigators of the absence of peritendinous scar in the majority of horses treated with intralesional βAPN-F.

Horses receiving intralesional βAPN-F were able to return to racing or competition with a lower incidence of clinical or sonographic reinjury compared with placebo-treated horses. Eighty-seven horses that received 7 or 8 mg of βAPN-F intralesionally in the affected tendon have attempted to return to racing; three of those horses were horses that initially received the placebo and were treated 4 months later with βAPN-F. The majority of horses receiving βAPN-F (67.8% or 59/87 horses) returned successfully to racing and started one or more times. Of those horses treated initially with βAPN-F, 66.7% or 56/84 horses were able to reach EL-7. Fifty percent of horses treated initially with βAPN-F (42/84 horses) were successful within 2.5 years of treatment, racing at least five times; 76.2% (32/42 horses) returned to racing or competition without clinical or sonographic evidence of reinjury, whereas the remaining 23.8% (10/42 horses) had clinical or sonographic evidence of reinjury in the same tendon or in the contralateral tendon. Partial success was achieved in 16.7% of horses treated initially with βAPN-F (14/84 horses). One of these 14 horses (7.1%) reached EL-7 but was only partially successful because of nontendon failure (2A, catastrophic metacarpal fracture). The majority (78.6% or 9/14 horses) reached EL-7 but had clinical or sonographic evidence of reinjury prior to racing five times (group 2B). Two of the 14 horses (14.3%) reached EL-7 but sustained a tendon injury in the contralateral forelimb prior to racing five times (group 2D). All three horses with bilateral bowed tendons reinjured the original, most severely affected tendon. All horses that failed to return successfully to racing (group 3) failed because of a tendon injury in the treated limb (78.6% or 22/28 horses) or in the contralateral forelimb (21.4% or 6/28 horses).

Three placebo-treated horses received intralesional βAPN-F 4 months after the placebo treatment. All three horses reached EL-7. Two of the three horses (66.7%) raced successfully for five or more starts within 2.5 years following the initial treatment with the placebo (group 1). One horse raced with no clinical or sonographic reinjury (1A), while the other horse had a very small area of reinjury in the treated leg (sonographic only, followed by clinical and sonographic injury in the superficial digital flexor tendon in the contralateral forelimb). One of the three horses reached EL-7 but did not race five times because of nontendon failure (2A).

Only four of 12 (33.3%) placebo-treated horses that never received intralesional βAPN-F were able to return successfully to racing and start at least five times (group 1). Of these four horses, two experienced clinical and sonographic reinjury before the five starts occurred but were still able to race five times within the 2.5 years from their initial treatment (group 1B). Three of 12 horses that received the placebo (25%) were able to reach EL-7 but experienced clinical and sonographic reinjury before five starts could be completed within the 2.5-year period beginning at the onset of treatment. Five of 12 placebo-treated horses (41.7%) that did not subsequently receive intralesional βAPN-F never reached EL-7. All but one of the 12 placebo-treated horses (91.7%) ultimately rebowed. The one (8.3% or 1/12 horses) placebo-treated horse that was able to return to racing successfully (group 1A) without experiencing clinical or sonographic evidence of reinjury was monitored for more than 3.5 years following treatment.

There was no placebo-treated horse that reached EL-7 with a total tendon cross-sectional area greater than 14.25 cm² or an initial total tendon injury percent greater than 46%. However, there were nine βAPN-F treated horses (five horses in group 1 and four horses in group 2) that reached EL-7 with an initial total tendon cross-sectional area in excess of 14.25 cm². The initial total tendon cross-sectional area exceeded 18.0 cm² in three βAPN-F treated horses (one horse in group 1 and two horses in group 2). There were also 13 βAPN-F treated horses (nine horses in group 1 and four horses in group 2) that reached EL-7 with an initial total tendon percent injury in excess of 46%. In eight of these horses (five horses in group 1 and three horses in group 2), the total tendon percent injury exceeded 60%. The mean number of starts per horse for horses reaching EL-7 that received the 7- or 8-mg dose of the drug compared with those receiving the placebo or 3.5-mg dose of the drug was 5.6 ± 3.4.

4. Discussion

The use of intralesional βAPN-F in the treatment of acute bowed tendons in horses has demonstrated statistically significant differences in the sonographic improvement of the affected tendon in horses receiving the 7- or 8-mg dose of the drug compared with those receiving the placebo or 3.5-mg dose of the drug.
These sonographic findings suggest a better quality tendon repair because the original lesion is no longer sonographically distinct, the overall cross-sectional area of the injured tendon and the cross-sectional area at the maximal injury zone are significantly decreased, the fiber alignment of the injured area is significantly improved, and there is little or no evidence of peritendinous scar formation.

The long-term follow-up data on these horses indicate a more successful return to performance, which is the ultimate goal of the treatment of equine athletes with tendon injuries. More horses receiving the 7- or 8-mg dose of intralesional βAPN-F return to EL-7 than those treated conservatively (receiving the placebo), and a greater number of these horses are able to race or compete at least five times without reinjury to the injured tendon or sustaining an injury to the contralateral tendon. Overall, the horses treated with the 7- or 8-mg dose of intralesional βAPN-F that reached EL-7 had more severe injuries than the placebo-treated horses that reached EL-7. Also, the horses that were treated with the 7- or 8-mg dose of intralesional βAPN-F and were successful at starting at least five or more times (group 1A or 1B) had more severe injuries than the horses that received the placebo and were similarly successful (group 1A or 1B).

References