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CASE REPORT

Journal of  
Science and  
Medicine in  
Sport

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# Systemic allergic reactions to aprotinin injection around the Achilles tendon

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Received 30 April 2006; received in revised form 4 July 2006; accepted 7 July 2006

## KEYWORDS

Aprotinin;  
Allergic reactions;  
Achilles tendon

**Summary** Local aprotinin injections are used in the treatment of chronic tendinopathy. Severe allergic reactions, although uncommon, have been reported. We highlight two instances of systemic allergic reaction, and discuss the potential side effects of local aprotinin injections in the orthopaedic setting as well as the evidence base for its use.

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An otherwise healthy 54-year-old female with an 8-month history of chronic left Achilles tendinopathy resistant to conservative management was injected peritendinously with 62,500 IU aprotinin (Bayer, Newbury, United Kingdom) and 3.75 ml of 1% lidocaine (Hameln pharmaceuticals, Gloucester, United Kingdom). Within 10 min from the injection, she developed itching and redness around the injection site. This progressed to dizziness, nausea and signs of a systemic allergic reaction. She was given intravenous fluids (Gelofusine 1.5 l, Braun, Melsungen, Germany), received 100 mg intravenous hydrocortisone (Pharmacia, Milton Keynes, United Kingdom) and 10 mg chlorpheniramine (Link pharmaceuticals, Horsham, United Kingdom), and was transferred to the Accident and Emergency Department, where she was observed. Her symptoms settled within 4 h, at which time she was discharged home. She experienced

no further problems, although her Achilles tendinopathy remains recalcitrant.

An otherwise healthy 55-year-old female with an 8-month history of chronic left Achilles tendinopathy resistant to conservative management was injected peritendinously with 62,500 IU aprotinin (Bayer) and 3.75 ml of 1% lidocaine (Hameln pharmaceuticals). She had received a previous injection of 62,500 IU aprotinin and 3.75 ml of 1% lidocaine 6 weeks earlier, with partial resolution of the Achilles tendinopathy symptoms and no problems following the injection. Within 20 minutes of this second injection, she developed itching, nausea and tingling in her mouth. Her blood pressure was un-recordable; and therefore she was managed according to Advanced Life Support protocol.<sup>4</sup> One hundred milligrams (mg) intravenous hydrocortisone (Pharmacia), chlorpheniramine 10 mg (Link pharmaceuticals) and 500 µg intra-muscular adrenaline (ALK-Abello, Hungerford, United Kingdom) were administered with appropriate fluid resuscitation (Gelofusine 1.5 l: Braun, Melsungen,

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Germany). She was transferred to the Accident and Emergency Department, where she subsequently settled and was admitted for overnight observation. She was discharged the following day, and has had no further problems. Although her Achilles tendinopathy has not settled fully, she was able to complete a 120 miles mountain hike over 7 days 4 weeks after this episode.

## Discussion

Achilles tendinopathy is the commonest sports injury, but the evidence basis for its management is not conclusive.<sup>5</sup> Eccentric exercise programs, topical nitrates and sclerotherapy injections have all been shown to be beneficial in terms of outcome and pain relief.<sup>6–8</sup> However, heel pads, non-steroidal anti-inflammatory drugs and corticosteroid injections have failed to show significant statistical improvement in the management of Achilles tendinopathy.<sup>9–11</sup>

In recent years, aprotinin has been increasingly used in the management of chronic tendinopathy<sup>1–3,13</sup> and more recently in scoliosis surgery.<sup>12</sup> Aprotinin is a broad spectrum serine protease inhibitor, derived from bovine lungs.<sup>1</sup> It acts on trypsin, plasmin, kallikrein, blocks matrix metalloproteinases and may specifically act as a collagenase inhibitor in tendinopathy.<sup>1,13</sup>

Both patellar and Achilles tendinopathy have similar histopathological features. In the management of patellar tendinopathy, statistically significant improvements were seen in a randomised controlled trial examining aprotinin versus cortisone or placebo injections in the management of patellar tendinopathy over a 12-month period.<sup>2</sup> Until recently evidence for aprotinin use in the management of Achilles tendinopathy was based on uncontrolled studies, reporting success rates of around 80%.<sup>13</sup> In the only randomised controlled trial to examine the role of aprotinin in Achilles tendinopathy, the authors concluded that there was no statistical significant improvement in outcome.<sup>13</sup> The authors did comment that a trend of improvement over placebo was noted and low patient numbers resulting in an under-powered study may account for the lack of significance.

The main side effect of aprotinin is that of allergic reactions. The risk of hypersensitivity/anaphylactic reaction with aprotinin is less than 0.1% on first exposure, but rises to 2.7% with re-exposure.<sup>14</sup> If re-exposure occurs within 6 months, the risk of a reaction is 5%, but the risk significantly decreases if second injection is after 6 months

(0.9%).<sup>14</sup> Orchard et al.<sup>1</sup> reported their experience with side effects in 121 patients, most of which were non-severe: 30% of patients reported an itch at the injection site, 10% rash, 9% sweating and 7% post-injection pain.<sup>1</sup>

Published rates for severe allergic reaction are 1–3%.<sup>1,15,16</sup> Severe allergic reactions are rare, but the literature supports the view that they mainly occur after second exposure.<sup>1,15</sup> Orchard et al. reported a 2.6% rate for severe allergic reactions after second injections, with no serious reaction reported after the first injection of aprotinin.<sup>1</sup>

Before these two cases the senior author (NM) did not routinely consent patients about systemic allergic reactions since there were no reported cases in the peer review literature. Since these two adverse effects, all patients now undergoing peritendinous aprotinin injection are made aware of possible systemic allergic reactions to the drug, in addition to other common side effects, when providing written informed consent. Patients who have had previous allergic reactions to aprotinin should not be offered another injection. We suggest that patients remain in the medical clinic after the injection for observation for up to 60 minutes. Appropriate resuscitation equipment must be available, and practitioners must be able to manage allergic reactions.

The senior author has used aprotinin since 1988 for the management of chronic tendinopathy in more than 1200 patients. To the senior author's knowledge, these are the only two cases of systemic allergic reactions. Case report 1 highlights a rare phenomenon since the patients systemic allergic reaction occurred on first exposure to aprotinin. Both cases reported systemic reactions in middle aged active but non-athletic women. The majority of patients who undergo aprotinin injections tend to be athletic individuals, and we can only hypothesise that the athletic state of a patient may be important. Since these two incidents, the senior author has become increasingly aware of injecting such patients. Severe allergic reactions are rare, but it is vital that practitioners are aware of and confident in the management of systemic allergic reactions.

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