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# Delay of 6 weeks between aprotinin injections for tendinopathy reduces risk of allergic reaction

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## KEYWORDS

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**Summary** Aprotinin is a collagenase inhibitor previously shown to be effective for treating tendinopathies but associated with systemic allergic reactions. This historical cohort study aimed to determine whether or not the injection regime used affected the risk of allergic reaction and outcome. It compared 223 tendinopathy cases (group R) generally treated with a rapid series of aprotinin injections spaced one to two weekly and 158 cases (group D) generally given a single injection or a delay in their repeat injection(s) of over 6 weeks. Side effects and outcome measures were documented by questionnaire with a response rate of 75%. Systemic allergic reactions occurred in 7% of group R cases compared with 2% in group D (NS). Injections given 2–4 weeks after a previous injection were significantly more likely to lead to allergic reactions (6%) than initial injections (0.3%) and injections given >6 weeks after a previous injection (0.9%) ( $P < 0.05$ ). Overall patient rated satisfaction and outcome measures were similar between groups. In summary the current published regime of multiple aprotinin injections over a period of a few weeks has a fairly high rate of systemic allergic reactions. This can be reduced by minimising repeat injections and recommending a delay of at least 6 weeks between injections. Practitioners using aprotinin must have available facilities to treat anaphylaxis. © 2007 Sports Medicine Australia. Published by Elsevier Ltd. All rights reserved.

## Introduction

Overuse or degenerative tendon injuries (tendinopathies) are common in sport, certain

occupations and even everyday life. They are difficult to manage because of the high failure rate of treatment, tendency towards chronicity and risk of recurrence. Some conservative treatment options, such as eccentric exercises,<sup>1,2</sup> nitrate patches<sup>3,4</sup> and polidocanol injections<sup>5</sup> have been shown to assist in the treatment of tendinopathy. Cortisone

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injections are helpful in giving short-term pain relief to upper limb conditions in particular, such as shoulder tendinopathy<sup>6</sup> and tennis elbow.<sup>7–9</sup> There is little evidence to support the use of cortisone injections in patellar tendinopathy<sup>10</sup> or Achilles tendinopathy.<sup>11</sup> Cortisone injections weaken tendons and are associated with tendon rupture, so are often considered contraindicated for heavy load-bearing tendons such as Achilles tendons in athletes.<sup>7,12</sup>

Aprotinin is a drug which is indicated for preventing blood loss during major surgery<sup>13</sup> and promoting soft tissue healing after surgery (as a component of 'fibrin glue').<sup>14</sup> It is a strongly basic polypeptide, currently derived from bovine lungs. Aprotinin is a broad spectrum serine protease inhibitor<sup>15</sup> capable of blocking trypsin, plasmin, kallikrein and a range of matrix metalloproteinases (MMP-1,2,8,9,13).<sup>16,17</sup> Collagenases (MMP-1 and MMP-13) and gelatinases (MMP-2 and MMP-9) have been shown to be present in excessive proportions in patellar tendinopathy,<sup>18</sup> Achilles tendinopathy<sup>19,20</sup> and rotator cuff tendinopathy,<sup>21</sup> although MMP-3 (a stromelysin) has been shown to have decreased concentrations in Achilles tendinopathy<sup>19,20</sup> and rotator cuff tendinopathy.<sup>21</sup> MMP inhibitors have recently been shown to preserve the mechanical properties of stress deprived tendon.<sup>22</sup> Aprotinin has also been shown to inhibit osteoblast-mediated degradation of type-I collagen *in vitro*.<sup>23</sup>

Aprotinin has been successfully used to treat tendinopathies in France since the 1970s<sup>24,25</sup> and has been used as an 'off-label' form of management for chronic tendinopathy in Italy,<sup>26</sup> England<sup>27</sup> and Australia.<sup>28</sup> There have been two randomised double-blind controlled trials published regarding the use of aprotinin in tendinopathy. One study involved athletes being injected every 2 weeks with two to four injections for patellar tendinopathy and showed statistically significant superior results for aprotinin at 12 months follow-up (72% good or excellent) compared to both cortisone (59%) and saline injections (28%).<sup>26</sup> A study with small patient numbers involving aprotinin injections for Achilles tendinopathy showed good clinical outcomes but no statistically significant improvement in 12 months of follow-up over saline and local anaesthetic injection.<sup>28</sup> For treatment of Achilles tendinopathy, there has also been one semi-controlled study showing promising results with aprotinin injections<sup>29</sup> and three other published case series all with good clinical results.<sup>30–32</sup>

The major potential negative of using aprotinin is the side effect of allergy, which is well

described in the anaesthetic literature.<sup>33,34</sup> Recent reports have shown that allergic reactions are associated with use of aprotinin as a fibrin sealant in surgical procedures<sup>35</sup> and for tendinopathy.<sup>31,36</sup> Allergic reactions from use of aprotinin range from local irritation to anaphylaxis with rates of 3–11% quoted.<sup>34,35</sup> These reactions may be mediated by both IgE and IgG antibodies. In cardiovascular surgery it has been observed that re-exposure to aprotinin under 6 months leads to a greater risk of anaphylaxis.<sup>35</sup> This study aimed to determine the rate of systemic allergic reactions from aprotinin injections for tendinopathy and also to determine whether or not re-exposure to aprotinin under 6 weeks was associated with a greater risk of reactions.

## Methods

This is a historical cohort study, conceived by the first author after noticing a series of systemic allergic reactions associated with aprotinin in his clinical practice. It is recognised that this form of retrospective study is not the best design for assessing treatment efficacy. However, it represents a good opportunity for assessing a less common side effect such as allergy, as sample size can be larger and the effect of confounders is not as relevant.

The primary author of this paper has been using aprotinin for peritendinous injection in chronic tendinopathies since the year 2000. The regimen as described by Capasso et al.<sup>26</sup> was initially recommended to patients, generally a series of three to four peritendinous injections performed 1–2 weeks apart. The dose used was 3 ml of Trasyolol (Bayer, Leverkusen, Germany) containing 30,000 KIU aprotinin, combined with 2 ml of the local anaesthetic lignocaine 2%. This was the same volume of fluid injected (5 ml) but a lower dose of active agent than used by Capasso et al., because of the more dilute aprotinin brand available.

During 2003 and 2004 a significant number of systemic allergic reactions were noted, prompting a case series review which was completed in December 2004. The findings of this review were that allergic reactions had not been seen in patients having an initial injection or in whom a subsequent injection had been given at a time greater than 42 days after the previous injection.<sup>31</sup> Subsequent to this review, in order to attempt to minimise the risk of allergic reaction, patients were advised to avoid rapid repetition of aprotinin injections. Despite the risk of allergy, the treatment was not discarded as the clinical success was good.

The objective of the current study was to assess the success of a less regular injection regime at reducing the risk of allergic reaction. This was attempted by retrospective follow-up of patients who had been treated for a tendon injury with aprotinin over the period February 2003–June 2006 by the primary author. The start date was chosen because of the installation of a new computer system at one of the clinics, which meant that a complete list of patients injected with aprotinin could be obtained.

A chart review of all patients in whom aprotinin was used for tendon injections over the designated time period was performed. The name and address of the patient was noted, along with diagnosis, time of symptoms, level of sport, dosage used, and any allergies which occurred were noted in the medical records.

A standard questionnaire was developed to assess side effects and perceived clinical response to aprotinin.<sup>31</sup> The questionnaire was sent to the last known address of the patient, along with a return stamped envelope. If no response was received within a month, a further questionnaire was sent. If no response was received within 2 weeks of this second mailout, the patient was contacted by phone to be asked the same questions. This mechanism of chart review followed the principles of the Declaration of Helsinki. While not all patients answered questions, of those who did, no patients objected to their data being included as part of this study.

A systemic allergic reaction to the drug was defined as either multiple systemic symptoms of allergy (nausea, vomiting, dizziness, bronchospasm, urticaria, angioedema) or one of the above symptoms combined with local rash and itch commencing within an hour of the injection.

The primary unit of analysis was cases rather than patients, as some patients were treated for bilateral or multiple tendinopathies. The cases were divided into two cohorts by dates: Group R (R=recommended a rapid repetition of aprotinin injections as per the Capasso protocol<sup>26</sup>). This included cases where treatment had commenced prior to December 2004. The comparison group D (D=a delay of 6 weeks recommended between injections) included cases commencing treatment from December 2004 onwards. The groups were split according to intention-to-treat, with a minority of patients in group R having a single injection or delays between injections and similarly a minority of patients in group D deciding to have repeat injection(s) within 6 weeks.

With respect to allergic risk, a further analysis was undertaken by injection rather than by case. Both groups were combined and the comparison for injection was primary and secondary aprotinin injections, with the secondary group split by both the injection number and time between the injection and most recent previous injection.

Statistical comparisons between groups were made using paired  $\chi^2$  tests, with  $P < 0.05$  chosen to represent statistical significance.

**Table 1** Comparison of groups

Characteristic	Cases in group R	Cases in group D
Time period	February 2003–November 2004 (22 months)	December 2004–June 2006 (19 months)
Number of patients <sup>a</sup>	178	133
Number of cases	223	158
Number of aprotinin injections used	605	278
Average number of aprotinin injections used/case	2.7	1.8
Percentage injections given within 2 weeks of a previous injection	40%	4%
Percentage injections given within 6 weeks of a previous injection	56%	24%
Average age	38.7	35.9
Percentage male	77%	70%
Percentage elite athlete	29%	15% <sup>#</sup>
Percentage cases Achilles tendinopathy	46%	49%
Percentage cases patellar tendinopathy	21%	21%
Follow-ups received	166 (74.4%)	119 (75.3%)
Average length of follow-up (months)	12.7	10.3

<sup>#</sup> $P < 0.01$ .

<sup>a</sup> Four patients were in both groups R and D as distinct cases.

**Table 2** Frequency of associated side effects

Side effects	Cases in group R (%)	Cases in group D (%)
Slight itch	23 (39)	18 (21)
Severe itch	7 (12)	3 (3)
Bleeding	1 (1)	0 (0)
Rash	9 (15)	4 (5)
Systemic allergic reaction <sup>a</sup>	7 (11)	2 (2) <sup>^</sup>
Nausea	5 (9)	3 (4)
Sweating	7 (11)	2 (2) <sup>^</sup>
Post-injection pain	6 (10)	0 (0)
Headache	3 (5)	2 (2)
Tendon damage	1 (2)	0 (0)

<sup>^</sup>  $P < 0.10$  but  $> 0.05$  (NS).

<sup>a</sup> As the average case had multiple injections used, the per injection rate is lower than this. Patients were only asked which side effects they had suffered, not on how many occasions they had suffered each. However, the systemic allergic reactions were only suffered once as no patient had a repeat injection after this time.

## Results

There were 307 patients treated with 883 aprotinin injections over the designated time period for 381 cases of tendinopathy. There were 225 cases in group R and 156 cases in group D (Table 1), with a follow-up of approximately 75% achieved in each group. Follow-up was achieved for all cases where an allergic reaction had been documented in the case notes.

The average duration between initial injection and follow-up was 11 months. The only significant difference between groups R and D was that group R had a greater percentage of elite athletes (Table 1). Side effects of injections (perceived or actual) were quite common (34–38% of patients) (Table 2), although the majority were not severe. The most common side effect was itch at the injection site which occurred in about 20%, sometimes seen with erythema. It should be noted that patients were warned prior to injection about this risk and itch is

**Table 3** Other treatments used by patients for tendinopathy

Other treatments used	Cases in group R (%)	Cases in group D (%)
Strengthening	72	65
Stretching	65	50
Manual therapy	53	55
Orthotic/brace	27	33
Cortisone injection	23	37*
Nitrate patches	6	55 <sup>#</sup>
ESWT	14	14
Surgery	11	8

\* $P < 0.05$ ; <sup>#</sup> $P < 0.01$ .

a symptom which may be exaggerated by the power of suggestion.

Patient assessment of the value of the injection and the progress of their condition was similar between groups. In group R, 72% of patients reported improvement, 27% of patients were similar and 1% reported being worse, compared to, respectively, 82, 16 and 3% in group D. In group R, 64% thought that the injections either definitely or may have helped their condition (group D 68%), with the remainder feeling that the injection(s) did not affect them either way. No patients thought that the injection(s) made their tendinopathy condition worse. None of the differences in patient outcomes or assessments of injection value was statistically significant between groups. However, there were differences between other treatments given to the groups because of the non-randomised nature of the study (Table 3). Nitrate patches (usually provided by the primary author) and cortisone injections (usually given by another practitioner) were more likely to have been used in group D.

There were 13 probable systemic allergic reactions in this case series, most occurring in group R after an injection which was given within 6 weeks of a previous injection (Tables 2, 4 and 5). One of the two cases considered to be a possible or likely systemic allergic reaction in group D occurred

**Table 4** Timing of injection and allergic risk

Delay between injections	Number of systemic allergic reactions	Injections without systemic allergic reactions	Rate of systemic allergic reactions per injection (%)
Index	1	362	0.3
1–14 days	4	251	1.6
15–28 days	6	99	6.1*
29–42 days	1	47	2.1
43 days+	1	111	0.9
All follow-up injections	12	508	2.4

\* $P < 0.05$  compared to initial injection and injections at  $> 42$  days from previous.

**Table 5** Number of injections and rate of systemic allergic reaction

Injection number	Number of systemic allergic reactions	Injections without systemic allergic reactions	Rate of systemic allergic reactions per injection (%)
First injection	1	362	0.3
Second injection	4	233	1.7
Third injection	2	142	1.4
Fourth injection	2	57	3.5
Fifth or subsequent injection	4	76	5.3

on the initial dose and involved 2 h of nausea and abdominal pain. Seven patients, all in group R, were treated within 30 min of the aprotinin injection with subcutaneous adrenaline (epinephrine), which resulted in successful reversal of the allergic symptoms. No patient required hospitalisation or further management other than a single adrenaline injection. There were no cases in which bronchospasm occurred, with the systemic reactions generally including gastrointestinal and vascular symptoms such as nausea, abdominal pain, dizziness, sweating and vomiting.

The overall trend was for fewer systemic allergic reactions in group D than in group R, although this did not achieve statistical significance. However, those injections given between 15 and 28 days after a previous injection were significantly more likely to cause systemic allergic reactions than initial injections and delayed injections (Table 4). The risk of allergic reaction increased with the number of injections given (Table 5), although one patient had aprotinin injections on 15 different occasions without suffering any allergic symptoms.

## Discussion

This study using aprotinin for the treatment of tendinopathies achieved a similar clinical results to previous published controlled trials,<sup>26,29</sup> but also demonstrated a risk of systemic allergic reactions. In the group generally receiving a rapid series of repeated injections, systemic allergy was recorded in 7% of cases (a 2.5% reaction rate per injection subsequent to the first). In a similar but not identical form of treatment (injectable immunotherapy or desensitisation) the systemic reaction rate is calculated at about 1% of injections.<sup>37</sup>

Allergic reaction to intravenous use of aprotinin occurs via immunological mechanisms, making the rate on initial exposure quite low, but approaching 3% when re-exposure occurs within 3–6 months.<sup>33,34</sup> The controlled trials of aprotinin use for tendon injuries<sup>26,28</sup> describe very few problems with allergy (two patients out of 32 had a 'local'

allergic reaction in one study),<sup>26</sup> although these prospective studies have had small sample sizes which limit their ability to study less common complications. Aubin et al<sup>30</sup> reported that 11% of 62 patients demonstrated allergic reactions, although this paper did not give a detailed analysis of the allergic symptoms. It is presumed that these were a combination of local and systemic reactions. Eleven deaths because of anaphylaxis have been reported with intravenous use of aprotinin,<sup>33</sup> although in these cases the patients received high intravenous doses of the drug during surgery and were also compromised with a pre-existing cardiac complaint. The test (loading) dose in major surgical cases is close to the therapeutic dose for tendon injections, while the subsequent surgical doses are 20 times greater than for tendon injections. The larger dose and intravenous route would increase the risk of severe anaphylaxis.<sup>38</sup>

Aprotinin is used in a variety of surgical procedures to decrease preoperative bleeding especially in cardiac surgery but also other areas such as ENT and orthopaedic surgery. As aprotinin is derived from bovine lung, it is potentially antigenic to humans and accordingly allergic reaction rates (local or systemic) of up to 11% have been described. Both IgE and IgG antibodies to aprotinin have been reported and in addition aprotinin is a direct secretagogue for basophils and mast cells which mediate anaphylaxis. After cardiac surgery up to 10% of patients have detectable IgG and IgE antibodies at 12 months. The presence of these antibodies has a poor positive predictive value (<20%) but a good negative predictive value (approaching 100%).<sup>33,34,39</sup> The combination of limited predictive value and difficulty in obtaining these tests probably does not justify their routine usage and the use of skin prick and intradermal testing has not been validated. For these reasons current guidelines for the use of aprotinin should suggest adequate spacing of exposure (6 months for surgery and 6 weeks for tendon injections), monitoring of the patient after injection (30–60 min) and the facilities to treat anaphylaxis. The use of prophylactic antihistamine medication

and combination of local anaesthetic injection with adrenaline could both reduce the risk of anaphylaxis, although these measures would not eliminate allergy risk.<sup>33</sup> The downside of these additional measures would be that any allergic reaction that was to occur may be delayed, necessitating a longer patient observation period.

This form of retrospective study is not ideal for assessing efficacy, but with a larger sample size than previous trials it is better placed to assess the risk of allergy. The best trials to assess efficacy are intervention trials, particularly randomised control trials, as such a study design minimises bias and confounding. In this study, it appears as if the clinical success of injections was not affected by the change in regime to use fewer injections. However, confounders can affect the observations here—for example, a far higher proportion of patients in group D used nitrate patches, on the basis of trials which had been recently published.<sup>3,4</sup> By comparison, confounding is probably not a significant issue when assessing allergic reactions, as they are unlikely to be affected by patient expectation or other factor. There is one relevant bias to this study in that it was conceived by the primary author after he had noticed a significant number of allergic reactions in the patients which were to become group R. Analysis of some of these patients prompted a change in regime of administration for group D. Some of the difference in rate of allergic reaction between group R and group D may have been a regression to the mean after observing a higher than usual rate of allergic reaction to the drug. In addition, it is possible that patients in group D were screened more thoroughly than group R for personal history of anaphylaxis. It is also possible (but less likely) that some of the observed allergic reactions were to the local anaesthetic agent lignocaine rather than the aprotinin. Although a moderately large sample size was used, the difference in rate of anaphylactic reaction based on intention-to-treat in groups did not quite reach statistical significance.

Despite these design limitations, it is most likely that the association between rapid repeat exposure to aprotinin injections and anaphylaxis is a true one, as evidence from the anaesthetic literature shows similar findings.<sup>33</sup> The rates of allergy in this study are very similar to those previously published, although the reactions were less severe, which is expected when comparing small doses of peritendinous injection to much larger doses injected intravenously. The rates of systemic allergic reaction in this study are higher than the rate of 0.2% described recently in the clinical practice of Maffulli,<sup>36</sup> although a broader definition of a systemic allergic reaction in this study (along

with follow-up of the majority of patients) has probably revealed an increased rate. The cases recently described by Rukin and Maffulli are certainly severe anaphylactic reactions,<sup>36</sup> whereas many of the systemic allergic cases described in this study would be best described as 'mild' or 'moderate' anaphylactic reactions. The expected rate of true anaphylactic reaction, particularly for initial or delayed aprotinin peritendinous administration, may well be under 1% but is almost certainly greater than 0.1%. At this stage, it would probably be unethical and impractical to design a large prospective trial to test the hypothesis further that rapid repetition of aprotinin injections for tendinopathy leads to a higher rate of anaphylaxis. Further prospective trials regarding efficacy could be performed, but these should use a protocol designed to minimise risk of allergic reaction (i.e., delay between any multiple injections). There have been recent attempts to manufacture aprotinin-like polypeptides in a recombinant fashion that could potentially give similar clinical effects yet not lead to nearly the same degree of allergic reactions.<sup>40</sup> If this is successfully introduced to the market (and hence allergy becomes a far less likely complication), aprotinin may become a first-line treatment for tendinopathy.

Aprotinin is a promising treatment for tendinopathy, with moderate current evidence to support its use in the form of controlled studies. This study shows results which are compatible with the previous work but also illustrates a fairly high risk of systemic allergy with repeated aprotinin injections within 6 weeks. There is a need to screen patients for prior exposure to aprotinin and prepare an emergency plan for an allergic reaction when aprotinin injections are used for tendinopathy. Despite the good clinical response rate, previous evidence of efficacy and good theoretical basis for use of a collagenase inhibitor, because of the risk of systemic allergy, aprotinin use in tendinopathy should probably be reserved for recalcitrant cases.

### Practical implications

- The previously described effective regime of multiple aprotinin injections spaced 2 weeks apart for treating tendinopathy is associated with a high rate of systemic allergic reaction.
- If a single injection is used, or injections are spaced apart greater than six weekly, the allergic reaction rate is lower, and patient satisfaction and other outcomes do not appear to change.

- Aprotinin should be reserved for treatment of tendinopathy where less risky options are unsuitable or have failed and should only be used where facilities are available to treat systemic allergic reactions.

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