Case reports of aprotinin in Achilles tendinopathies with athletes

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Summary : Aprotinin is an antifibrinolytic agent used in many ways. This retrospective study on 62 medical charts, reports its use in chronic or nodular Achilles tendinopathies with athletes. The most common treatments for Achilles tendinopathies are NSAIDs but all in all they are not very effective. The study was performed in the Sport Unit of the University Hospital of Rennes. Patients were treated with 4 x 20 000 KUI peritendinous injections, each one given at interval of 7 days. Aprotinin enables 84 % of the patients to resume sporting activity and is effective in athletes who had not previously responded to NSAID treatment.

Keywords : sport medicine, aprotinin, Achilles tendinopathies.

Introduction

Aprotinin has several uses in clinical medicine[1]. The retrospective study carried out at the Sport Unit of the University Hospital of Rennes over 5 years allows us to review its benefits in the treatment of Achilles tendinopathies of the athletes from an experiment.

Aprotinin [5, 14, 16], otherwise known as Kunitz inhibiter, is the antifibrinolytic of reference. This basic polypeptide is water soluble and is obtained by extraction from the pancreas or lung of cattle.

Table I. ***Preparations containing aprotinin***

	Zymofren®	**Antagosan®**	**Trasylol®**
Doses	2.5 ml 10ml	10ml 50ml	10ml 50ml
Ph. Eur. Units /ml	5	5	5.5
KIU/ml	10000	10000	10000
Excipient: NaCl/ml	8.8mg +sodium mercurothiolate	8.5mg	-
Put on the market	1970 Withdrawn 1991	1976	1991

Aprotinin was first commercialised under the name Zymofren® (Specia) and withdrawn from market in 1991. Two preparations are now available: Antagosan® (Hoechst) and Trasylol® (Bayer).They are reserved for hospital use (table I). There are different units of dosage for Aprotinin: the oldest is the Kallikrein inhibitor unit (KIU) or the unit of Frey; generally the quantity of Aprotinine is expressed in European Pharmacopeia Units (Ph. Eur. Units) such that
1 Ph. Eur. unit = 2 000 KIU.

Aprotinin is a serine protease (trypsin, plasmin, kallikrein, chymotrypsin) inhibitor. Its antifibrinolytic activity is essentially due to its anti plasmin activity, and this is the reason for its sole indication (by the AMM) for fibrinolytic hemorrhagic syndrome [15].

In practice, it is used for several indications: cardiac surgery, extracorporeal circulation, acute pancreatitis, liver transplant, gynecology and certain states of shock. The side effects following IV administration are allergic reactions, thromboembolic complications and renal complications.

Aprotinin is also used in rheumatology by intra-disk injection for the treatment of discoradicular conflicts [1, 16, 17]. The authors explain its action via its effects on the kinins involved in inflammatory response.

The potential of Aprotinin in sport medicine was discovered to be in the treatment of tendinopathies during the 1970s [7]. In fact, it appears to present an important therapeutic contribution in Achilles tendinopathies.

The Achilles Tendon and Tendinopathies of the Achilles Tendon

Anatomopathologic review

The Achilles tendon (calcaneal tendon) is the most voluminous and the strongest tendon of the body. It is the terminal tendon of the triceps surae resulting from the union of the terminal fibers of the gastrocnemius muscle (superficial layer of the triceps surae) and the soleus muscle (deep layer of the triceps surae) [2, 4]. The fibers of the Achilles tendon are very distinct and are arranged in spirals.

From a microscopic point of view, the Achilles tendon is composed of:

- Fibroblastic cells or tendinocytes. These cells are oriented parallel to the axis of the tendon and possess long cytoplasmic extentions. They synthesize collagen and proteoglycans;

[1] AMM: Autorisation de Mise sur le Marché.

- Collagen fibers grouped in tight bundles parallel to the axis of the tendon. These fibers account for 70% of the dry residue of the tendon in adults, and give the tendon its solidity and strength;
- Elastic fibers;
- Ground substance.

The vascularisation of the Achilles tendon is poor, particularly at the middle third where there is a zone that is practically avascular.

Achilles Tendinopathies and their treatment

Achilles tendinopathies in sport are linked to degenerative and vascular defects of the tendon. Three types of injuries can be described [2-4, 12, 13]:

- *Nodular tendinopathies* or *tendinoses*: these are intra-tendinous degenerative type lesions. The formation of nodules corresponds to scar tissue secondary to histological microruptures. Degeneration of the ground substance, thickening of the collagen fibres and loss of cellularity are observed.

- Peritendinitis corresponds to fibrous and inflammatory thickening of the sheath of the tendon or peritendineum; in chronic forms they are fibrous and sclerous lesions resulting from fibrin deposits.

- insertional tendinitis.

In general, Achilles tendinopathies result from an excessive mechanical load leading to inflammation of the peritendon (peritendinitis stage). This stage can remain asymptomatic and ischaemia of the body of the tendon can therefore lead to intratendinous degenerative lesions, forming a tendinose.

The medical treatment of Achilles tendinopathies requires different techniques [10, 12]; it always includes resting the tendon. If classical massages are not very effective, in 70% of cases results can be obtained with deep transverse massage. Cryotherapy is used for its analgesic effect, it acts against edemas and it augments the microcirculation. But it is only of moderate efficacy. Some clinicians also use physiotherapy (ionization and ultrasound). Also, the results obtained using mesotherapy and acupuncture are very controversial.

The number of medicines available to treat Achilles tendinopathies is quite small. They consist of NSAIDs – these are very efficacious in only 10% of cases, but allow a short or long term improvement in 60% of cases. Local injections of corticoids are also used – they are not, however, efficacious over the long term and there is a significant risk of local necrosis and rupture.

A therapy is chosen according to the symptoms and the etiopathology. There is no a treatment of reference for Achilles tendinopathies and the practitioner often uses different treatments successively. They are more or less empirical.

Aprotinin has been used in sports medicine since the 1970's. Genety and Penin gave local injections of Zymofren® in 103 tendinopathies of various locations. After a delay of 30 days they reported a recovery rate of 65% and very good results [7]. Guedj also used Zymofren® in 23 Achilles tendinopathies with a recovery rate of 65% and good results [9].

Aprotinine has been part of the therapeutic arsenal for tendinopathies in the Sport Unit of the University Hospital of Rennes for many years. A retrospective study made in 1980 [10] showed 90% good results and complete recovery in simple tendonitis (11 cases) and 71.4% in nodular tendonitis (21 cases). Zymofren® was used by itself or in association with orally administered NSAIDs. The dose of Zymofren® used in local injections was 5ml, i.e. 50,000 UKI, given 3 to 4 times.

Methods - retrospective study 1989 to 1994

Table II. *Profile of patients treated with aprotinin*

Profile	**Chronic Tendinopathies**	**Nodular Tendinopathies**	**Total**
Number of patients	17	45	62
Sex			
• Male	16	42	58
• Female	1	3	4
Average age	32.5 ± 6.5 years	39 ± 7 years	37 ± 7 years
Sport			
• Soccer	9	10	19
• Jogging	4	21	25
• Tennis	1	7	8
• Other	5	11	16
Affected tendon			
• right	9 (53%)	19 (42%)	28 (45%)
• left	6 (35%)	23 (51%)	29 (47%)
• both	2 (12%)	3 (7%)	5 (8%)
Duration of symptoms	12 months	12 months	12 months
Failure of previous treatments			
• one previous treatment			
• more than one previous treatment	8 (47%)	25 (55%)	33 (53%)
• none	6 (35%)	13 (29%)	19 (31%)
	3 (18%)	7 (16%)	10 (16%)
NSAIDs	10	31	41
NSAIDs Only	6	20	26
NSAIDs + mesotherapy	3	1	4
NSAIDs + injections	0	4	4
NSAIDs + kinestherapy	0	1	1
NSAIDs + physiotherapy	1	2	3
NSAIDs + 2 or 3 treatments	0	3	3
Kinestherapy	3	5	8
Kinestherapy only	2	1	3
Mesotherapy (massage)	5	7	12
Mesotherapy only	0	2	2
Physiotherapy	1	5	6
Corticoid injections	0	8	8

The retrospective study focused on 62 patient files treated with aprotinin from 1989 to 1994 for a chronic or nodular tendinopathy in the Sport Unit of the University Hospital of Rennes.17 patients were suffering from chronic tendonitis and 45 from nodular tendonitis.

Diagnosis was established from the clinical examination, an X-Ray of soft tissues and/or an ultrasound. The effectiveness of treatment with aprotinin was evaluated after a minimum period of one year.

94% of patients of the patients were male. 90% of those regularly practiced an activity. The tendinopathies affected the left or right tendon indiscriminately, but affected both tendons in 8% of cases. Patients complained of a tendon lesion for one year in average. 84% had already tried another treatment based on

NSAIDs alone or associated with another treatment in 78% of cases, and had resorted to at least two techniques in 30 % of cases.

Table III. *Methods of treatment with aprotinin*

Method of treatment	**Chronic Tendinopathies**	**Nodular Tendinopathies**	**Total**
Number of patients	17	45	62
Preparation			
• Antagosan®	7	15	22 (35%)
• Zymofren®	10	30	40 (65%)
Treatment			
• Number of injections	4.41 ± 0.94	3.91 ± 1.08	4.04 ± 1.06
• Rhythm of administration	7.37 ± 1.95 days	7.46 ± 2.37 days	7.43 ± 2.24 days
• Total dose given	8640 ± 2050µl	7810 ± 2650µl	8030 ± 2520µl

Patients were treated with Zymofren® (40 files) until 1991, then by Antagosan® (22 files).
The injections were given in the peritendineum at the rate of 4 injections on average (2 to 5) in the space of 7 days. The total dose of aprotinin injected was 8 mL (80 000 UKI) on average, i.e. 1.98 mL (19 800 UKI) per injection.

Results

Treatment of Achilles tendinopathies with aprotinin allowed resumption of sporting activities in 84% of patients.

81 % of the athletes treated for their tendinopathies before hand responded well. There were 78% good and average results in those that didn't respond previously to NSAIDs.
Among the 10 patients who did not respond to treatment with aprotinin, 9 were suffering from Haglund disease complicated or not by intra-tendinous microruptures, observed by MRI, and 7 of them needed surgery. One patient presented with a large isolated nodule which required surgery.

Tolerance to treatment

Table IV. *Results after treatment with aprotinin*

Results	**Chronic Tendinopathies**	**Nodular Tendinopathies**	**Total**
Number of patients	17	45	62
Results			
• Good	11 (65%)	35 (78%)	46 (74%)
• Average	2 (12%)	4 (9%)	6 (10%)
• Fail	4 (23%)	6 (13%)	10 (16%)
Patients already treated			
Number of patients	14	38	52
• Good	9	29	38
• Average	1	3	4
• Fail	4	6	10
Patients already treated with a NSAID	10	31	41
Number of patients	6	23	29
• Good	0	3	3
• Average	4	5	9
• Fail			
Allergies	2	5	7
• Antagosan®	2	4	6
• Zymofren®	0	1	1

An allergy to aprotinin occurred in 11 % of cases. Six allergies to Zymofren® and one allergy to Antagosan® were been reported. They appeared after an average of 2 or 3 injections and led to an interruption of treatment in all cases.

Discussion and conclusion

This retrospective study over 5 years, done on 62 athletes shows that injections of aprotinin in the peritendinum gives average or good results in 84 % of chronic or nodular Achilles tendinopathies. These results are in accord with those obtained by Guedj in 1973. For the treatment of nodular tendinopathies, 77 % of good results were obtained using aprotinin, confirming a study conducted in 1980 in the same unit on 21 files (71.4 % good results) [9]

Aprotinin is efficacious in the treatment of both chronic and nodular tendinopathies. It results in complete recovery in 74 % of cases and is, therefore, more efficacious than NSAIDs given orally (10 % good results) [12]. Its efficacy in comparison to other pharmaceutical treatments could justify its use as the first choice of therapy; the 10 patients treated straight away in this study responded to treatment with aprotinin.

77 % of patients who had not responded to previous treatments were able to resume their sporting activitites after treatment with aprotinin. This shows the interest in using aprotinin in cases of failure of classical therapies for Achilles tendinopathies.

The ten cases where treatment failed can be explained by intratendinous microruptures and/or Haglund disease, as seen on MRI. These required surgery. MRI is a useful diagnostic tool [6, 8] for intratendinous microruptures. However it isn't conceivable to use MRI systematically to look for intratendinous microruptures as it is very expensive compared to treatment with aprotinin which would cost in the order of US$25.These results, nevertheless, do not prove the ineffectiveness of aprotinin on intratendinous microruptures since MRI was not conducted on those patients who responded to treatment.

Allergies to aprotinin are observed, however they appear more frequently with Zymofren® than with Antagosan®. This can be explained by the presence of mercurothiolate as an excipient in Zymofren®.

This open and non-controlled study allows us, all the same, to take into account the precedence of tendinopathies treated, to show a certain action of aprotinin in the treatment of chronic or nodular Achilles tendinopathies of the athlete, in particular in the cases of failure of treatment by orally administered NSAIDs. Its mechanism of action, however, is not elucidated; its superiority in comparison to anti-inflammatory treatments leads us to assume a different mechanism of action.

It would be interesting to put into action a randomized study against placebo to confirm the effects of aprotinin in this situation. However, the feasibility of such a study in elite athletes must be questioned.

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