Actovegin Equals to Performance Enhancing Drug Doping: Fact or Fiction?

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Introduction

Actovegin is a biological drug that has been used for the treatment of sports muscle injuries. Several in vitro studies have shed light on potential mechanisms of action and the drug has consistently demonstrated its potential to reduce return from injury time for muscle tears in elite athletes. Yet it was banned for a time under the International Olympic Committee (IOC) as a blood doping agent, this ban was based on presumptuous conclusions and subsequently lifted after no indisputable evidence could be provided. This editorial aims to provide readers with some of the key, objective facts relating to Actovegin and then based on this, will offer an informed opinion on its role in sports medicine. We also hope to highlight the importance of evidence-based medicine, particularly in the volatile field of Sports Medicine, and the need for facts, not fiction.

Actovegin

Actovegin (Takeda Pharmaceutical Company Ltd, Osaka, Japan) is a biological drug produced from deproteinised haemodialysate of calf serum. Its high standard of quality control and long 50-year history of clinical evidence has provided much evidence to support its efficacy [1]. Functioning in a similar vain to other calf blood derivatives, it can be compared to foetal bovine serum (FBS) which is well known for its established role in maintaining cell viability in in vitro tissue culture methods. Thus, Actovegin may be considered as a highly controlled and approved form of FBS with an excellent track record for human use in the clinical setting.

In vitro Evidence

The active component and mechanism of Actovegin has yet to be identified, its effects are likely due to a mixture of ingredients instead of a single active compound. Study has shown the drug to not contain peptide, growth factor or hormone-like substances [2]. Further, in vitro evidence suggests that Actovegin promotes oxidative metabolism and shifts the redox-balance of cells to produce more oxidized substrates, possibly protecting against hypoxic cell injury [2]. This mechanism can be logically extrapolated to the first few hours of muscle injury where the goal of any therapeutic intervention would be to interrupt the process of cell damaging events, and therefore importantly preserve cell viability at the injury site. In vitro evidence has also pointed towards Actovegin’s protective effect on injured cell types ranging from neuroblastoma cells [3], neutrophils [4] and renal cells [5]. It has also been postulated that Actovegin could have a beneficial effect as an injective therapy for osteoarthritis [6].

One of the properties of Actovegin is to promote oxidation and energy production in cell cultures, its efficacy is assumed to benefit post-ischemic metabolic events clinically. A recent in vitro study has made unsubstantiated, optimistic claims about the potential performance enhancing qualities of Actovegin for clinical use [7]. Søndergård et al. inflicted cell membrane injuries to the muscle cells with a cytotoxic detergent, Saponin then treated the cell culture with Actovegin and analysed mitochondrial activity of the cells. They concluded that as the Actovegin groups had higher mitochondrial activity, it must be able to enhance sports performance and failed to consider the fact that Actovegin may also have membrane stabilizing properties which stabilized cells and allowed the mitochondria to function normally. As discussed in the previous section, Actovegin is a drug that has been proven to have protective effects on ischemic cells. Therefore, it is important that we highlight here that the study by Søndergård et al. should be viewed as an in vitro cell membrane injury study and not a performance analysis. Care must be taken when extrapolating conclusions from in vitro evidence, as results will not necessarily translate. In fact more care must be taken in concluding whether or not any substance will improve performance in humans from in vitro studies. This misleading conclusion may have contributed to the fictitious hype with article exposure and media attention, thus having a detrimental effect on science and medical research.

Legality and Ergogenic Potential

In December, 2000, the IOC banned the use of Actovegin as an ergogenic substance after noting its prolific use at the Sydney Olympic Games and that year’s Tour de France [8]. The ban was lifted however, 2 months later after no indisputable evidence was provided demonstrating Actovegin had performance enhancing potential. The current stance from World Anti Doping Agency (WADA) is that Actovegin is legal under 50 mL every 6 h. However, 50 mL is 25 fold higher than the amount injected for a muscle tear and that is without concentrating the drug; making these guidelines somewhat ill-informed. Further, neither intravenous nor intramuscular injections of Actovegin are prohibited in or out of competition according to latest search in Global Drug Reference Online, which is approved by UK Anti-Doping (UKAD), the Canadian Centre for Ethics in Sport (CCES), the United States Anti-Doping Agency (USADA) and WADA [9,10].

A study of 567 diabetic patients showed no improvement in muscle strength or condition was found after maximal Actovegin infusion for 160 days [11]. Further, Lee et al. performed another, more recent blinded, crossover peak aerobic capacity study in healthy human participants [12]. Lee et al. provide definitive clinical evidence that Actovegin did not improve aerobic capacity compared to saline control in humans. No significant differences were observed in peak values.

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for aerobic power. Additionally, values of gross and net efficiency, and calorific energy equivalents associated with VO₂ were similar. Therefore, in brief, results from this study provide definitive clinical evidence that Actovegin in its maximum permitted dose does not improved human peak aerobic capacity. Thus, showing the claims by Sondergard et al. do not extrapolate to a human population. Interestingly, in a recent series of studies with human macrophages using RT-PCR and flow cytometry, they have tentatively demonstrated a possible role of Actovegin as an anti-inflammatory agent, which is consistent with the finding that Actovegin can reduce the recovery time in mild muscle injuries.

**Muscle Injuries - Current Strategies and Issues**

Muscle injuries are common in sports, recently different injection treatment options such as growth factors have demonstrated encouraging results, however, with their anabolic properties, interventions that utilize growth factors, autologus blood or autologous conditioned serum are unfeasible therapeutic options for professional athletes, being banned by WADA [10]. Interventions such as Platelet Rich Plasma (PRP) and Autologous Conditioning Serum (ACS) have become popular augmentative therapies in Sports Medicine, being proposed to facilitate muscle healing by optimizing provision of growth factors and improving cell oxidative metabolism. The evidence provided in this editorial delivers updated evidence on anecdotal and subjective opinion. Current evidence is suggestive that Actovegin is a non-ergogenic, safe and potentially beneficial biological drug for the treatment of sports related muscle injury in elite athletes. Further research will tease out mechanisms and identify active ingredients, while clinical trials could confirm efficacy and establish a dose-response relationship. We should remain cautious in generating facts over anecdotal fiction and tailor the use of any intervention to an individual athlete's need above anything else.

**Clinical Evidence**

The use of Actovegin as an intramuscular injection therapy for acute muscle tears was first documented by Pfister and Koller [16]. They reported a reduction in recovery time from 8.3 weeks to 5.5 weeks in treatment groups. However, their partially blinded case control study of 103 patients received several criticisms. Patients were recruited from different levels of sport and thus treatment regime and rehabilitation protocols were therefore not standardised. Further, Actovegin was mixed with local anaesthetic, which could have altered the clinical response to treatment regimen. Buchmayer et al. [17] conducted a double-blind, randomized placebo controlled trial, showed no significant difference in return to play time in injured, professional footballers of 8 days when compared to physiotherapy alone (p=0.033) [17]. This study using Actovegin was mixed with local anaesthetic, which could have altered the clinical response to treatment regimen. Double-blind, randomized placebo controlled trial, showed no significant difference in return to play time in injured, professional footballers of 8 days when compared to physiotherapy alone (p=0.033) [17]. This study using Actovegin was mixed with local anaesthetic, which could have altered the clinical response to treatment regimen. Further, clinical evidence has demonstrated that standalone Actovegin therapy is safe and effective to treat muscle injuries in elite sports professionals [17]. It is important therefore, particularly in a volatile field such as Sports Medicine, that an evidence based medicine approach is taken throughout and treatments are not judged on anecdotal and subjective opinion. Recent evidence is suggestive that Actovegin is a non-ergogenic, safe and potentially beneficial biological drug for the treatment of sports related muscle injury in elite athletes. Further research will tease out mechanisms and identify active ingredients, while clinical trials could confirm efficacy and establish a dose-response relationship. We should remain cautious in generating facts over anecdotal fiction and tailor the use of any intervention to an individual athlete's need above anything else.

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