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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 ~~to~~ 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 ~~hopes~~ to provide readers with some of the key, objective facts relating to Actovegin and then based on this, will offer an 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 ~~have~~ 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 for aerobic power. Additionally, values of gross and net efficiency, and calorific energy equivalents associated with VO_2 were similar. Therefore,

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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. ~~does~~ 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, autologous 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 from promising animal study [13-15]. However, again these results do not necessarily translate to human trial. Reurink et al. in a recent, double-blind, randomized placebo controlled trial, showed no clinical or statistical difference between PRP and placebo treated groups [15]. This study did highlight the heterogeneity in PRP preparation protocol, distinct lack of consistency in quality control and thus, variation between individual PRP injections. This is an issue we as authors have highlighted previously [6]. The information thus ~~provided~~ suggests that there is a lack of an effective, legally utilizable option for professional athletes to treat acute muscle injuries. It also dictates that the use of blood products as biological drugs for muscular injury is nothing new and ~~the~~ Actovegin is a logical option.

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 its pharmacodynamic and kinetic properties. Finally, the outcome scores were made on subjective observation by patients and clinicians with no pre-injury data to compare with.

Since this study there has been limited supporting evidence for its role in the treatment of muscle injuries. Lee et al. have published a study on the effects of standalone Actovegin therapy, reporting a reduction in return to play time in injured, professional footballers of 8 days when compared to physiotherapy alone (p=0.033) [17]. This study using players from the same elite football club allowed for standardization of intervention, physical fitness and rehabilitation protocol.

Conclusion

The evidence provided in this editorial delivers updated evidence that hopefully can dispel the shroud of criticism that has surrounded Actovegin. The *in vitro* evidence provides insight into the mechanism by which this biological drug is improving cell oxidative metabolism and its role in shifting redox balance to maintain cell viability. The clinical evidence provided has highlighted the importance of care in extrapolating *in vitro* findings, which do not necessarily extrapolate clinically. Further, ~~the~~ clinical evidence has ~~suggested~~ 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. 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.

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