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Zaangażowanie Autorów
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F – Opracowanie piśmiennictwa
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DIFFERENT APPROACHES IN USING DEPROTEINIZED CALF BLOOD HEMODIALYSATE BY ELITE AND NON-ELITE ATHLETES

RÓŻNE PODEJŚCIA DO STOSOWANIA HEMODIALIZATU ODBIAŁCZONEJ KRWI CIELĘCEJ PROFESJONALNYCH I AMATORSKICH SPORTOWCÓW

Key words: *protein-free hemoderivative of calves blood, athletes, sport, anti-doping, doping*

Summary

Deproteinized hemodialysate obtained from calf blood is the component of some biological medicines registered in selected countries in Europe and Asia e.g. Actovegin, Solcoseryl. However, these drugs are not approved by the U.S. Food and Drug Administration (FDA). The use of deproteinized calf blood hemodialysate by elite athletes could be the reason for some discrepancies in sport events. To some extent, the effects of protein-free calf blood hemodialysate resemble the regenerative activity of peptides, such as BPC-157 which in last time was included in World Anti-doping Agency (WADA) Prohibited List in group S0 (Non-Approved Substances). Protein-free calf blood hemodialysate contains amino acids, peptides, nucleosides, glycosphingolipids, and inositol-phospho-oligosaccharides. It has been shown that these mixture aforementioned components showed antioxidant activities, increased mitochondrial oxidative capacity, activation of macrophages and stimulation of expression NF-kB. The aim of this review was to analyze the current knowledge about deproteinized calf blood hemodialysate in relation to the anti-doping regulations of sports organizations, and some discrepancies in the fields of sports pharmacy and sports medicine.

Streszczenie

Odbiałczony hemodializat pozyskiwany z krwi cielęcej jest składnikiem niektórych leków biologicznych zarejestrowanych w wybranych krajach Europy i Azji m.in. Actovegin, Solcoseryl. Jednak leki te nie są zatwierdzone przez amerykańską Agencję ds. Żywności i Leków (FDA). Stosowanie hemodializatu odbiałczonej krwi cielęcej przez zawodowych sportowców może być przyczyną rozbieżności podczas imprez sportowych. W pewnym stopniu działanie bezbiałkowego hemodializatu z krwi cielęcej przypomina działanie regeneracyjne peptydów, takich jak BPC-157, który w ostatnim czasie znalazł się na liście środków zabronionych Światowej Agencji Antydopingowej (WADA) w grupie S0 (Non-Approved Substances). Bezbiałkowy hemodializat z krwi cielęcej zawiera aminokwasy, peptydy, nukleozydy, glikosfingolipidy i inozytol-fosfooligosacharydy. Wykazano, że wymienione wyżej składniki mieszaniny wykazały działanie antyoksydacyjne, zwiększoną zdolność oksydacyjną mitochondriów, aktywację makrofagów oraz stymulację ekspresji NF-kB. Celem pracy była analiza aktualnej wiedzy na temat odbiałczonych hemodializatów krwi cielęcej w kontekście przepisów antydopingowych organizacji sportowych oraz rozbieżności w zakresie farmacji sportowej i medycyny sportowej.

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Background

There is a lot of confusion on the use of protein-free calf blood hemodialysate, filtered to remove prions, which is the main component of two biological drugs registered in some countries in Europe under the brand name Actovegin or Solcoseryl by elite athletes [1,2]. According to the manufacturer, Actovegin contains peptides, amino acids, nucleic acids but does not contain cells or proteins. Independent analysis of the product has not detected prohibited growth factors, proteins in general, or steroids. According to this information, Actovegin is not prohibited except if it is used as an intravenous infusion or injection of more than 100 mL each 12 hours [3].

In Poland, in the 2022, the Regulatory Authority (the Office for Registration of Medicinal Products) issued decisions on the shortening of the validity period of admission to trading, for Solcoseryl gel, eye gel, ointment, dental adhesive paste, and injection solution [4]. Composition and formulations of Actovegin and Solcoseryl are deproteinized, apyrogen hemodialysate obtained from calf blood, manufactured from natural source, in several steps by ultrafiltration. Containing numerous low weight components (molecular weight up to 5000 Daltons). The analysis of the protein-free calf blood hemodialysate show that contains a mixture of natural substances, inorganic components like common blood electrolytes (e.g. chloride, phosphate, sodium, potassium, calcium, and magnesium), and organic components like amino acids, glucose, acetate and lactate, oligopeptides, nucleosides, glycosphingolipids, inositol-phospho-oligosaccharides (IPOs) and products of the intermediate metabolism [5]. Deproteinized calf blood hemodialysate contains amino acids (such as cystathionine, o-phosphoserine), in significantly higher and some in lower concentrations compared to human adult serum [6].

Actovegin is available as cream, gel, ointment, dragees or tablets, and injectable solution. Single one dragee or tablet contain 200 mg of deproteinized calf blood hemodialysate. Actovegin solution for injections is available in dose 40, 80, 200, 400 mg/mL and indications to intravenous, intramuscular, intraarterial injections [5].

Solcoseryl is available as gel, eye gel, ointment, dental adhesive paste, and injection solution. In Central and Eastern Europe, the use of Solcoseryl has been commonly used topically (on the skin, mucous membranes in stomatology and ophthalmology) or as injection in orthopedics. Solcoseryl solution for injection 42.5 mg/mL (clear, yellow to yellowish solution for injection) per 1 ampoule (a 2 mL of liquid) contains 85 mg deproteinized calf blood hemodialysate [7,8]. Topical application of deproteinized calf blood hemodialysate is indicated for auxiliary/adjunct treatment of small wounds, venous ulcers and other poorly healing wounds, first and second degree burns, burn scars, frostbite, trophic changes in patients with arterial occlusive diseases, bedsores, skin collection sites for transplantation, large mesh skin grafts, and radiation damage to the skin [4].

Dental adhesive paste of this preparation is indicated for painful and inflammatory diseases of the oral mucosa, gums and lips, aphthae, herpes labialis, gingivitis, periodontitis, stomatitis, pressure pains caused by dentures, pains occurring during the eruption of wisdom teeth, as a dressing after such procedures as lace application, curettage and tooth extraction, and after insertion of direct dentures [4].

Eye gel was intended to be uses to treat cuts caused by "foreign bodies", burns with alkalis or acids, keratitis corneal ulcers caused by bacteria, viruses, fungi and caused by trophic disorders, degenerative and dystrophic keratitis [4,5].

Systemic administration of protein-free calf blood hemodialysate is indicated for acute and chronic vascular damage to the central nervous system, peripheral arterial occlusive disease (stages II-IV according to Fontaine), diabetic foot, wound healing disorders (varicose leg ulcers, bedsores), burns, skin and mucosa damage by radiation, transplants dermal. Its off-label use is for the treatment and recovery of muscle injuries also in athletes [4,9,10,11].

On *in vitro* experiment Actovegin with the dose of 50 µl/mL showed to increase the mitochondrial oxidative phosphorylation capacity in human skeletal muscle fibres [2]. The effect of Actovegin in various concentrations (1, 5, 25, 125, 250 µg/mL) on proliferation muscle cells (C2C12 myoblasts) was analyzed. Actovegin improves myoblasts proliferation in all examined range of doses. The greatest increase in the number of myotubes was observed for the lower concentrations Actovegin 1, 5, 25 µg/mL. While the high dose 250 µg/mL induced a fusion tendency was revealed an increase of myotube size/area [6]. In another *in vitro* experiment, Actovegin in concentrations at 125 and 250 µg/mL exerts an anti-inflammatory effect via reduced of production the reactive oxygen species (ROS), previously induced by lipopolysaccharide (LPS) and Phorbol 12-myristate 13-acetate (PMA). Actovegin decreased the secretion of pro-inflammatory cytokine IL-1β induced by PMA, but did not impact on production IL-1β induced by LPS. Actovegin in all tested range doses 1, 5, 25, 125, 250 µg/mL, not contribute to significant changes in the production of IL-6, IL-10 and TNF-α [12].

Among elite football players in the group treatment of Actovegin were able to return to the game 8 days earlier than the physiotherapy group (not use Actovegin). However this study has some limitations such as being a non-blinded and non-randomized observational pilot study, and where there were small numbers of participants [13].

Methodology

In the identification step data was collected from PubMed between 01 December 2022 – 31 February 2023. The strategies were constructed based on the search terms [((actovegin) OR (aktovegin) OR (solcoseryl) OR (solkoseryl) OR (deproteinized calf blood) OR (protein free calf blood)) AND ((exercise) OR (performance) OR (aerobic capacity) OR (health) OR (safety) OR (condition) OR (tissues) OR (muscles) OR (oxygen))]. First search provided 841 records (n=841).

In the eligibility step, excluded records due to review and systematic review, and applied specify studies as only clinical trials. Finally received 80 records (n=80). In the next stage, all collected records screened by title and abstract. Excluded records due to topical intervention and not related to review issue (n=72).

Included: To the final review inclusion 8 works (n=8).

Results and discussion

Clinical trials

Limited studies were available with on the use of Actovegin or Solcoseryl on healthy subjects or athletes. Most of the clinical trials which included systemic use, have been conducted in elderly and non-healthy subjects [14,15,16,17]. In patients with type 2 diabetes mellitus and symptomatic polyneuropathy, demonstrated that intravenous infusions of Actovegin in dose 2.0 g/day for 20 days, followed by oral administration 1.8 g/day for 140 days, improves neuropathic symptoms [16]. Actovegin showed to have a beneficial effect on cognitive outcomes in patients with post-stroke cognitive impairment [18].

In prospective double-blind randomized study, Actovegin can shorten the rehabilitation time in patients with acute muscle injuries [19]. Among professional athletes with strain injuries, it showed after 15 days treatment with Actovegin and Traumeel contributed to mild regression since initial diagnostic symptoms. The recovered 70% of the muscle function [9].

However, in physically active males Actovegin demonstrated no ergogenic effect and did not influence on exercise capacity in the exhaustive test [20]. These three studies conducted on sportsmen presented in Table 1.

Sports regulations

Actovegin was allegedly used by some cyclists in Tour de France 2000 due to the similarity of its effects to erythropoietin without raising hematocrit and where clear statement/rules were not available by sport organizations about these products and contained bioactive substances [21,22,23].

Actovegin has been temporarily banned by the International Olympics Committee (IOC) in 2000, due to the incident occurring on the Tour de France 2000, however later on it was no longer prohibited due to insufficient scientific evidence to support these claims [22,24].

Table 1. Human studies conducted on sportsmen

Drugs	Participants	Specification of clinical trial	Methods	Investigated parameters	Results	Additional comments	Reference
Actovegin + Traumeel	18 males Professional football, basketball and ice hockey players	Non-randomized and non-blinded pilot study	MRI scan of muscle	Muscle strains General mobility Time of recovery	Improved time of recovery after injury	–	[9]
Actovegin vs Placebo	103 males Physically active	Prospective double-blind randomized study	–	Time of rehabilitation	Improved time of rehabilitation after injury	Not performed MRI scan Actovegin combined with local anesthetics	[19]
Actovegin vs Placebo	8 males Physically active	Single-blind placebo study	Arm crank ergometer test Selected biochemistry parameters	Peak power (Wpeak) VO2 RER Blood lactate level Blood glucose level	No significant difference between assessed parameters Reported only subjective opinion of 4 participants that Actovegin compared to Placebo, improved tolerance to effort in exercise test	No investigated VO2max	[20]

The use of Actovegin is also mentioned in some events in elite football [25,26]. Primarily the use of Actovegin in sports medicine was associated with orthopedist, in Germany's national football team, and physician of Bayern Munich football club. Despite criticism from the scientific community due to this unconventional method, intervention with Actovegin was highly appreciated by the elite football community, not only from Germany but from around the world. Actovegin gained recognition among athletes from other disciplines who received Olympic medals [27,28].

Data from sports events provide some information about frequency of use of this medication. In sixteen cases of athletes attending Doping Control in the Athens Olympic Games in 2004 use of Actovegin has been declared; commonly in non-aerobic power sports, e.g. wrestling, boxing, judo, weightlifting [29]. This preparation was mentioned in the category of "Miscellaneous substances" which made up <1% of all declarations by athletes at the Olympic Games Rio 2016 [30]. The use of this drug was recognized in athletes at the Paralympic Games in Athens 2004 and PyeongChang 2018 [31,32]. Actovegin was also mentioned in works describing the issues of counterfeit on selected biopharmaceuticals [33,34].

In the past, Actovegin and Solcoseryl focused the attention of anti-doping authorities, as potential doping agents. Based on primary guideline the WADA, introduced some restrictions, depending on the route of administration these drugs [35].

The Global Drug Reference Online (Global DRO) provides athletes and support personnel with information about the prohibited status of specific medications. Solcoseryl is not included in the Global DRO database. Only Actovegin has been found in the Global DRO database. Topical or intramuscular use of Actovegin is not prohibited in or out of competition via Canadian Centre for Ethics in Sport (CCES) and the United States Anti-Doping Agency (USADA). Other names sometimes used as alternatives are „protein-free bovine blood extract" or „protein-free calf/calves blood extract" [36].

Actovegin and Solcoseryl are not approved by the U.S. Food and Drug Administration (FDA), but only in selected Asia and European countries [37].

The pharmacokinetics of deproteinized calf blood hemodialysate cannot be studied by conventional pharmacokinetic methods as it contains many various substances with multiple pharmacodynamic effects such as peptides mainly oligopeptides, amino acids, glycoproteins. The pharmacodynamics mechanism of action deproteinized calf blood hemodialy sate was not full clarify, however mentions through antioxidant, antiapoptotic activity, and increases mitochondrial oxidative capacity and improve oxygen uptake, activation of macrophages and nuclear factor (NF) – kB pathway, stimulate cells proliferation. Deproteinized calf blood hemodialysate has the following properties: supports cellular metabolism, stimulates oxidative phosphorylation, insulin-like effect and enhances glucose transport, accelerated wound healing and supports regenerative processes in damaged tissues [6,2,13,19,21].

Actovegin or Solcoseryl, directly are not classified by the World Anti-doping Agency (WADA) and not covered in the Prohibited List. The WADA Prohibited List in section M2 (Chemical and physical manipulations), notifies that the intravenous infusion and/or injection of any substance of more than 100 mL per 12 hour period is a prohibited method, even if the substance Actovegin or Solcoseryl) directly was not prohibited, unless it is received while being treated at the hospital, during surgery, or during clinical diagnostic investigation [38,39,40]. The WADA Prohibited List and the Monitoring Program are expanding every year. Examples are peptide substances e.g. BPC-157, included in the WADA Prohibited List in group S0 Non-Approved Substances, or ecdysterone from group 1. Anabolic Agents covered by the Monitoring Program [38,39]. The amount of scientific evidence related to the BPC-157 are negligible, nevertheless it was included on the Prohibited List [2,38].

To some extent, the effects of protein-free hemodialysate of calf blood resemble the regenerative activity of peptides, such as BPC-157 [23]. According to the WADA criteria for inclusion of a substance or drug as a doping agent are such that any two of the three criteria listed below applies:

1. the potential to enhance sports performance;
2. the use represents an actual or potential health risk to the athlete;
3. the use violates the spirit of sport [40].

In the past, an adverse event has been associated with the use of Actovegin. Intravenous administration of Actovegin can cause life-threatening anaphylaxis. A case of a 22-year-old male (amateur cyclist) was reposted which had no significant medical history. Self-injected intravenous Actovegin at the dose of 5 mL, over 5 minutes the night before a competition. Then, the patient developed fever, abdominal pain, and vomiting. Three hours later, the patient presented to the emergency department and required hospitalization [41].

Actovegin and Solcoseryl as regenerative and antihypoxic agents were investigated in the past, however access to many scientific works are limited [42–47]. In the last years observed slight increase of attention for deproteinized hemodialysate of calf serum in orthopedics, likewise in oncology clinical trials as treatment and prevention of oral mucositis induced by chemotherapy or radiotherapy [48,49,50]. In the systematic review from 2022 year, which evaluate effectiveness of Actovegin administration in patients after ischemic stroke, concluded that benefits from intervention of Actovegin are uncertain [51]. Actovegin as a supplemental agent improving cognitive functions and oxygenation of tissues, used in the course of COVID-19 infection [52,53].

Conclusions

Some scientific evidence indicates that deproteinized calf blood hemodialysate, can improve regeneration of tissues. Also confirmed the use of Actovegin by elite athletes in sports events in various years, likewise reported adverse events related to use of this medication in non-elite athletes. Protein-free calf blood hemodialysate contains active substances such as peptides, which demonstrated in many studies that can support the regeneration of tissue damage, analogical like some peptides such as BPC-157. Bearing in mind the pursuit of transparency of rules, consistency and clarity, and easy accessibility for medical personnel or athletes, it is worth considering to clarify statements related to the use of deproteinized calf blood hemodialysate by athletes In and Out-of-Competition.

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