THE EFFECTS OF EPO: FROM EPIC TO EPISODIC?

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Introduction

Perspective

The use of doping is still common practice in many competitive sports, despite strict supervision by the World-Anti-Doping Agency (WADA) and public rejection of doping users such as Lance Armstrong and other cyclists in the past. Interestingly, scientific evidence supporting the ban of certain doping substances turns out to be scarce. Researchers from the Centre for Human Drug Research (CHDR) in Leiden questioned the performance-enhancing ability of recombinant human erythropoietin (rHuEPO), an infamous type of blood doping. In a recent double-blind, randomized, placebo-controlled trial, they proved that rHuEPO did not significantly improve the performance of well-trained cyclists in representative exercise tests. Here, we discuss the introduction and development of rHuEPO in medicine and sports (medicine). Looking critically at the CHDR study, both the evidence on its stimulating effects and potential adverse effects will be evaluated. Finally, we speculate about the potential concerns when EPO turns out to be nothing more than a placebo.

About EPO

Erythropoietin (EPO) is a hormone produced by the kidneys that regulate red blood cell production (RBC) in the bone marrow. Additionally, this glycoprotein is crucial for the synthesis and functioning of several erythrocyte membrane proteins, particularly those facilitating lactate exchange. Normally, this hormone is released after a decline in RBC concentration or a decrease in arterial blood pressure [1]. The first time researchers discovered the effects of erythropoietin was in 1863, when Denis Jourdanet found that people living at high altitude had more viscous blood than those living at sea level. Soon it became known that hypoxia or a loss of red blood cells seemed to stimulate red blood cell production. Evidence for a humoral factor influencing erythropoiesis came in 1906, discovered by professor Paul Carnot. He extracted serum from rabbits that had experienced bleeding and injected this into healthy recipient rabbits, resulting in increased red blood cell production in the recipient rabbits. In 1977, EPO was purified for the first time and a few years later it was discovered that exogenous recombinant human EPO, rHuEPO, was effective as a treatment in anaemic renal disease patients. In the late '80s, the Food and Drug Administration (FDA) approved rHuEPO and since then it has been used to treat patients with chronic renal failure, as well as anaemic HIV patients, cancer patients with anaemia-induced chemotherapy and pregnant and anaemic women [2]. A six-week treatment with EPO increases haemoglobin and haematocrit (the percentage of RBCs in whole blood) with 12%, which was - at least previously - supposed to improve endurance exercise performance. Self-administration is believed to increase haematocrit levels by even more than 60% [1].

Shortly after the FDA gave approval for the therapeutic use of rHuEPO, athletes discovered the potential of EPO to enhance their performance and soon the widespread use of rHuEPO was a fact, especially in endurance sports [3]. In the early '90s, the use of rHuEPO was officially banned as a performance enhancing substance as it was assumed to result in unfair play [4]. Since its abuse could not be detected at that time, haematocrit was used as an indirect measure, with a maximum allowed of 50% [5]. The first doping-test for artificial EPO was introduced at the Olympic Games in 2000 and was composed of blood screening combined with a urine test [4]. Other detection methods are the use of serum blood markers and electrophoretic testing of urine and blood [3]. Since 2000, new detection methods for EPO have been developed with refined sensitivity and new interpretation criteria [4]. However, it remains difficult to detect exogenous EPO [6,7], either because athletes - or their (team) doctors - will develop ways to mask the use of the substance or because new types of EPO will become available, e.g. with a shorter half-life. This is typical for the continuous 'doping arms race' between WADA and athletes or their support teams.

The efficacy of EPO

The demonstrated increase in haematocrit and VO_{2max} after EPO injections leads to the assumption that EPO has performance enhancing abilities. In 2013, however, a research group from the CHDR published a qualitative systematic review of the available literature on the actual effect of EPO, in which the authors concluded that there is a lack of evidence concerning the efficacy of rHuEPO on endurance performance in elite cyclists [8].

In their review, Heuberger et al. explain that many studies on the effects of rHuEPO in cyclists are difficult to translate to real-life cycling performance. First of all, a population mismatch between the study population and professional cyclists often exists. Many studies included either 'recreational athletes', 'well-trained individuals' or 'healthy normal subjects', but - albeit logically - never professional cyclists. In some cases, the level of training of the study population was not even reported, but it was clear that none of the subjects would be able to compete with professionals. Secondly, eight out of thirteen studies were placebo-controlled, only five of which were double-blinded. Finally, the measure VO_{2max}, e.g. the maximal oxygen uptake, was often reported primarily, whereas other endurance performance factors remained unstudied. In the review, four main key factors are mentioned that influence and determine the endurance performance of elite cyclists: VO_{2max}, the lactate threshold (LT, reflecting the onset of anaerobic metabolism), work economy (C, the ratio of speed or power and oxygen cost) and the lactate turnpoint (LTP, when lactate concentrations suddenly rise in a sustained manner). The authors claim that the relative importance of each factor varies per training level: whereas moderately trained athletes can easily improve all factors, elite athletes can mainly increase performance by adapting LT, LTP and C. In line with this, they suggest it would be more relevant to look at the effect of EPO on submaximal intensities. Professional cyclists often compete in multi-day events (e.g. the Tour de France), during which they need to distribute their powers and only work for a small amount of time at their peak intensities, approaching only 3% of the total race time [9,10]. Other performance-related factors that could additionally be taken into account include capillary density, heart rate and volume, muscle mass and breathing pattern.

The authors conclude that not VO_{2max} distinguishes recreational from professional athletes, but rather other parameters such as LT and C, which is why these parameters should be studied. Furthermore, the methodologic quality of studies on rHuEPO should be increased regarding both design and study population. In addition, the awareness of the possible harmful effects of rHuEPO in athletes should be raised. Next to some case reports on professional cyclists, patient studies have reported several negative cardiovascular effects, an increased risk of thrombotic events, encephalopathy and other complications. The authors suggest these risks may be even higher in cyclists, due to improper handling and storage of rHuEPO associated with its illicit use. Further research on the effectiveness of rHuEPO on endurance performance in professional cyclists may elucidate the matter. According to the authors, it may even incline cyclists to stop taking rHuEPO and officials to cease the costly and perhaps unnecessary efforts to detect rHuEPO [8].

The CHDR study

To put this into practice, the same researchers from the CHDR set up an experiment to determine the actual effect of EPO on sports performance [11]. Forty-eight well-trained, Dutch cyclists (male, 18-50 years) were recruited and divided into two groups: one received a weekly injection of rHuEPO, the other received a placebo. Both researchers and athletes were blinded for the treatment. During eight weeks of therapy and training, the performance of the athletes was monitored in maximal and submaximal exercise tests. The study was concluded with an uphill road race on the Mt. Ventoux, to more closely mimic the "clinical" setting. In addition to exercise performance as primary outcomes, the occurrence of adverse events was reported. This study by Heuberger et al. showed that rHuEPO significantly improved performance in maximal exercise test, but submaximal exercise test performance and road race performance - supposed to be more clinically relevant - were unchanged. Additionally, except for increased thrombogenic markers in rHuEPO-users, no difference was observed in incidence or severity of adverse effects between study groups [11].

In two controversial ways, the CHDR study marks a turning point in doping history. On the one hand, it weakens the effect of a substance that has been used intensively by many professional cyclists in the 1990s and 2000s. On the other hand, as claimed by the authors, the study design provides a basis for subsequent clinical trials into the (adverse) effects of other potential doping substances. Still, the study definitely has its limitations. Although participants were carefully selected, their performance can - inevitably - still not be fully compared to elite cyclists. According to the authors, the VO_{2max} and maximal power output of the subjects are similar to those of elite-cyclists when tested in a relatively long, more representative protocol. They seem, however, to have forgotten the contribution of other relevant parameters as discussed in their review: the comparison of factors such as LT and C with those of professional cyclists is lacking. Moreover, it should be noted that the amateur cyclists tested are physically less adapted to cycling performance regarding, for example, capillary density, muscle mass and breathing pattern. The effect of rHuEPO could potentially be more pronounced when all factors are optimised, like in professional cyclists. To make it even more complicated, other studies have suggested effects of EPO on, for instance, recovery after exercise, skeletal muscle or motivation. In case rHuEPO partially or only has an effect on these parameters, the current study protocol is suboptimal, as the authors acknowledge. Furthermore, we doubt whether the authors possess all information on rHuEPO use from back in the days. Although the researchers claim to have used similar doses as known practices in cycling (based on a book by Olympic gold medalist Tyler Hamilton), the administration of rHuEPO in their study is more controlled and safer compared to that in the real-life, illicit and therefore, obscure practice. For this reason, also the severity of the side effects in the CHDR study might be an underestimation. Finally, during the '90s and '00s, a period known for the widespread use of rHuEPO, cyclists did not limit their doping supply to EPO: testosterone, steroids and later, blood transfusions, were common practice as well [12]. Although this justifies the aim of the CHDR study - what does rHuEPO actually contribute? - it also complicates the relevance of the study design. Perhaps it was a combination of substances that lead to peak performance.

Further speculations

Irrespective of the translatability of the CHDR study, its results call for new questions. For instance, what if rHuEPO does not enhance endurance performance in professional cyclists? It is important to note that encouraging fair play is not the only reason why WADA promotes a clean sports culture. The agency also aims to protect athletes from the dangers and consequences of doping use. The safety of rHuEPO can still not be warranted, based on both patient studies and case reports on professional cyclists. Despite some translational limitations, the CHDR study might comprise a small ray of hope by offering a study protocol for further clinical trials into performance-enhancing drugs. This will often be too late for the cheating athlete, though, who will keep looking for novel substances and methods that are not yet under investigation. Finally, would we advocate for compensation for the athletes that were tested positive and suspended? Probably not, as the athletes broke the existing rules and thus intended to cheat. It is, moreover, not unlikely that these athletes used multiple doping substances to maximally enhance performance. And if they did not, they did quite well on a placebo!

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