Comments on Delanghe and Joyner’s Editorial “Testing for recombinant human erythropoietin”

PREANALYTICAL AND ANALYTICAL ISSUES IN INDIRECT HEMATOLOGICAL TESTING

TO THE EDITOR: In their recent editorial on the disappointing disagreement between two World Anti-Doping Agency (WADA)-accredited laboratories evaluating samples for detecting recombinant human erythropoietin (Epo) in urine, Delanghe and Joyner (1) concluded that blood-based indirect Epo tests offer an interesting alternative (2). This is ideally true, considering that the urine test is proven unreliable (4). However, indirect testing, which is designed to establish an individual hematological profile (the “hematological passport”), is a hard task to accomplish. Under ideal conditions (centralized phlebotomy, standardized and traceable procedures for handling and storage of the specimens, adherence to rigorous programs for internal and external quality assessment), laboratory tests are still intrinsically biased by a certain degree of preanalytical and analytical variability (3). In the athletic field, such biases are enormously amplified and hardly governable. Strenuous physical exercise, temperature, and humidity all have substantial influences on several hematological parameters (1). Some hematological markers are also liable: this might be an additional problem when samples are collected under various environmental and technical conditions, stored and shipped for miles to distant accredited laboratories (1, 3). Finally, longitudinal comparison of several hematological variables, especially hematocrit (Ht) and hemoglobin (Hb), lacks of clinical significance if various analytical technologies are used by different accredited laboratories (i.e., Siemens ADVIA hematological analyzers substantially overestimate Hb and Ht compared with instruments from other manufacturers, such as Sysmex and Coulter; Ref. 5). When left uncontrolled and unstandardized, all these variables would dramatically affect the reliability of indirect hematological testing to detect cheating.

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THE IMPORTANCE OF A STRONG COLLABORATION BETWEEN PHARMACEUTICAL COMPANIES AND WADA-ACCREDITED LABORATORIES

TO THE EDITOR: In the editorial on the detection of recombinant human erythropoietin (rhEpo) in urine, Delanghe and Joyner (1) bring up the low number of “positive” rhEPO test results from the American WADA-accredited laboratory and the “negative” analysis results of athletes that “were clearly doping.” Several additional cases of the latter exist in Europe, where ex-cyclists have admitted doping after ending their careers. It is a well-known fact that every time a new doping test is developed, cheating athletes and their doctors scrutinize the test for weaknesses and consequently change their doping habits to avoid a positive test result. Documents from the Spanish doping scandal “Operation Puerto” documented this practice by revealing detailed doping administration schedules developed to minimize the chances of being caught in a test. It is therefore encouraging each time a new test is implemented without notice and consequently “nails” cheating, ignorant athletes, as was the case with the implementation of the blood test for homologous transfusions (3) during the 2004 Olympic Games in Athens and the test for a new rhEpo product during the recent Tour de France (2008). In the latter case, a test for Continuous Erythropoietin Receptor Activator (CERA) was developed during a collaboration between WADA-accredited laboratories and the pharmaceutical company that had developed the product. Such collaborations are essential in the future, if the old dogma of the “anti-doping institutions always are one step behind the cheaters” shall be turned around.

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TO THE EDITOR: The editorial commenting on the study of Lundby et al. does not seem to bring any new aspects into the discussions of an optimal strategy against EPO abuse. The authors briefly discuss the diverging results from the Lundby report regarding testing of two WADA-accredited laboratories, but then refer to rather common issues concerning testing in athletes and technical problems with the EPO method. The amount of EPO in blood is very small, only 5 pmol/l; in urinary samples even less. However, there are very small, but distinct molecular differences between natural hEPO and rhEPO (2, 4), making a detection of rhEPO possible. Due to the small
amounts in urine, the EPO test needs to be very sensitive, and not until the double-blotting technique was introduced by Lasne (2) did it become possible to demonstrate EPO abuse by direct analyses. This was a major step toward a better control of blood doping. Delanghe and Joyner (1) claim that an improved regimen in anti-doping testing would be to introduce indirect testing of blood parameters known to be affected by EPO, and to establish blood profiles related to personalized acceptance limits. Indirect testing (3) has previously been struggling with great inherent variations and has not proved more efficient in detecting EPO abuse than the direct analysis. A promising new aspect is the blood profiling of athletes being discussed recently, but this should nevertheless be used in combination with other more specific methods.

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