The Use of Performance-Enhancing Substances in Athletics:

Human beings are competitive by nature. There is a long history of athletes and their sponsors seeking competitive advantages by a variety of techniques including the use of performance-enhancing substances. Recent media accounts concerning professional baseball, football, cycling, and track athletes have brought attention to the problem. However, it should be emphasized that the use of such substances is not limited to professional athletes since many college, high school and recreational athletes also dabble in their use. These substances can range from over-the-counter "sports supplements" such as creatine, ephedra or androstenedione to actual manipulation of the body's oxygen carrying capacity using techniques collectively known as "blood doping".

Blood doping is defined as the use of artificial methods or substances for increasing oxygen transport and delivery to tissues such as skeletal muscle by an athlete with the sole intent of improving aerobic performance and ability. The most common blood doping methods are blood transfusion, either autologous or homologous, and the injection of substances such as recombinant human erythropoietin (EPO).

Autologous blood doping involves withdrawing blood from the athlete and then reinventing it several weeks later, immediately before an athletic event. Homologous blood doping is similar but involves the transfusion of blood collected from a different individual. Either of these methods results in a temporary increase in the number of red blood cells per unit of plasma (increased hematocrit) with a resultant increase in oxygen carrying capacity of the blood. Medical personnel are often involved in order to safely perform the phlebotomy, store the blood appropriately with the requisite preservatives, and then transfuse the blood product. It must be emphasized that the hazards associated with all blood transfusions also apply in these situations. These include the potential for infusing the wrong type of blood into an individual (which can cause a fatal transfusion reaction), the potential for infection with HIV or hepatitis viruses, and bacterial contamination of the product.

Erythropoetin is a hormone that is produced by the kidney in response to anemia. The hormone stimulates red blood cell production by the bone marrow. Recombinant human erythropoietin (EPO) is an artificial substance developed and used to treat anemia such as that caused by chemotherapy or chronic renal failure. Potential side effects of long-term use include hypertension, an increased risk...
of blood clots, and heart failure.

Laboratory monitoring for blood doping includes both indirect and direct detection methods. One way to indirectly detect and limit blood doping is to set standard upper limits for hematocrit values. Normal hematocrit levels may range from 41 - 53% in men and from 36 - 45% in females. Professional cycling currently has a hematocrit limit of 50%. If a cyclist has a value greater than 50% before a race then he is not allowed to compete in that event and is suspended for two weeks. This rule has been criticized on two fronts. First since approximately 3% of competitive cyclists, especially those that live and/or train at high altitudes, have a baseline hematocrit of greater than 50%, then non-doping individuals could be unfairly excluded from competition. On the other hand by setting an upper hematocrit limit of 50% then professional cycling is essentially acknowledging that blood doping exists and in a sense are implying that they will allow some but not too much of it. A better method might be to monitor hematocrit levels over time since it is more likely that an individual whose baseline hematocrit of 46% suddenly spikes to 50% just before a race is doping than an individual whose hematocrit is always just above 50%.

There are other indirect tests to detect blood doping. Native serum erythropoietin levels transiently decrease after transfusions or after the injection of artificial EPO. Serum iron and bilirubin levels transiently increase after transfusion. Reticulocyte counts increase after EPO injection. Various mathematical models have been established that use a combination of these indirect tests to detect blood doping.

There are no specific laboratory tests to detect autologous transfusion. However, there are specific tests to detect homologous transfusion and EPO use. A type of immunoelectrophoresis known as isoelectric focusing has been developed to detect recombinant human erythropoietin in urine. This test can detect EPO for up to 72 hours after injection. Unfortunately, it has recently been publicized that one can decrease the detection time down to 12 hours by utilizing multiple small bolus injections of the drug at 24 hour intervals. David Millar, a British cyclist, recently completed a two-year racing ban after testing positive for EPO and admitting use of the drug. Marion Jones, a local professional sprinter, was recently under suspicion after an initial positive result on a urine test for EPO. This is particularly interesting since a higher hematocrit level has not been shown to convey a competitive advantage during a sprint competition. However it has been noted that higher hematocrit levels may allow for more intensive training regimens. Her follow-up test was negative which serves to illustrate the fact that the interpretation of these tests can be subjective and that false positive results can occur.

Homologous transfusions can be detected using flow cytometry to detect differences amongst minor blood group antigens between an individual’s native red blood cells and recently transfused cells. Theoretically this technique can detect the transfusion of as little as a few milliliters of homologous blood. After winning a gold medal in the 2004 Olympic cycling time trial Tyler Hamilton became the first high profile athlete to be accused of blood doping using the results of this flow cytometry test.

With so much media attention focused on this problem recently it may seem that everyone is doing it. This might lead some amateur athletes to decide to try some of these methods particularly since there is no testing of individuals at most amateur events. However it should be emphasized that there are many dangers inherent in the use of these blood doping methods. It is not possible for the average athlete to safely obtain, test, store and administer these blood doping agents and it is unlikely that any reputable physician or laboratory would agree to do so. Nevertheless it is possible that a patient might have questions about blood doping. The best course of action is to recommend that your athletic patients train hard, eat a nutritious diet and avoid the temptation to cheat nature.

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Cockcroft Gault Formula

(Edited Note: Courtney Meredith is a Pharm. D. Candidate, who recently completed a drug information clerkship at Rex Hospital. Ms. Meredith was an intensive care nurse before enrolling in the clinical scholars program at the UNC School of Pharmacy. During her rotation at Rex Hospital in June 2006, Ms. Meredith researched drug information questions, developed formulary monographs, and conducted a medication use evaluation (MUE) on caspofungin, among other projects. Ms. Meredith also completed a clinical clerkship with Dr. Robert Schmidt, nephrologist, in July of this year.)

Introduction

In 1976 the Cockcroft Gault (CG) formula was developed to predict creatinine clearance (CrCl) based upon the serum creatinine (Scr) alone, rather than a formal creatinine clearance which requires additional measurement of urine creatinine in a timed urine collection.¹

Since then, it has become a common method to estimate renal function, as it is widely available, relatively quick and inexpensive. It provides a quick estimate of creatinine clearance that may be helpful in determining the appropriate dosages of nephrotoxic drugs or drugs that rely on renal excretion. The formula takes into account the increase in creatinine production with increasing weight, and the decline in creatinine production with age. For women, the formula requires multiplication by 0.85 (15% factor) to account for smaller muscle mass compared to men. When using this formula, it is important to understand its advantages, limitations, and accuracy. This overview will provide pertinent information and general tips for using the CG formula.

Advantages and Disadvantages of Cockcroft Gault Formula

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<td>Quick results</td>
<td>Cannot be used in children</td>
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<td>Avoids errors made in other measurement techniques like 24 hr urine collection</td>
<td>May over or underestimate CrCl due to variations in age and weight</td>
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<td>Minimal inconvenience patient</td>
<td>Not accurate when renal to function is not stable</td>
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<tr>
<td>Minimal cost involved</td>
<td>Large error in renal failure and liver failure</td>
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<td>Not standardized for body surface area</td>
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Cockcroft Gault Formula

\[
\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{body weight [kg]}}{\text{Serum Cr [mg/dL]} \times 72} - 0.85 \text{ (for females)}
\]

Limitations of the CG formula

The CG formula has limitations in certain populations. It may not be as accurate in people with factors affecting their creatinine production, because Scr is a component of the formula. This includes people who are malnourished, obese, vegetarian, very muscular, elderly, amputees, people who ingest a lot of cooked meat or nutritional supplements with creatine, and people with fluctuating renal status.² In these populations, it may be necessary to obtain direct measurements of CrCl such as 24 hour urine creatinine clearance, inulin clearance or 125 I-iothalamate clearance.

Obese patients - When using this formula it is often recommended to use ideal body weight (IBW), especially for those patients who are obese.³ The CG formula, originally calculated using total body weight (TBW) in male patients, was found to underestimate CrCl in patients with normal weight and overestimate it in obese patients.⁴ ⁵ Using IBW in the formula can help correct for this. Another option for obese patients is to use the adjusted body weight (AjbW).⁶ This is done when the patient has a BMI which is > 30 kg/m² or their actual body weight (ABW) is > 25% over ideal weight (meeting the definition of obesity).⁶ ⁷ Using AjbW will prevent underestimating the CrCl with the IBW.

Estimated Ideal body weight:

Males: IBW = 50 kg + 2.3 kg for each inch over five feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over five feet.

Adjusted body weight:

\[
\text{AjbW = IBW + 0.3 (ABW - IBW)}
\]

Malnourished/underweight patients - Patients with substantial muscle wasting may have a low level of creatinine generation and the CG equation may overestimate CrCl in this population. Therefore, it is recommended to use actual body weight. Some recommend empirically reducing the estimated CrCl by 30%. It is very difficult to estimate an accurate CrCl in this population.

Spinal cord injury patients - Using the CG equation will overestimate CrCl in paralyzed patients. This is because the CG formula does not correct for the loss of muscle mass in these patients. Using lean body mass does not improve this much. It is therefore not recommended to use the CG
Limitations of Cockcroft Gault Formula in Select Patient Populations

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Weight used in CG formula (*preferred weight)</th>
<th>Estimated CrCl compared to actual</th>
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<tr>
<td>Obese</td>
<td>Actual *Ideal *Adjusted</td>
<td>Overestimate Accurate (Could slightly underestimate) Fairly accurate</td>
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<tr>
<td>Normal/average wt</td>
<td>Actual or ideal</td>
<td>Slightly underestimates</td>
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<tr>
<td>Lean/underweight</td>
<td>Actual or ideal</td>
<td>Underestimate</td>
</tr>
<tr>
<td>Severe muscle wasting or liver disease causing falsely low Scr</td>
<td>*Actual</td>
<td>Overestimate, reduce estimate by 30%</td>
</tr>
<tr>
<td>Spinal cord injury patients</td>
<td>Actual or ideal</td>
<td>Overestimates</td>
</tr>
<tr>
<td>Elderly</td>
<td>Actual or ideal</td>
<td>Underestimates</td>
</tr>
</tbody>
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MDRD simplified method:

\[ GFR = 186.3 \times (\text{SCR})^{-1.134} \times (\text{age in years})^{0.203} \times 1.212 \times (\text{if patient is black}) \times 0.742 \times (\text{if female}) \]

Formula in this population.

Age- There is a progressive decrease in glomerular filtration rate (GFR) with increasing age no matter how it is estimated or calculated. The CG formula tends to underestimate CrCl in the elderly, however, it has been suggested that if a patient is over 65 years old and their creatinine is <1.0, the creatinine value should be rounded up to one when calculating CrCl. This is controversial, and some studies are showing this will underestimate the GFR in elderly with normal renal function. Clinical judgment should be used in these cases. The CG formula cannot be used in children because it is very inaccurate in this population.

Drugs affecting creatinine secretion- Drugs such as trimethoprim, cimetidine, and cefoxitin can inhibit creatinine secretion, thereby reducing creatinine clearance levels and elevating the serum creatinine level without affecting GFR. The CG equation will not be accurate in this situation.

An Alternative Formula

Another popular method to estimate renal function is the Modification of Diet in Renal Disease (MDRD) formula listed above. The MDRD may be more accurate than some other formulas, especially in the elderly and those with more severe kidney disease. The MDRD underestimates GFR in general. The MDRD is not affected by body weight (no weight parameter is included).

Conclusion

It is important to remember that all formulas are less reliable when a patient's renal function is rapidly fluctuating, and the best estimate will be obtained when renal function is stable. These calculations are dependent on many variable factors, and may overestimate or underestimate renal function. No formula is as accurate as direct creatinine clearance measurement (or use of other methods such as inulin, iothalamate, EDTA clearance).

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References: