

Editorial

The synergistic combination of trimetazidine, hypoxen and L-carnitine in endurance sports

In 2022 Winter Olympics, a 15-year-old star figure skater got into the centre of a doping scandal after testing positive for trimetazidine, an angina drug that is listed in the prohibited substances list from World antidoping agency, along with hypoxen and L-carnitine, both legally permitted.^[1] This raised questions among experts on the role of trimetazidine, hypoxen and carnitine combination in high performing sports. Albeit, trimetazidine alone had previously been known drug of abuse among endurance athletes.^[2,3]

Trimetazidine is an angina drug and has been purported by the media to improve blood flow to the cardiac muscles via coronary arteries after the recent figure skating event in Olympics. Contrary, unlike other angina drugs, trimetazidine works very differently. It is a metabolic agent that stimulates glucose oxidation, this helps glucose break down faster providing energy in hypoxic situations than the oxygen intense beta-oxidation process. Trimetazidine works by inhibiting long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT), the enzyme involved in the final steps of beta-oxidation.^[4] The drug, in turn, reduces oxygen usage and cellular energy, and therefore optimises the myocardial energy metabolism and cardiac function under ischemic conditions, i.e., the lack of blood or oxygen supply to the heart muscles that occurs during angina. In short, the drug helps provide a continued supply of energy under anaerobic conditions (extreme lack of oxygen).

In intense exercises or high-performance sports, the oxygen and energy demand of the body increases tremendously resulting in increased breathing rate. This also forces the heart to beat faster (increased heart rate) to meet increasing oxygen demands. This ultimately impacts on athletes stamina during performance sports and results in increased fatigue. Trimetazidine reduces the oxygen demand and helps

provide energy to the heart muscles even when the oxygen supply is extremely short.

Trimetazidine, for its neurological side effects, had been restricted by the European Medicine Agency for use as an 'add-on only' drug amid safety concerns; it is licensed for use in angina patients who are not adequately controlled by the first-line treatments or are intolerant to the usual angina drugs due to safety concerns.^[5] The drug is usually available as a 35mg modified release tablet that maintains the plasma concentration of the drug for 11 hours, providing a steady benefit without needing frequent doses. The drug is mainly eliminated unchanged via kidneys, the elimination half-life of the drug in healthy young subjects is ~7 hours.^[6] The washout period can, therefore, be up to two days for the drug after a single dose, hence, its traces can still be detected in urine for a longer period. Trimetazidine abuse in athletes, in particular, adolescents and minors, raises significant safety and ethical concerns.

Besides trimetazidine, the young figure skater was also tested positive for two supplements, hypoxen and L-carnitine, both of which were legally permitted, albeit the United States Anti-Doping Agency had unsuccessfully attempted to ban hypoxen in the past due to its performance-enhancing capabilities.^[7] Nevertheless, the combination of these two substances with trimetazidine raised concerns over a potential deliberate attempt to enhance performance.

Hypoxen is an interesting synthetic analogue that provides a source of energy to the body under hypoxic conditions, i.e., when the body is deprived of oxygen supply. During intense exercise when oxygen demand is increased and the supply gets short (anaerobic condition), lactate is naturally produced that is converted into energy by the tissues without needing oxygen to meet the body's demands. This

lactate builds up in the blood much faster than our body can burn it off, known as the 'lactate threshold'. The increased lactate levels in the blood cause a burning feeling in muscles, cause cramps, nausea, weakness, and the feeling of being exhausted. Studies have shown that using hypoxen accelerates the utilisation of lactate during intense exercises^[8-9], that increases the lactate threshold and help improving endurance. This drug is not registered in most western countries and remains unlicensed for any clinical, medicinal or nutraceutical purposes, therefore, there is no toxicological data available as yet to ascertain the safety of this drug or any associated adverse reactions on chronic use. Hypoxen use among athletes, therefore, raises significant ethical concerns amid its limited toxicology and long-term safety implications for athletes.

L-Carnitine, on the other hand, is derived from an amino acid that is naturally found in the body and plays a critical role in energy production. Carnitine is naturally concentrated in skeletal and cardiac muscles to help utilise fatty acids as a dietary fuel when glucose is short in supply for instance during intensive exercises.^[10] Carnitine helps transport fatty acids into the mitochondria and also aids removal of toxic metabolites out of the cells. Usually, carnitine is not needed to take as part of routine nutritional supplements since the body can produce enough amounts needed; besides it is also abundantly found in foods, in particular meat, fish, poultry, and milk. The research has not yet proven a direct link of carnitine supplementation with increased athletic performance. However, the combination of the three drugs might prompt a red flag.

During intense physical exercise, there is a likely synergistic relationship of trimetazidine along with hypoxen and carnitine. The trimetazidine can reduce the oxygen demand and may help provide energy to the heart muscles, carnitine could help produce more energy, and hypoxen, can help provide that energy even when the body is oxygen-deprived (extremely hypoxic or anaerobic conditions). The drugs, however, pose a health and safety risk to the athletes, in particular the effects on cardiac muscles and potential risks of skeletal muscle disorders such as Parkinsonian symptoms.

Athletes in endurance sports face magnificent psychological 'stressors' driven by ambitious goals and outcomes. Athletes success hinges on their mental endurance and an extraordinary psychological strength that is required to keep going to push beyond boundaries to stand out. Importantly, we may not expect young athletes to have enough scientific understanding of the use of these substances to make a fully informed judgement without an specialist advice. Often athletes are tightly counselled and coached by highly specialist sports nutritionists and trainers, especially in global competitions like Olympics, and therefore this is an opportunity for all practitioners in sports nutrition and physical training to reflect on ethical implications of using drugs and supplements in young athletes in enhancing their performance in endurance sports.

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