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PRACTICAL ISSUES IN EVIDENCE-BASED USE OF PERFORMANCE SUPPLEMENTS: SUPPLEMENT INTERACTIONS AND REPEATED USES

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- Current sports nutrition guidelines recommend that athletes only take supplements following an evidence-based analysis of their value in supporting training outcomes or competition performance in their specific event.
- While there is sound evidence to support the use of a few performance supplements under specific scenarios (e.g., creatine, beta-alanine, bicarbonate, caffeine, nitrate/beetroot juice and, perhaps, phosphate), more research is needed around several challenges involved with their real-life use in competitive sport.
- There is limited knowledge around the strategy of combining the intake of several products in events in which performance benefits are seen with each product in isolation. Supplement combinations have the potential to produce additive, neutral or counteractive outcomes.
- The repeated use of the same supplement in sports involving two or more events within a 24 hr period is also of interest, but has received even less attention. In theory, protocols for subsequent use may need to be adjusted to account for effects ranging from residual activity from the first dose or a desensitization effect.

INTRODUCTION

Although there is concern about the indiscriminate use of performance supplements by athletes, many expert groups now take a pragmatic approach to the use of products and protocols which have passed a risk:benefit analysis of being safe, effective and legal, while also being appropriate to the athlete's age and maturation in their sport (AIS Sports Supplement Framework). Indeed, a number of supplements have received serious attention from sports scientists to produce robust evidence of the scenarios in which they can enhance sports performance. These include caffeine (Burke et al., 2013), creatine monohydrate (Buford et al., 2007), bicarbonate (Carr et al., 2011b), beta-alanine (Blancquaert et al., 2015), and beetroot juice/nitrate (Jones, 2014). This work was assessed by a recent consensus conference and accompanying published statement as it applies to the high performance athlete (Maughan et al., 2018).

Although there is general support for the isolated uses of these performance supplements, several issues related to their real-life use in competitive sport remain relatively ignored. These include the additive and interactive effects of combining the use of several performance supplements for a single event as well as the repeated use of a performance supplement in sports which require several bouts or events within 24 hr. This Sports Science Exchange article will examine the current state of knowledge around these issues, with focus on the performance supplements which were previously identified as having support for their benefits to the performance of a single competitive event.

POTENTIAL OUTCOMES FROM COMBINING THE USE OF SEVERAL SUPPLEMENTS

Supplements can enhance performance of specific events by mechanisms including increased substrate availability, reduced perception of pain or effort, buffering of disturbances to muscle pH and/or increased efficiency of muscle contraction. Some sporting events can benefit from several of these effects and studies may show that different supplements can improve performance when used in isolation. Therefore, there is some logic to trialing the use of these supplements in combination. In some events, in fact, it is possible that at least four identified performance supplements could be valuable – for example, in theory, a 2,000 m rowing event might benefit from beetroot juice, caffeine, bicarbonate and creatine supplementation. It would take enormous organization to conduct a study in which the separate and combined effects of each of these products could be investigated. Therefore, it is not surprising that this evolving branch of research has only tackled independent and additive effects of two supplements to date. A range of possible outcomes could be expected:

- The supplements work by different mechanisms and the combined effects are additive
- The supplements work by different mechanisms and the combined effects cancel each other out or fail to have an additive effect
- The supplements work by different mechanisms but the combination interacts in a negative way to reduce the benefit
- The supplements work by the same mechanism and the combination can be additive, neutral or counterproductive

The available literature on the single and additive effects of evidence-based performance supplements on protocols of interest to competitive sports is summarized in Table 1 (supplements which have similar mechanisms of action) and Table 2 (supplements which have different mechanisms of action). Beta-alanine (chronic protocol) and bicarbonate (acute protocol) are an obvious combination, providing a potential benefit to events that are limited by excessive hydrogen ion production from anaerobic glycolysis by increasing intracellular and extracellular buffering capacity, respectively. The available studies of their use involve differences in the types of athletes, protocols of supplementation and measures of sporting performance included in investigations. Not surprisingly, there are differences in the observed outcomes ranging from the absence or presence of performance benefits from each of the supplements individually, and interactions that are counteractive, neutral and additive (Table 1). The lack of consistency in outcomes can be attributed partially to limitations in study designs including small sample sizes and low statistical power. However, the benefit of either supplement or their combined use is also likely to be dictated by the type of sporting event and the degree to which performance is limited by excessive acidosis.

Caffeine and bicarbonate have also received some attention as supplements that might be combined in sporting events involving high-intensity exercise (Table 2), with the separate effects of reduced perception of effort and enhanced buffering being added to further enhance performance. Again, the literature shows a lack of consistency in findings, with observations of positive, neutral and possibly negative outcomes from the individual substances, and a range of additive, neutral and counteractive effects when they are used in combination. Although one study involving a judo-specific test has reported that the small and unclear benefits of each supplement in isolation might combine to produce a significant performance improvement (Felippe et al., 2016), it appears there is also a potential for one product to cancel the need for the other when both are individually valuable. For example, whereas caffeine and bicarbonate supplementation protocols were both successful in improving the performance of a 3 km cycling time trial when used in isolation, there were no further benefits from their combined use (Kilding et al., 2012). However, interactions in other studies include a removal of the positive effects of caffeine due to gastrointestinal disturbances arising from bicarbonate use (Carr et al., 2011a), but also a beneficial effect of using bicarbonate to address greater acidosis associated with a faster effort due to caffeine support (Pruscino et al., 2008). Here again, the scarcity of studies makes it difficult to derive a general conclusion, and the benefits are likely to be event-specific. Other supplement combinations that have received some attention in the literature (Table 2) include the pairing of nitrate/beetroot juice with caffeine (Glaister et al., 2015; Lane et al., 2014). In both studies, nitrate supplementation failed to produce a detectable benefit, and provided no additive effect on the enhancement achieved by caffeine intake.

Finally, although no studies sufficiently fit the criteria around sports performance to be included in the targeted review in Table 2, the combination of creatine and caffeine supplements requires comment. Previous reports (Hespel el al., 2002; Vandenberghe et al., 1996) indicated that daily intake of caffeine while creatine loading caused a loss of the ergogenic properties of enhanced phosphocreatine stores, attributing this finding to the opposing effects of the two supplements on muscle relaxation time. However, more recent investigations of chronic creatine supplementation have reported that the acute addition of caffeine prior to a protocol of exercise capacity or performance does not impair the improvements due to caffeine supplementation (Doherty et al., 2002; Trexler et al., 2016). Although additional sports-specific research on this combination of performance supplements is required, at present there does not seem to be good evidence to prevent athletes from using both of these products in their appropriate scenarios.

REPEATED USE OF SUPPLEMENTS FOR SUCCESSIVE EVENTS

In many sports, competition outcomes are decided through a series of heats and finals, stages in a race or games in a tournament. In other sports, gifted athletes may compete in more than one event on the competition program. In some cases, the interval between bouts is measured in hours and may fall within the half-life of a supplement or the body's return to normal physiological status or homeostasis following the first event. In these situations, athletes want to know if their use of a supplement known to enhance performance of an event can be repeated for a subsequent event with the same benefits. There are several ways in which the carryover of the first use of the supplement might lead to a modified protocol in the second event:

- A reduced dose might be needed if there is still some presence from the first dose that needs to be topped up
- No use if the supplement is still exerting its full physiological effect in this time frame
- An increased dose if desensitization to the supplement requires a larger amount to achieve the same effect
- No use or special pacing strategies for the first event, if the use of the supplement for the first event allows a greater physiological effort with undesirable fatigue

Despite the obvious application of information on this topic, very few studies have been conducted. Caffeine is a supplement of particular interest for several reasons. It was previously believed that the benefits of caffeine on exercise were reduced by habitual use, suggesting that it might be unsuitable to use in a multi-day sport. The need to have a period of caffeine withdrawal to produce optimal performance outcomes has now been dismissed (Irwin et al., 2011), meaning that it is theoretically possible to use in these situations. However, the additional concern relates to the effects of performance-related caffeine use on sleep quality and recovery during multi-day competition. Indeed, caffeine has been reported as a key contributor to sleep problems in other areas of sport, such as the recovery after night matches in team sports (Fullagar et al., 2016). Furthermore, there are anecdotal reports of a cyclical use of caffeine and sleeping tablets in some multi-day competitions as athletes seek to counter the effects of each drug. Of course, many confounding variables such as competition arousal, high-intensity exercise, travel across time-zones and disruptions to daily routines are also involved and their effect needs to be accounted for or removed from future studies. In the meantime, the only available study of repeated use of caffeine in a simulation of cross-country skiing competition (Stadheim et al., 2014) found that modest (3 and 4.5 mg/kg body mass) doses were associated with consistent and significant performance benefits (4-5% enhancement of work done in a cross-country skiing time trial) when implemented on two occasions, 24 hr apart. It was noted that the first bouts undertaken with caffeine were associated with increased muscle damage and soreness, presumably because of the greater effort achieved. However, the use of caffeine on the second occasions was able to mask these effects.

Only a few other supplements have been studied in sports-specific protocols involving repeated use. One investigation involved beetroot juice in a study simulating different protocols for use in two bouts of the Olympic Games track cycling 4 km pursuit program, 75 min apart (Hoon et al., 2014). Other studies have investigated bicarbonate supplement protocols simulating a rowing regatta with two events undertaken within 48 hr (Carr et al., 2011a) while another examined the performance of two 200 m swimming races undertaken a day apart as occurs in major swimming meets (Joyce et al., 2012). All of these studies failed to find a clear performance advantage from the use of the supplement in either bout. Unfortunately, it is likely that the supplementation protocols were not optimal in any of these studies: The beetroot juice dose was probably too low to achieve effects, particularly in highly trained individuals (Wylie et al., 2013), and the bicarbonate supplementation studies used a 3-5 day serial dosing protocol which finished prior to the first bout (Carr et al., 2011a; Joyce et al., 2012). Therefore, further studies are needed with different protocols. Indeed, a study using the more traditional acute bicarbonate supplementation (300 mg/kg body mass undertaken in the hours before the exercise bout) found that it was able to increase high-intensity cycling capacity when repeated over five consecutive days (Mueller et al., 2013).

DIRECTIONS FOR FUTURE RESEARCH

In real life, athletes use supplements in complex scenarios including combining the use of products that individually enhance performance in a single event, as well as the repeated use of products for successive events in multi-event or multi-day competitions. These uses are justified, but the present sports science literature fails to provide adequate information which would allow an athlete to make an evidence-based decision about if and how these practices should be implemented. Further research is needed to remedy this situation. In order to achieve outcomes that are clear and applicable to competitive sport, researchers need to undertake research projects with the following features (Hopkins et al., 1999):

- Use of well-trained subjects who demonstrate the characteristics of the population to which the study is targeted, and who have experience with pace judgment and skill execution according to the demands of their event
- Choice of performance protocols that adequately simulate competitive events
- Opportunity for study participants to practice performance protocols to achieve acceptable and measured reliability
- Adequate sample sizes that allow small but worthwhile performance changes to be detected
- Implementation of conditions that mimic real-life sport (e.g., warm-ups, event time tables and optimal nutritional practices) to optimize the application of the study results
- Standardization of as many extraneous variables as possible to enhance study reliability (e.g., background fitness, recent training, nutritional status)
- Use of suitable statistical analyses to allow small but worthwhile changes in performance to be detected
- Use of supplement protocols that represent best practice and are likely to achieve performance changes if they are relevant to the targeted event
- Use of pure or tested forms of supplements to ensure freedom from contaminants and achievement of desired doses
- In the case of investigating multiple supplements: a study design that involves individual and combined uses of the products of interest so that the context of the single use of products can be checked, and the interaction of products can also be measured

A CAUTIONARY NOTE ABOUT COMMERCIAL MULTI–INGREDIENT SUPPLEMENTS

Multi-ingredient pre-workout supplements, weight loss and muscle gain products are among the current best-selling performance and health supplements. They can sometimes contain up to 30 individual substances, including "proprietary blends" which claim the need to protect the intellectual property around their ingredient list and doses. This class of products has not been included in the current review, although they clearly constitute a scenario in which performance supplements are combined. Many of these products fail to disclose their full list of ingredients and can contain large or undeclared amounts of stimulants and/or banned substances (Cohen et al., 2014; 2015). In other cases, even where they contain evidence-based ingredients, the doses provided in a recommended serving of the supplement may be sub-optimal for that ingredient. These characteristics create concern related to health, doping safety and efficacy/value for money.

From a research perspective, many studies involving commercially available multi-ingredient supplements are unable to contribute to our understanding of the effects of supplement combinations because they typically lack independent verification of the product contents. Furthermore, most studies involve a comparison of the commercial product to a single placebo/control substance. These features prevent detectable effects from being attributed to a single ingredient or allow the interaction between ingredients to be isolated.

SUMMARY AND PRACTICAL IMPLICATIONS

In some sports events or sporting scenarios, several supplements are known to provide performance benefits when used individually. Athletes are therefore interested in the potential to further enhance performance by combining the use of these products. Furthermore, athletes may also need to consider whether evidence-based performance supplements can be used several times in succession when their sport involves repeated events or bouts. The current literature is not sufficiently thorough in its range or design to provide evidence of the additive or repetitive effects of all the supplement uses that could be justified on theoretical grounds. Further research is required to provide athletes with better information to guide their decisions about the use of several supplements at the same time or the successive use of supplements. However, it is unlikely that conventional study designs will be able to consider all the permutations of product uses. Therefore, athletes may need to conduct their own systematic experiments to identify practices that offer benefits to their training and competition goals. The potential outcomes of combining or repeating the use of evidence-based supplements can range from a positive to a counterproductive effect.

Study	Subject of Study Design	Dose	Performance Measure	Performance Benefit
Bicarbonate (Acute Use) and Beta-alanine (Chronic Use)				
Tobias et al., 2013	Well-trained judo and jiu-jitsu athletes (n = 37 M) Parallel group design (n = 9-10) to achieve Bicarbonate, Beta-alanine, Combined and Placebo groups	7 d @ 500 mg/kg/d sodium bicarbonate split into 4 doses and /or 28 d @ 6.4 g/d beta-alanine: Total = 179 g	Combat sports simulation • 4 x 30 s upper body Wingate tests with 3 min recovery	Bicarbonate: Yes Beta-alanine: Yes Combination: additive benefits
Ducker et al., 2013	Competitive team sport athletes (n = 24 M) Parallel group design (n = 6 M) to creatine Bicarbonate, Beta-alanine, Combined and Placebo groups	300 mg/kg sodium bicarbonate @ 60 min pre-exercise and/or 28 d @ 80 mg/kg BM/d beta-alanine: Total ~ 168 g	Team sport simulation • 3 sets @ 6 x 20 m sprints on 25 s with 45 s recovery	Bicarbonate: Perhaps Beta-alanine: No Combination: possible counteractive effect
De Salles Painelli et al., 2013	Well-trained junior swimmers (n = 6 M, 7 F) Crossover design (Bicarbonate or Placebo) undertaken before and after parallel group design (Beta-alanine or Placebo)	300 mg sodium bicarbonate @ 90 min pre-exercise (first swim) and/or 1 w @ 3.2 g/d + 3.5 w @ 6.4 g/d beta-alanine: Total = 202 g	Swimming • 100 m • 200 m 30 min recovery	200 m Bicarbonate: Yes Beta-alanine: Yes 100 m Bicarbonate: Yes Beta-alanine: Possibly Combination: possible additive effects
Mero et al., 2013	International and national swimmers (n = 13 M) Crossover design (bicarbonate) before and after all subjects supplemented with beta-alanine	300 mg/kg sodium bicarbonate @ 60 min pre-exercise (first swim) and 28 d @ 4.8 g/d beta-alanine: Total = 134 g	Swimming • 2 x 100 m 12 min recovery	Bicarbonate: Possibly Beta-alanine: No Combination: no additive effects
Hobson et al., 2013	Well-trained male rowers (n = 20 M) Crossover design (Bicarbonate or Placebo) undertaken after parallel group design (Beta-alanine or Placebo)	300 mg/kg sodium bicarbonate: 200 mg/kg @ 4 h pre-exercise + 100 mg/kg BM @ 120 min pre-exercise and/or 30 d @ 6.4 g/day beta-alanine: Total = 192 g	Rowing • 2000 m ergometer TT	Bicarbonate: Possibly Beta-alanine: Probably Combination: possible additive benefits
Bellinger et al., 2012	Highly trained cyclists (n = 14 M) Crossover design (Bicarbonate or Placebo) undertaken after parallel group design (Beta-alanine or Placebo)	300 mg/kg sodium bicarbonate @ 90 min pre-exercise and/or 28d @ 65 mg/kg/d beta- alanine: Total = 129 g	Cycling • 4 min ergometer TT Tests conducted pre and post 28 d of beta-alanine/placebo	Bicarbonate: Yes Beta-alanine: No Combination: no additive effects

Table 1. Summary of studies of combined use of supplements with similar mechanisms of actions

Study	Subject of Study Design	Dose	Performance Measure	Performance Benefit
Bicarbonate and Caffiene				
Felippe et al., 2016	Regional and national level judo players (n = 10 M) Crossover design to produce Bicarbonate, Caffeine, Combined, and Placebo trials	300 mg/kg sodium bicarbonate @ 60-120 min pre-exercise and/or 6 mg/kg BM caffeine @ 60 m pre-exercise	Judo • 3 x judo specific fitness test (JSFT) interspersed by 5 min	Bicarbonate: Perhaps Caffeine: Perhaps Combination: Additive benefit
Christensen et al., 2014	International level rowers (n = 11 M, 1 F; 6 lightweight and 6 heavyweight) Crossover design to produce Bicarbonate, Caffeine, Combined, and Placebo trials	300 mg/kg sodium bicarbonate @ 75 min pre-exercise and/or 3 mg/kg caffeine @ 45 m pre-exercise	Rowing • 6 min ergometer TT	Bicarbonate: No Caffeine: Yes Combination: No additive effect
Kilding et al., 2012	Well-trained cyclists (n = 10 M) Crossover design to produce Bicarbonate, Caffeine, Combined, and Placebo trials	300 mg/kg sodium bicarbonate @ 90-120 min pre-exercise and/or 3 mg/kg caffeine @ 60 min pre-trial	Cycling • 3 km ergometer TT	Bicarbonate: Yes Caffeine: Yes Combination: No additive effect
Carr et al., 2011a	Well-trained rowers (n = 6 M, 2 F) Crossover design to produce Bicarbonate, Caffeine, Combined, and Placebo trials	300 mg/kg sodium bicarbonate @ 90 min pre-exercise and/or 6 mg/kg caffeine @ 30 min pre-exercise	Rowing • 2000 m ergometer TT Overnight fasted	Bicarbonate: No Caffeine: Yes Combination: Counteractive effect
Pruscino et al., 2008	Highly trained swimmers (n = 6 M) Crossover design to produce Bicarbonate, Caffeine, Combined, and Placebo trials	300 mg/kg sodium bicarbonate spread @ 30-120 min pre-exercise and/or 6 mg/kg caffeine @ 45 min pre-exercise	Swimming • 2 × 200 m 30 min recovery	Bicarbonate: Perhaps Caffeine: No, perhaps harm Combination: Unclear additive effect
Caffeine and Nitrate/ Beetroot Juice				
Glaister et al., 2015	Well-trained cyclists (n = 14 F) Crossover design to produce Beetroot juice (BJ), Caffeine, Combined, and Placebo trials	7.3 mmol/d nitrate in BJ @ 2.5 h pre-exercise and/or 5 mg/kg BM caffeine @ 1 h pre-exercise	Cycling • 20 km ergometer TT	Nitrate: No Caffeine: Yes Combination: no additive effect

Table 2. Summary of studies of combined use of supplements with different mechanisms of actions

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