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FORUM

Athletes and blood clots: individualized, intermittent anticoagulation management

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Essentials

- Athletes on anticoagulants are typically prohibited from participation in contact sports.
- Short-acting anticoagulants allow for reconsideration of this precedent.
- An individualized pharmacokinetic/pharmacodynamics study can aid patient-specific management.
- Many challenges and unresolved issues exist regarding such tailored intermittent dosing.

Summary. Athletes with venous thromboembolism (VTE) are typically prohibited from participating in contact sports during anticoagulation therapy, but such mandatory removal from competition can cause psychological and financial detriments for athletes and overlooks patient autonomy. The precedent of compulsory removal developed when options for anticoagulation therapy were more limited, but medical advances now allow for rethinking of the management of athletes with VTE. We propose a novel therapeutic approach to the treatment of athletes who participate in contact sports and require anticoagulation. A personalized pharmacokinetic/pharmacodynamics study of a direct oral anticoagulant can be performed for an athlete, which can inform the timing of medication dosing. Managed carefully, this can allow athletic participation when plasma drug concentration is minimal (minimizing bleeding risk) and prompt resumption of treatment after the risk of bleeding sufficiently normalizes (maximizing therapeutic time).

Keywords: anticoagulants; athletes; exercise; sports medicine; venous thromboembolism.

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Background

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and/or pulmonary embolism (PE), occurs in athletes as described in case reports and small case series [1–3]. Although VTE is common in the general population, its incidence in athletes has not been studied.

Athletes tend to be young and healthy compared with the population at large, factors that are associated with a lower risk of VTE. However, frequent exposure to trauma, immobilization after trauma or surgery and routine long-distance travel are risk factors for VTE to which athletes are often exposed [4,5]. It is not known how physical differences (e.g. extreme height and very high lean body mass), dehydration or repeated extreme exertion affect the risk of VTE [1,4].

When athletes develop VTE, the medical literature provides little guidance on appropriate management. Consensus has argued for removal from participation in athletic activities while anticoagulation is required [6]. This strategy avoids the complexity of managing the risks of an athlete competing while anticoagulated, but in simplifying decision-making for the physician it effectively removes the patient's autonomy.

Mandatory removal from activity is appropriate if the risk to the patient is so high that allowing continued participation is unethical. For athletes with VTE, however, medical advances now allow for reconsideration of the historical precedent and inclusion of the athlete in the decision-making process.

Direct oral anticoagulants (DOACs) have received regulatory approval worldwide for treatment of VTE over the past 7 years. The pharmacokinetic/pharmacodynamics

(PK/PD) profiles of these medications share properties conducive to more flexible, individualized therapy than was possible with the previously available vitamin K antagonist anticoagulants. Following oral dosing of DOACs, therapeutic anticoagulation is achieved quickly (peak activity within 1–4 h) and the drugs are cleared rapidly (half-lives, 7–14 h) [7,8].

Traditional management

Treatment of acute VTE is well studied, with widely agreed-upon guidelines [9]. Three months of full-dose uninterrupted therapy is considered appropriate to complete 'active treatment' [10]. A provoked proximal DVT or PE is treated with 3 months of anticoagulation, whereas extended (long-term) anticoagulation is typically considered for unprovoked VTE or VTE provoked by risk factors that remain present [9,10].

Light exercise resumed soon after VTE is safe [11]. However, participation in competitive athletics during early acute treatment for VTE raises some concerns. Endothelialization and vessel wall adhesion of a thrombus occur during the first 3 weeks of DVT development, during which time the risk of embolization is highest [2].

A gradual return to non-contact athletic activity has been proposed, starting after 3 weeks with resumption of full participation as soon as 6 weeks, even while the patient is anticoagulated [2,6]. Yet for contact sport athletes requiring anticoagulation, return to play has not been considered at any point during treatment, and scientific and public discussion is lacking.

Indefinite removal from play can end an athlete's career, with potentially drastic psychosocial and financial consequences. Ensuring patient safety is a cornerstone of medical practice, but no endeavor in medicine or sports is entirely without risk. Patients differ in willingness to accept risk by personal preference, which is balanced against context-specific benefits. The core ethical principle of patient autonomy mandates that patients be afforded input regarding their willingness to accept risk when reasonable treatment options exist.

Proposed management

The 'fast on/fast off' characteristic of the DOACs fundamentally changes how physicians can approach anticoagulation in athletes.

Once the time needed for an athlete to adequately clear a DOAC is established, ideal dose scheduling prior to competition can be predicted and bleeding risk, thus, minimized. This information can be obtained with a personalized PK/PD study, wherein the athlete ingests a DOAC and interval measurements of plasma drug concentration are taken over 24 h. Obtaining multiple plasma drug levels during this time allows determination of a drug's elimination half-life and identifies when the plasma drug concentration reaches the level at which bleeding risk is considered minimal.

Measuring additional drug level values 36 and/or 48 h after drug intake may be helpful in patients who demonstrate a particularly long drug half-life. In addition, significant intra-individual drug level variability may exist for DOACs [12]. This has been shown for dabigatran, but other DOACs have not been similarly evaluated. Repeat measurements after a first, more intensive PK/PD study may, therefore, be advisable. Such confirmatory testing could be simplified to more limited testing focused around the time of the previously determined threshold level.

Armed with these data, DOAC dosing can be scheduled so that the plasma drug level has fallen below the acceptable threshold (where risk of bleeding is increased only minimally or not at all) at the time of sports participation. Once the risk of trauma or bleeding normalizes after athletic competition, a single dose of medication quickly reestablishes therapeutic anticoagulation.

Risk considerations

Assessment of whether a novel anticoagulation strategy is reasonable must include consideration of bleeding and recurrent thrombosis risk.

After unprovoked VTE, those who complete acute treatment for 3 months and then discontinue anticoagulation have a 10.4% rate of recurrent VTE over the next 6 months [13]. Fatal recurrent VTE occurs at a rate of 0.3/100 patient-years for patients who discontinue anticoagulation after acute treatment [14]. From this data we can estimate a risk of recurrent VTE of $< 1/3500$ per day and risk of fatal recurrent VTE of $< 1/100\,000$ per day for athletes no longer on anticoagulation after completing initial therapy, indicating that absolute risk incurred by brief intermittent interruption in therapy is very low. Previously, concern has been raised that interruption of anticoagulation might lead to a rebound hypercoagulability, but there are no scientific data to date to support this as a clinically relevant concern [15].

Armed with precise, patient-specific information from a customized PK/PD study, the medical provider/team can guide the scheduling of medication dosing to maximize therapeutic time (minimizing risk of recurrent VTE) while ensuring appropriately low plasma drug levels at the time of sports participation (minimizing bleeding risk). The timing of safe athletic participation relative to the last dose of anticoagulant medication will vary by specific medication, individual patient PK/PD profile and intended activity.

Although this strategy is supported by scientific principles and clinical reasoning, more research is needed to evaluate feasibility and further optimize safety and efficacy.

It has been demonstrated in phase 3 trials that lower drug plasma levels (trough values for dabigatran, edoxaban and rivaroxaban, area under the curve for apixaban)

correlate with lower risk of major bleeding [16–19]. However, precise drug levels below which the risk of major bleeding is only minimally or not at all increased have not been defined. Future studies will need to define these levels. It can be speculated that these levels may be at the lower end of the normal trough range for an individual DOAC [20]. The ongoing PAUSE trial (Perioperative Anticoagulant Use for Surgery Evaluation Study; NCT02228798) is expected to shed further light on the correlation between DOAC plasma drug levels and bleeding risk after surgery. Some of the resultant data may help improve our estimates of bleeding risk from trauma associated with athletic activities.

There is no evidence regarding appropriate timing for resumption of anticoagulants after play. Restarting medication within 1–2 h of an uncomplicated sporting event is likely to be safe, but if trauma is sustained then delayed reinitiation of therapy may be necessary. Without established guidelines, decisions need to be made on a case-by-case basis with expert guidance after careful consideration of the specific circumstances. It will need to be clarified who will assist the athlete in the decision-making process regarding when after trauma to restart the anticoagulant.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used by athletes participating in contact sports. Some evidence suggests that individuals who sustain trauma while routinely taking NSAIDs are at increased risk of bleeding complications [21,22]. In a study of geriatric patients who sustained falls, the risk of developing intracranial hemorrhage among those treated with warfarin was not significantly different to those taking aspirin [23]. How bleeding risk after trauma compares between athletes taking NSAIDs and those with subtherapeutic plasma DOAC levels at the time of competition is unknown.

The risk of trauma varies by sport. Trauma may occur in any sport, but classifications exist to help stratify risk [24]. Non-contact sports are those in which trauma or contact is inadvertent and unexpected (e.g. running and swimming). Limited contact sports pose a higher risk of trauma, but contact remains unintentional and infrequent (e.g. baseball and volleyball). In contact sports, some degree of trauma routinely occurs during play, but acceptable contact is tightly regulated (e.g. basketball and soccer). Collision sports require significant contact as a major component of the activity (e.g. American football and ice hockey).

Participation in non-contact sports is safe without interruption of anticoagulation, but participation in limited contact, contact and collision sports while on anticoagulation has historically been regarded as impossible [2,6]. The risk of injury ranges widely across the latter three classifications, yet if plasma anticoagulant drug levels are below a level at which there is any increase in bleeding risk, an athlete's participation in these sports would not increase the risk, regardless of the sport.

For some athletes whose practice and game schedules frequently pose a high risk of major trauma or who, by history, are more prothrombotic, intermittent dosing may not be suitable, as it could carry too high a risk of bleeding or recurrent thrombosis.

Further considerations

Personalized PK/PD studies, frequent adjustments to dosing schedules and case-by-case assessment of when to resume therapy is not feasible for all athletes. In order to justify acceptance of a potential, if small, increase in the risk of re-thrombosis and the costs of deploying such a management strategy, the benefit to a patient must be considerable. Elite athletes, typically professionals, generally have the most to gain by continuing to compete and are more likely to have adequate resources to support a labor-intensive and costly treatment plan. That said, our proposed management could be applied to any athlete or other patient taking a DOAC, provided appropriate supports are available and decision-making occurs in accordance with the patient's interests.

Practical and ethical considerations abound when new treatments become available. Particularly for professional athletes, the roles of decision makers outside the patient–physician dyad (e.g. teams, leagues and sponsors) in the medical decision-making process can be complex. Beyond medical considerations, financial, public relations and liability issues may play a part in the decision for all involved parties.

Appropriately managed, the absolute risk of participation in many sports while on anticoagulation can be low, but this does not mean that all athletes must elect to proceed with this strategy. Patients who find the benefit–cost ratio unfavorable must be protected against suggestions that they are refusing to participate despite 'medical clearance'. Medical possibility does not imply that compulsory implementation is either necessary or appropriate.

The rates of and risk factors for VTE specific to athletes still need to be explored, and more PK/PD studies in high-level athletes are required. More precise determination of the plasma DOAC levels at which bleeding risk increases with and without trauma is needed, as is better definition of when it is safe to resume anticoagulation after trauma.

Developing a registry of athletes who require anticoagulation could help expedite achievement of these goals. In the interim, we call for open discussion among experts in the field in order to work towards consensus.

Addendum

Both authors made substantial contributions to the content, including review of the literature, critical writing and revision, and both authors provided final approval of the submission.

Disclosure of Conflict of Interests

S. Moll has served as a consultant to Boehringer-Ingelheim and Janssen Pharmaceuticals.

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