Brief Review

Weekly missing dose ("6/7" SSU protocol): A rational approach in warfarin use

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Abstract. Warfarin is still used as a standard drug for long term oral anticoagulation. We hypothesized that chronic warfarin use six days a week ("6/7" SSU protocol) is a safe and effective method in order to minimize the burden of frequent blood testing. Our unpublished data indicated that weekly missing dose of warfarin a day per week could attain an ideal therapeutic goal with a need to less frequent blood samplings without the risk of warfarin toxicity (bleeding) or significant drop in therapeutic serum level. Our rationale was rather a high half-life of warfarin (20-60 hours) with more than 97% protein bounding. So, disruption of daily oral prescription of warfarin by off-days (a day each week) can effectively halt the risk of bleeding without considerable impact on its anticoagulation effects. We hypothesized that due to unappreciated long elimination half-life, this mode of dosing (six days a week) could be more justified than the continuous daily oral prescription. This fact has been experienced for years regarding practice with digoxin (with 36-48 hours half-life). Similarly this concept could be true for every drug with "more than a day" half-life like warfarin.

Keywords: Warfarin, anticoagulation, weekly dose, "6/7" SSU protocol

Introduction

Thrombotic events are among the most frequent causes of morbidity and mortality worldwide even in young people [1]. Abnormal tendency to coagulation and underlying comorbidities leading to hemostasis such as valvular or some conductive heart diseases or atraial fibrillation are the major indications for anticoagulation therapy.

Several agents are used to fight abnormal coagulation or block physiologic clotting processes. Among them intravenous or subcutaneous heparin injections are the standard method of initial anticoagulation in most settings for decades [2]. However chronic heparin use has some burden such as heparin induced thrombocytopenia (HIT) and negative bone mineral balance [3]. However except for pregnancy, long term use of heparin is never clinically indicated. Instead, warfarin still is a standard drug for long term oral anticoagulation in most series. Effect of warfarin on bone loss is a matter of debate [4]. The most dread complications of warfarin use are unsteady blood level and risk of fatal and non-fatal bleeding. However, the clinical advantage of this drug has been partially offset by its very high individual variability in the dosing in order to attain ideal results [5]. This variability in part is due to strong individual pharmacogenetics of warfarin.

Two major problems with clinical use of warfarin are warfarin resistance and the other, warfarin overdose. Although the issue of warfarin resistance is sometimes a clinical problem, however, the thrombotic events secondary to under-therapeutic level of warfarin could be as fatal as warfarin overdose. Albeit not so rare in clinical practice, there are limited data on the frequency of warfarin resistance due to diverse etiologies [6]. Warfarin overdose on the other hand, may be secondary to drug intake or interaction with other drugs. To prevent this, serial daily blood tests for INR is recommended especially during first days. Considering life-long need for anticoagulation therapy in almost all cases and fluctuations in serum therapeutic level, the issue of exhausting serial blood sampling is also a big problem [7]. D showed that low-dose warfarin protocol (5 mg per day without loading dose) with infrequent blood testing is a safe and effective alternative in addition data show that the burden of blood testing is high, even in cases of rather good blood control to maintain a safe state [8]. This dilemma has led to searching new drugs (oral direct thrombin inhibitors such as *ximelagatran* or *dabigatran*) with better safety margin, however, the issue of cost and effectiveness and global availability are still their major disadvantages [9].

Many clinicians try to minimize warfarin overdose/ adverse reactions using "low-dose protocols" with less frequency of blood samplings [8]. In this protocol, starting daily dose of 5 mg warfarin is followed by daily blood tests for INR during first days of treatment. Several studies showed that warfarin induction with low oral doses could be safe even in the absence of concurrent heparin use [6].

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This approach may prevent paradoxical thrombosis as may be seen in high-dose loading protocols. As initial "low-dose" warfarin (without loading dose) has "*anticoagulant*" activity so it may boost the standard "*anti-thrombotic*" effects of chronic warfarin use [10]. This favorable event could be more amplified if prescription intervals could prevent warfarin overdose and bleeding.

We hypothesized that chronic warfarin use six days a week ("6/7" SSU protocol) is a safe and effective method in order to minimize the burden of frequent blood testing. Our unpublished data indicated that weekly missing doses of warfarin a day per week (after 3-5 times the half-life period) could attain an ideal therapeutic goal with a need to less frequent blood samplings without the risk of warfarin toxicity (bleeding) or significant drop in therapeutic serum level.

Our rationale was rather a high half-life of warfarin (20-60 hours) with more than 97% protein bounding [11]. So, disruption of daily oral prescription of warfarin by off-days (a day each week away from warfarin) can effectively halt the risk of bleeding without considerable impact on its anticoagulation effects. We hypothesized that due to unappreciated long elimination half-life, this mode of dosing (six days a week) could be more justified than the continuous daily oral prescription. This fact has been experienced for years regarding practice with digoxin (with 36-48 hours half-life). Considering the fact that continuous daily oral dosing is associated with a great risk of digoxin toxicity, many clinicians use under-dose protocol or off-days to prevent digoxin toxicity [12]. Similarly this concept could be true for every drug with "more than a day" half-life like warfarin.

Acknowledgment

Conflict of Interest

The author declares no conflicts of interest.

References

1. Montiel-Manzano G, de la Pena-Diaz A, Majluf-Cruz A, et al. National evaluation of the diagnosis of activated protein C resistance. Rev Invest Clin 55:358-369, 2003.

2. Linhardt, R., Heparin: an important drug enters its seventh decade. Chemist Indust 2:45-50, 1991.

3. Nelson-Piercy C. Hazards of heparin: allergy, heparin-induced thrombocytopenia and osteoporosis. Baillieres Clin Obstet Gynaecol 11: 489-509, 1997.

4. Rezaieyazdi Z, et al. Reduced bone density in patients on long-term warfarin. Int J Rheum Dis 12:130-135, 2009.

5. Takahashi H, Echizen H. Pharmacogenetics of warfarin elimination and its clinical implications. Clin Pharmacokinet 40:587-603, 2001.

6. Osinbowale O, Al Malki M, Schade A, Bartholomew JR. An algorithm for managing warfarin resistance. Cleve Clin J Med 76:724-730, 2009.

7. Stewart S, Murphy NF, Walker A, McGuire A, McMurray JJ. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. Heart 90:286-292, 2004.

8. Harper P, Monahan K, Baker B. Warfarin induction at 5 mg daily is safe with a low risk of anticoagulant overdose: results of an audit of patients with deep vein thrombosis commencing warfarin. Intern Med J 35:717-720, 2005.

9. Pink J, Pirmohamed M, Lane S, Hughes DA. Cost-effectiveness of pharmacogene-tics-guided warfarin therapy vs. alternative anticoagulation in atrial fibrillation. Clin Pharmacol Ther 95:199-207, 2014.

10. Jaffer A, Bragg L. Practical tips for warfarin dosing and monitoring. Cleve Clin J Med 70:361-371, 2003.

11. Palareti G, Legnani C. Warfarin withdrawal. Pharmacokinetic-pharmacodynamic considerations. Clin Pharmacokinet 30:300-313, 1996.

12. Ahmed A, Waagstein F. Low-dose digoxin and reducti on in mortality and morbidity in heart failure. Int J Cardiol 136:91-92, 2009.