Rehman, J Clin Case Rep 2013, 3:12
DOI: 10.4172/2165-7920.1000e121

Journal of Clinical Case Reports

Editorial Open Access

Paradoxical Increased Risk of Thrombosis after Initiation of Vitamin K Antagonists in Thromboembolic Disease

Rehman HU*

Department of Medicine, Regina Qu'Appelle Health Region, Regina General Hospital, Canada

Introduction

Vitamin k Antagosnist Oral Anticoagulants (VKA) are effective in the primary and secondary prevention of venous thromboembolism, in the prevention of systemic embolism and stroke in patients with prosthetic heart valves or atrial fibrillation. In patients with thromboembolic disease Low Molecular Weight Heparin (LMWH) and oral VKA are started at diagnosis. LMWH is than stopped once the International Normalised Ratio (INR) values are in the therapeutic range. The timing of stopping LMWH is important since its discontinuation too soon after a therapeutic INR has been achieved may paradoxically increase the risk of thrombosis. In a recent study, only 20% of the patients met the currently recommended treatment guideline of 4 days or more of heparin and warfarin overlap, until the international normalized ratio is greater than 2.0 for 2 consecutive days [1]. The manuscript will discuss the mechanisms behind the increased risk of thrombosis after initiation of oral anticoagulation therapy and how to avoid these risks.

Vitamin K Dependent Proteins

Hepatic synthesis of vitamin K-dependent factors and proteins involves gamma-carboxylation of precursors of these substances. A specific carboxylase enzyme converts glutamic acid residues found in the NH_2-terminal region of these precursors to form γ-carboxyglutamic acid [2]. This reaction requires vitamin KH_2 (hydroquinone), a reduced form of vitamin K. Vitamin KH_2 is than oxidised to vitamin K 2,3-epoxide, an inactive form of vitamin K. Since adequate supplies of itamin KH_2 are required for the production of vitamin K-dependent coagulation factors, vitamin KH_2 stores are replenished by a hepatic recycling process involving first reduction of vitamin KO to vitamin K via vitamin K epoxide reductase and than to vitamin KH_2 via vitamin K1 reductase [3].

Warfarin inhibits vitamin K epoxide reductase and vitamin K1 reductase. This results in an accumulation of vitamin KO and depletion of vitamin KH_2 [4]. As a consequence γ-carboxylation of the vitamin K-dependent coagulant proteins (prothrombin, factors VII, IX and X) and anticoagulant proteins (proteins C and S) is limited, resulting in production of acarboxylated proteins which are unable to bind calcium. These acarboxylated forms are more slowly activated to form thrombin than their normal counterparts due to their inability to bind to phospholipid bilayers, a calcium-dependent process and a prerequisite for normal thrombin production [5].

Haemostatic Balance

The aim of the VKA anticoagulation therapy is to reduce the formation of thrombin by interfering with the vitamin K-dependent coagulation factors. Warfarin does this by decreasing the vitamin K-dependent procoagulant factors but it also inhibits coagulation inhibitors, proteins C and S. Therefore the net effect of warfarin depends on the haemostatic balance between the procoagulant factors and the inhibitors of coagulation.

The half-life of factor VII is 6 hours, whilst the half-lives of factors II, IX and X are 72 to 96 hours. This means that factor VII is depleted much sooner than factors II, IX and X [6]. Initial changes in the prothrombin time indicate initial depletion of factor VII and do not provide protection against thrombosis [7]. The antithrombotic effect of warfarin, caused primarily by a reduction in the activity of factor II, is delayed for as long as 72 to 96 hours [8].

Adequate anticoagulation with warfarin requires selective suppression of factors II and X. *In vitro* studies have shown that the rate of prothrombin activation is linearly related to the concentration of factor II [9]. *In vivo*, prothrombin activation can be monitored by measuring the levels of prothrombin fragment 1.2 (F1+2) [10]. A significant reduction in F1+2 takes 88 and 120 hours after the initiation of anticoagulant treatment in patients and in healthy volunteers, respectively [11]. In another study, factor II and F1+2 levels were observed to be high in the initial phase of oral anticoagulant therapy despite achieving therapeutic INR [12].

Oral anticoagulation, liver disease, and disseminated intavascular coagulation (DIC) cause deficiencies of protein C and S and systemic lupus erythematosus, nephrotic syndrome, pregnancy and certain hormones cause deficiency of proten S. Protein C, once activated, functions as a physiologic anticoagulant by proteolytically degrading activated factors V and VIII [13]. Homozygous protein C deficiency is associated with extensive thrombotic disease and death in infancy [14]. Patients with partial protein C deficiency also experience recurrent thrombotic episodes [15]. The heterozygotes are at increased risk of warfarin-induced skin necrosis, a condition caused by diffuse thrombosis of small venules [16]. Protein C is rapidly reduced to a low level following warfarin administration [17]. This may occur prior to adequate suppression of factors II and X [18]. There is therefore a prothrombotic phase early on after initiation of warfarin therapy. Protein S is a vitamin K-dependent glycoprotein, which serves as an activated protein C binding protein that is essential for assembly of the anticoagulant complex on cell surfaces [19]. Protein S functional levels are often low in patients with an acute thromboses and its activity is reduced further after initiation of warfarin therapy. The levels decline more slowly than protein C, reaching a nadir at 46 hours [12]. In a study of 51 patients stabilised on warfarin, total protein S was reduced to 64.6 ± 16.4% compared with a level in healthy subjects of 114.7 ± 21.7% [20]. Low levels of protein S are associated with thrombosis [21].

Since patients with protein C levels of less than 65% are at risk of thrombosis, an early decline of proteins C and S, preceding the fall of

***Corresponding author:** Rehman HU, Department of Medicine, Regina Qu'Appelle Health Region, Regina General Hospital, 1440 – 14th Avenue, Regina, SK, S4P 0W5, Canada, E-mail: habib31@sasktel.net

Received October 16, 2013; **Accepted** October 24, 2013; **Published** October 26, 2013

Citation: Rehman HU (2013) Paradoxical Increased Risk of Thrombosis after Initiation of Vitamin K Antagonists in Thromboembolic Disease. J Clin Case Rep 3: e121. doi:10.4172/2165-7920.1000e121

the vitamin K dependent procoagulants results in a prothrombotic state [22]. The antithrombotic effect can be achieved only after the vitamin K-dependent procoagulants reach levels of about 25% [23]. Such antithrombotic levels cannot be achieved during the first days of treatment with warfarin. *In vivo* prothrombin activation is a function of the balance between factor II and protein C concentrations and thrombosis is not prevented until nadir concentrations of factor II are obtained, which can take 40-192 hours. During this time patients are paradoxically at increased risk of thromboembolic disease. It is therefore important to overlap heparin and warfarin treatment for at least 48 hours after therapeutic INR values have been achieved. This will cover the period of hypercoagulability until protein C rises again to sufficient levels to regulate factors Va and VIIIa.

Conclusions

During commencement of oral VKA therapy a there is a transient hypercoagulable state when the patients are at high risk of further thromboembolic disease. This is due to the difference in plasma half-lives between the vitamin K-dependent pro-coagulation factors II and X, and the vitamin K-dependent anticoagulant proteins C and S. The antithrombotic effect of warfarin, caused primarily by a reduction in the activity of factor II, is delayed for as long as 72 to 96 hours. Protein C has a half-life of 6 hours and decreases at the same rate as factor VII in the first three days of therapy. Higher doses of warfarin initially may rapidly deplete protein C prior to adequate suppression of factors II and X. Similarly protein S activity is markedly reduced after initiation of warfarin therapy, reaching a nadir at 46 hours. During this phase of treatment, low levels of proteins C and S in association with inadequate suppression of factors II and X incurs a high risk of thrombosis. There is therefore a prothrombotic phase early on after initiation of warfarin therapy. It is therefore important to overlap heparin and warfarin treatment for at least 48 hours after therapeutic INR values have been achieved to cover the period of hypercoagulability until a balance in favour of antithrombotic effects of warfarin is achieved.

References

1. Hylek EM, Regan S, Henault LE, Gardner M, Chan AT, et al. (2003) Challenges to the effective use of unfractionated heparin in the hospitalized management of acute thrombosis. Arch Intern Med 163: 621-627.
2. Suttie JW (1988) Vitamin K-dependent carboxylation of glutamyl residues in proteins. Biofactors 1: 55-60.
3. Whitlon DS, Sadowski JA, Suttie JW (1978) Mechanism of coumarin action: significance of vitamin K epoxide reductase inhibition. Biochemistry 17: 1371-1377.
4. Fasco MJ, Hildebrandt EF, Suttie JW (1982) Evidence that warfarin anticoagulant action involves two distinct reductase activities. J Biol Chem 257: 11210-11212.
5. Stirling Y (1995) Warfarin-induced changes in procoagulant and anticoagulant proteins. Blood Coagul Fibrinolysis 6: 361-373.
6. Weiss P, Soff GA, Halkin H, Seligsohn U (1987) Decline of proteins C and S and factors II, VII, IX and X during the initiation of warfarin therapy. Thromb Res 45: 783-790.
7. Blanchard RA, Furie BC, Jorgensen M, Kruger SF, Furie B (1981) Acquired vitamin K-dependent carboxylation deficiency in liver disease. N Engl J Med 305: 242-248.
8. Hellemans J, Vorlat M, Verstraete M (1963) Survival time of prothrombin and factors vii, ix and x after completely synthesis blocking doses of coumarin derivatives. Br J Haematol 9: 506-512.
9. Xi M, Béguin S, Hemker HC (1989) The relative importance of the factors II, VII, IX and X for the prothrombinase activity in plasma of orally anticoagulated patients. Thromb Haemost 62: 788-791.
10. Bauer KA, Broekmans AW, Bertina RM, Conard J, Horellou MH, et al. (1988) Hemostatic enzyme generation in the blood of patients with hereditary protein C deficiency. Blood 71: 1418-1426.
11. D'Angelo A, Valle PD, Crippa L, Fattorini A, Pattarini E, et al. (2002) Relationship between international normalized ratio values, vitamin K-dependent clotting factor levels and in vivo prothrombin activation during the early and steady phases of oral anticoagulant treatment. Haematologica 87: 1074-1080.
12. Dahm M, Lotz J, Hafner G, Oelert H, Prellwitz W (1998) Value of molecular markers for administration of anticoagulant therapy after heart valve replacement. Z Kardiol 87: 42-45.
13. Marlar RA, Kleiss AJ, Griffin JH (1981) Human protein C: Inactivation of factor V and VIII in plasma by the activated molecule. Ann NY Acad Sci 370: 303-310.
14. Estellés A, Garcia-Plaza I, Dasí A, Aznar J, Duart M, et al. (1984) Severe inherited "homozygous" protein C deficiency in a newborn infant. Thromb Haemost 52: 53-56.
15. Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wideman C (1981) Deficiency of protein C in congenital thrombotic disease. J Clin Invest 68: 1370-1373.
16. McGehee WG, Klotz TA, Epstein DJ, Rapaport SI (1984) Coumarin necrosis associated with hereditary protein C deficiency. Ann Intern Med 101: 59-60.
17. Viganò S, Mannucci PM, Solinas S, Bottasso B, Mariani G (1984) Decrease in protein C antigen and formation of an abnormal protein soon after starting oral anticoagulant therapy. Br J Haematol 57: 213-220.
18. Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, et al. (1997) Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. Ann Intern Med 126: 133-136.
19. de Fouw NJ, Haverkate F, Bertina RM, Koopman J, van Wijngaarden A, et al. (1986) The cofactor role of protein S in the acceleration of whole blood clot lysis by activated protein C in vitro. Blood 67: 1189-1192.
20. Takahashi H, Tatewaki W, Wada K, Shibata A (1989) Plasma protein S in disseminated intravascular coagulation, liver disease, collagen disease, diabetes mellitus, and under oral anticoagulant therapy. Clin Chim Acta 182: 195-208.
21. Zöller B, Berntsdotter A, García de Frutos P, Dahlbäck B (1995) Resistance to activated protein C as an additional genetic risk factor in hereditary deficiency of protein S. Blood 85: 3518-3523.
22. Broekmans AW, Veltkamp JJ, Bertina RM (1983) Congenital protein C deficiency and venous thromboembolism. A study of three Dutch families. N Engl J Med 309: 340-344.
23. Loeliger EA, Hensen A, Mattern MJ, Hemker HC (1963) Behaviour of factors II, VII, IX, and X in bleeding complications during long-term treatment with coumarin. Thromb Diath Haemorrh 9: 74-89.