LECTURE
ΔΙΑΛΕΞΗ

Optimal duration of anticoagulation therapy after venous thromboembolism

The duration of anticoagulation therapy after venous thromboembolism has been the subject of controversial suggestions. After short review of the latest trials, the results of our own studies are presented. It is suggested that in order to better adjust the duration of anticoagulation after venous thromboembolism we have to take into account the triggering event, the location of the thrombus and the presence of thrombophilic abnormalities. In general, longer than three months duration is indicated.

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Η άριστη διάρκεια της αντιπηκτικής αγωγής μετά από φλεβική θρομβοεμβολή

Περίληψη στο τέλος του άρθρου

Key words

Cancer
Hemorrhage
Oral anticoagulation
Recurrence
Venous thrombosis

1. INTRODUCTION

Reduction of the risk of hemorrhage during anticoagulant therapy can be achieved in several ways. Limitation of the treatment to indications where the benefit has been strictly proven, balancing the intensity at a target with minimal recurrences and hemorrhages, adequate monitoring and education of the patient are important factors in this context. The monitoring can be improved by using centralized anticoagulation clinics, computer assisted adjustment of dose and also by self-testing. Last but not least, the duration of anticoagulant therapy needs optimization. This is of great interest in patients with venous thromboembolism, since recurrent events are rarely fatal or crippling, as opposed to the events that can be expected on the arterial side, where life-long therapy is common.

2. PREVIOUS TRIALS

When does the impact of major hemorrhages becomes more severe than the effect of recurrent venous thromboembolism? Four randomized trials between 1972 and 1987 gave results that were interpreted in a way that the duration was progressively shortened form 3–6 months down to 3–6 weeks.[1,4] This was based on studies with inadequate power and a large type II error.

The Research Committee of the British Thoracic Society demonstrated for the first time in 1992 that a difference existed between 4 weeks and 3 months (P=0.04) and the 12 months rate of recurrence.[5] The risk of recurrence also appeared to be lower among patients with a temporary risk factor for thrombosis.

3. OWN STUDIES

In the even larger DURAC I-trial with its 897 patients included after the first episode of venous thromboembolism and randomized to 6 weeks or 6 months with mainly warfarin, the odds ratio for recurrence was 2.1 in the 6-week group after a 2 year follow-up.[6] There was not any difference in major hemorrhages or deaths

between the groups. Unfortunately, the risk of recurrence continued to be about 4–5% per year after the cessation of anticoagulation, as shown by Prandoni et al.[7] In the DURAC material, we have followed the patients for more than 6 years, and this pattern did not change appreciably during that period.[8] Venous thromboembolism is therefore to be considered a chronic disease, but does that mean that the patient requires secondary prophylaxis for ever?

The DURAC II-trial is the only one so far exclusively with patients after a second event of venous thromboembolism.[9] Here we compared 6 months with an indefinite duration of anticoagulation. After a 4 year follow-up we showed an obvious disadvantage for the 6-month group regarding recurrences during 4 years (relative risk 8.0, $P<0.001$) and as a matter of fact, not a single patient who continued anticoagulation per protocol had a recurrence. The price paid was a trend to more major hemorrhages (relative risk in the 6 month group 0.3, $P=0.084$). A further analysis of the cost and importance of these hemorrhages compared to that of thromboembolic recurrences gives a clearer picture to the disadvantage of long-term anticoagulation. On the other hand, 6 months appear to be insufficient for these patients. As shown by Prandoni et al, ipsilateral recurrences convey a high risk of development of the post-thrombotic syndrome.[7] Thus, we need to provide a longer, but also safer, secondary prophylaxis to these patients.

3. SUBGROUPS WITH HIGH RISK OF RECURRENCE

The patient population in DURAC I and II was a mixture of cases with distal and proximal thrombosis as well as symptomatic, objectively verified pulmonary embolism. Furthermore, patients with idiopathic thromboembolism or with permanent or temporary triggering factors were included. The size of the material in DURAC I has allowed for subgroup analysis, which demonstrated that the serious implications of an idiopathic thrombosis (or with a permanent risk factor) are of the same magnitude as those of a proximal deep vein thrombosis or symptomatic pulmonary embolism, with a recurrence rate of 4% per year over 6 years.[8] The combination of the two is of course even worse with 5% recurrences per year over 6 years. The absence of these risk factors is associated with such a low risk of recurrence, that only 6 weeks of secondary prophylaxis is justified.

The group of patients with idiopathic venous thromboembolism has been specifically addressed in two trials with warfarin of different durations. In the Canadian LAFIT trial 162 patients were randomized to 3 or 27 months of therapy,[10] and the long-term anticoagulation group enjoyed, much like in DURAC II, an obvious protective effect (hazard ratio=0.05), but unfortunately was associated with a trend to more hemorrhages (hazard ratio 4.0; $P=0.09$). The follow-up will be prolonged in order to investigate what happens after discontinuation of 27 months of anticoagulation. In the Italian WODIT trial 225 patients, randomized to 3 or 12 months of secondary prophylaxis, completed 2 years in the study, but without any apparent difference in the risk of recurrence.[11] The 18% power of the study is, however, a limitation to the conclusion that no difference would exist.

A recent meta-analysis of trials, where patients were randomized at the time of the index event to two durations of anti-vitamin K therapy, showed that 12–24 weeks is better than 3–6 weeks with a relative risk of recurrence of 0.60 ($P<0.001$) and no difference regarding the risk of hemorrhage.[12]

4. BIOCHEMICAL RISK FACTORS

The presence of biochemical risk factors that result in a state of thrombophilia with a significantly increased risk of recurrence are deficiency of antithrombin, protein C, or protein S, presence of cardiolipin antibodies, a lupus anticoagulant, homocysteinemia and possibly increased level of factor VIII, factor, XI, factor IX and other procoagulant proteins. For patients with congenital antithrombin deficiency the risk is among the highest and long-term anticoagulation is often considered. For patients with deficiency of protein C or protein S the annual risk of recurrence is approximately 10%,[13] and it is of the same magnitude for those with cardiolipin antibodies.[14] The latter have, however, in addition an increased risk of fatal thromboembolic arterial as well as venous events after discontinuation of anticoagulation.[14] Patients with combinations of defects[15] or with homozygosity for deficiency of protein C, protein S or the factor V-Leiden mutation with APC-resistance have even higher risks of recurrence. Although life-long anticoagulation would be a tempting solution, it cannot be generalized to this population. Some patients have poor

compliance or a life style, which is incompatible with such therapy. Thus, after the first 6 months it is recommended to reevaluate the therapy and take into account the risk of hemorrhage versus the risk of recurrence, and then repeat this procedure annually.[16]

There is now evidence from several studies that for the thrombophilic defects factor V mutation[10,15,17,18] or prothrombin G20210A-mutation[17,19] in heterozygous form influence the risk of recurrence so little –if at all– so that the duration of anticoagulation should not be adjusted according to any of those results.

The mutation, which in its homozygous form results in thermolabile methylenetetrahydrofolate reductase, is the most common cause for hyperhomocysteinemia, but the correlation between this mutation and risk of thromboembolism is much poorer than of the phenotype hyperhomocysteinemia and thromboembolism. The latter combination may, however, be better treated with vitamins than with vitamin K antagonists.

5. THROMBOSIS AND CANCER

The association between thrombosis and cancer was already reported by A. Trousseau in 1872.[20] More recently two large studies, entirely based on registry data, showed that there is an increased incidence of cancer, of at least 3 times the expected rate, during the first year after a thrombotic event but that the risk remains slightly elevated for up to 10 years.[21,22] In the prolongation of the DURAC I-trial we prospectively followed the patients, who had not had cancer diagnosed before the thrombosis, and there was an annual question put to the patient about occurrence of a new cancer. We supplemented these data by running our patient material against the Swedish Cancer Registry. Our results confirm the two above mentioned trials. However, we also offered the patients some good news in as much as the 6 month anticoagulation group attained a cancer incidence identical to the one expected from the national population after the first two years. In other words, the accumulated incidence of cancer at 6 years after the thrombosis was 10.3% in the 6 month-group versus 15.8% in the 6 week-group.[23] Since the trial was not originally designed to answer questions regarding the incidence of cancer, the results need to be interpreted with some caution. Still, the results give another dimension to the ongoing discussion regarding duration of anticoagulation and provide additional support for the 6 months in most of the cases.

6. CONCLUSION

In conclusion, we have now got the tools to better adjust the duration of anticoagulation after venous thromboembolism according to individual situations, taking into account the triggering event, the location of the thrombus and the presence of thrombophilic abnormalities. Further research is being directed towards safer secondary prophylaxis, examining low-intensity vitamin K antagonism, oral thrombin inhibitors and factor Xa inhibitors. If the expectations on these entities are realized, the recommendations for optimal duration of therapy will again be subject to change-for even longer.

ΠΕΡΙΛΗΨΗ

Η άριστη διάρκεια της αντιπηκτικής αγωγής μετά από φλεβική θρομβοεμβολή

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Η ενδεικνυόμενη διάρκεια της αντιπηκτικής αγωγής μετά από φλεβική θρόμβωση αποτελεί αντικείμενο αντικρουόμενων απόψεων. Παρουσιάζονται ευρήματα μετά από εφαρμογή αγωγής διαφόρου διαρκείας και οι προσωπικές μελέτες του συγγραφέα. Υποστηρίζεται ότι, προκειμένου να ρυθμιστεί η άριστη διάρκεια της αντιπηκτικής αγωγής, πρέπει να λαμβάνεται υπόψη ο αιτιολογικός παράγοντας της φλεβικής θρόμβωσης σε συνδυασμό με την εντόπιση του θρόμβου, την ύπαρξη θρομβοφιλίας ή άλλων ειδικών καταστάσεων. Γενικά ενδείκνυται διάρκεια άνω των τριών μηνών θεραπείας.

Λέξεις ευρετηρίου: Αιμορραγία, Αντιπηκτικά από το στόμα, Καρκίνος, Υποτροπή, Φλεβική θρόμβωση

References

1. O'SULLIVAN EF. Duration of anticoagulant therapy in venous thromboembolism. *Med J Aust* 1972, 2:1104–1107
2. HOLMGREN K, ANDERSSON G, FAGRELL B, JOHNSSON H, LJUNGBERG B, NILSSON E ET AL. 1 month versus 6 months therapy with oral anticoagulants after symptomatic deep vein thrombosis. *Acta Med Scand* 1985, 218:279–284
3. SCHULMAN S, LOCKNER D, JUHLIN-DANNFELT A. The duration of oral anticoagulation after deep vein thrombosis-a randomized study. *Acta Med Scand* 1985, 217:547–552
4. FENNERTY AG, DOLBEN J, THOMAS P, BACKHOUSE G, BENTLEY DP, CAMPBELL IA ET AL. A comparison of 3 and 6 weeks' anticoagulation in the treatment of venous thromboembolism. *Clin Lab Haematol* 1987, 9:17–21
5. RESEARCH COMMITTEE OF THE BRITISH THORACIC SOCIETY. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. *Lancet* 1992, 340:873–876
6. SCHULMAN S, RHEDIN A-S, LINDMARKER P, CARLSSON A, LARFARS G, NICOL P ET AL. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995, 332:1661–1665
7. PRANDONI P, LENSING AWA, COGO A, CUPPINI S, VILLALTA S, CARTA M ET AL. The long-term clinical cause of acute deep venous thrombosis. *Ann Int Med* 1996, 125:1–7
8. SCHULMAN S AND THE DURATION OF ANTICOAGULATION STUDY GROUP. The effect of the duration of anticoagulation and other risk factors on the recurrence of venous thromboembolism. *Wien Med Wschr* 1999, 149:66–69
9. SCHULMAN S, GRANQVIST S, HOLMSTROM M, CARLSSON A, LINDMARKER P, NICOL P ET AL. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1997, 336:393–398
10. KEARON C, GENT M, HIRSH J, WEITZ J, KOVACS MJ, ANDERSON DR ET AL. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999, 340:901–906
11. AGNELLI G, PRANDONI P, SANTAMARIA MG, BAGATELLA P, ASCANI A, BAZZAN M ET AL. Three months compared with one year of oral anticoagulant treatment after a first idiopathic deep vein thrombosis: The Warfarin Optimal Duration Italian Trial (WODIT). *Thromb Haemost* 1999, 82(Suppl):684–685 (Abstract)
12. PINÉDE L, DUHAUT P, CUCHERAT M, NINET J, PASQUIER J, BOISSEL JP. Comparison of long versus short duration of anticoagulant therapy after a first episode of venous thromboembolism. A meta-analysis of randomised, controlled trials. *J Intern Med* 2000 (In press)
13. VAN DEN BELT AGM, SANSON BJ, SIMIONI P ET AL. Recurrence of venous thromboembolism in patients with familial thrombophilia. *Arch Intern Med* 1997, 157:2227–2232
14. SCHULMAN S, SVENUNGSSON E, GRANQVIST S, THE DURATION OF ANTICOAGULATION TRIAL STUDY GROUP. The predictive value of anticardiolipin antibodies in patients with venous thromboembolism. *Am J Med* 1998, 104:332–338
15. MARGAGLIONE M, DANDREA G, COLAIZZO D, CAPUCCI G, DEL POPOLO A, BRANCACCIO V ET AL. Coexistence of factor V Leiden and factor II A20210 mutations and recurrent venous thromboembolism. *Thromb Haemost* 1999, 82:1583–1587
16. LANE DA, MANNUCCI PM, BAUER KA ET AL. Inherited thrombophilia: Part 2. *Thromb Haemost* 1996, 76:824–834
17. LINDMARKER P, SCHULMAN S, STEN-LINDER M, WIMAN B, EGBERG N, JOHNSSON H AND THE DURAC TRIAL STUDY GROUP. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. *Thromb Haemost* 1999, 81: 684–689
18. DE STEFANO V, MARTINELLI I, MANNUCCI PM, PACIARONI K, CHIUSOLO P, CASORELLI I ET AL. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrothrombin mutation. *N Engl J Med* 1999, 341: 801–806
19. EICHINGER S, MINAR E, HIRSCHL M, BIALONCZYK C, STAIN M, MANNHALTER C ET AL. The risk of early recurrent venous thromoembolism after oral anticoagulant therapy in patients with the G20210A transition in the prothrombin gene. *Thromb Haemost* 1999, 81: 14–17
20. PHLEGMASIA ALBA DOLENS. In: Trousseau A (ed) *Lectures on clinical medicine, delivered at Hotel-Dieu*, Paris, France. Cormack JR, trans. London, New Sydenham Society, 1872:281–295
21. BARON JA, GRIDLEY G, WEIDERPASS E, NYREN O, LINET M. Venous thromboembolism and cancer. *Lancet* 1998, 351:1077–1080
22. SORENSEN HT, MELLEMKJAER L, STEFFENSEN FH, OLSEN JH, NIELSEN GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med* 1998, 338:1169–1173
23. SCHULMAN S, LINDMARKER P FOR THE DURATION OF ANTICOAGULATION TRIAL. Incidence of cancer after prophylaxis with warfarin against recurrent venous thromboembolism. *N Engl J Med* 2000, 342: 1953–1958

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