Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.Thromb Haemost 2000; 84: 918.
4. Oger E, Scarabin PY. Assessment of the risk for venous thromboembolism among users of hormone replacement therapy. Drugs Aging 1999; 14: 55-61.
5. Hulley S, Crady C, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E for the heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998; 280: 605-13.
6. Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal Estrogen/Progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. Arterioscler Thromb Vasc Biol 1997; 17: 3071-8.
7. Van Baal MW, Emeis JJ, van der Mooren MJ, Kessel H, Kenemans P, Stehouwer CDA. Impaired procoagulant-anticoagulant balance during hormone replacement therapy? A randomized, placebo-controlled 12-week study. Thromb Haemost 2000; 83: 29-34.
8. Caine YG, Bauer KA, Barzegar S, ten Cate H, Sacks FM, Walsh BW, Schiff I, Rosenberg RD. Coagulation activation following estrogen administration to postmenopausal women. Thromb Haemost 1992; 68: 392-5.
9. The Writing group for the clotting factors study. Effects on haemostasis of hormone replacement therapy with transdermal estradiol and oral sequential medroxyprogesterone acetate: a 1-year, double-blind, placebo-controlled study. Thromb Haemost 1996; 75: 476-80.

Received January 22, 2001 Accepted after revision March 12, 2001

Thromb Haemost 2001; 86: 714–5

No Increased Risk of Venous Thrombosis in Women Taking Tranexamic Acid

Dear Sir,

Antifibrinolytic treatment with tranexamic acid (TA) has been used clinically since the 1960s in a variety of conditions associated with excessive bleeding (1-3) and is an effective treatment for heavy menstrual bleeding, menorrhagia (4, 5). More than 1% of Swedish women of fertile age use TA for the treatment of heavy menstrual bleeding (6, 7). The potential of an increased risk of thrombosis in women taking TA has been a matter for discussion since the introduction of the drug 30 years ago. Isolated cases of thromboembolic disease in women have in fact been reported in association with TA treatment for heavy menstrual bleeding (4, 5). In a case control study we have estimated the prevalence of TA usage during the month prior to the thromboembolic event and compared this prevalence with that in a control group recruited from the general population.

The present investigation was an open, retrospective, case-control study of female patients with diagnosed thrombosis registered at the Department for Coagulation Disorders at Malmö University Hospital (DCDMUH). The patients were interviewed regarding their intake of TA and other medication, and regarding other risk factors in the month preceding their thromboembolic event. The control women were interviewed regarding their intake of TA and other medication during the month preceding the interview. The size of the patient group was determined by the number of women of fertile age who had been treated for thrombosis and were registered at DCDMUH. It has been calculated that the consumption of TA for menorrhagia in Sweden corresponds to a regular use, at the recommended dose for 13 menstrual periods a year, by approximately 15,000 women (6, 7). In 1996, the total population of women aged 18-49 was 1,777,108 (6). This means that out of 1000 women with thromboembolic disease it could be expected that at least 8 women would have used tranexamic acid. With 450 women in the patient group and 1500 women in the control group, it would be possible to discover a 2-3 times higher usage of tranexamic acid in the patient group at the 5% significance level.

Correspondence to: Erik Berntorp, MD, PhD, Department for Coagulation Disorders, Malmö University Hospital, SE-205 02 Malmö, Sweden – Tel.: +46 40 332392, Fax +46 40 336255, E-mail: erik.berntorp@medforsk.mas.lu.se

The thrombosis register comprised 899 women born between 1950 and 1981 (15-49 years of age) who had been referred to DCDMUH for a coagulation check-up during the years 1994-1999 due to venous thromboembolic disease verified by radiological methods, e.g. phlebography and/or CT scan, isotope pulmonary scanning or ultrasound. Completed interviews could be obtained from 662 of the 858 women. The control women were matched according to age and geographical area (postal code). One thousand five hundred and six control women were interviewed. The main results from the study are presented in Tab1e 1. The results show that the TA usage in thrombosis women was not higher than in the control women. On the contrary the odds ratio associated with TA appeared to be marginally reduced ($p = 0.04$). The use of oral contraceptives was significantly more common in the patients than in the control women ($p < 0.0001$). The odds ratio associated with oral contraceptives was increased two to three times.

Table 1 The usage of tranexamic acid (TA), oral contraceptives (OC), and injected contraceptives (IC) in women with thrombosis and in matched control women. Total group percentages are given in parentheses

	Total group N	TA n	OC n	IC n
Women with thrombosis	662	15 (2%)	292 (44%)	21 (3%)
Control women	1506	61 (4%)	372 (25%)	58 (5%)
Odds ratio		0.55	2.41	0.82
95% CI		0.31-0.97	1.98-2.92	0.49-1.36
P-value		0.04	<0.0001	N.S.

N. S. = not significant

Six of the 15 women with thrombosis in association with TA were not exposed to any apparent risk factor for thrombosis. Three of the 15 were on oral contraceptives, whereas the six remaining women had combinations of TA and surgical operations, plaster casts or prolonged air travelling (more than 8 h at sedentary).

In conclusion, this study demonstrates that the use of TA was not higher in women having had a thrombosis than in carefully matched control women. Thus there is no increased risk of thrombosis associated with intake of TA in this clinical setting. This stands in contrast to what has been written in several recent reviews such as the recent RCOG Guidelines for the initial treatment of menorrhagia (4, 5). In these guidelines is stated that "the main reported adverse effect of tranexamic acid is thromboembolism". Such an unfounded statement constitutes a deterrent to the use of TA and will lead to many patients being deprived of the effective treatment that TA constitutes.

Erik Berntorp, Christina Follrud, Stefan Lethagen
Department for Coagulation Disorders, Lund University, Malmö University Hospital, Malmö, Sweden

References

1. Ogston D. Antifibrinolytic drugs; chemistry, pharmacology and clinical usage. John Wiley & Sons 1984.
2. Reynolds JEF (ed). Martindale; The extra pharmacopoeia. London: Royal Pharmaceutical Society 1996.
3. Dunn CJ, Goa KL. Tranexamic acid. A review of its use in surgery and other indications. Drugs 1999; 57 (6): 1005-32.
4. Royal College of Obstetricians and Gynaecologists. The initial management of menorrhagia. Evidence-based clinical guidelines No. 1. RCOG Press 1998, pp 1-43.
5. Cooke I, Lethaby A, Farquhar C. Antifibrinolytics for heavy menstrual bleeding (Cochrane Review). In: The Cochrane Library, Issue 3, 2000. Oxford: Update Software.
6. Statistisk årsbok för Sverige 2000. Statistiska centralbyrån 2000; 86:59.
7. National Corporation of Pharmacies in Sweden 2000.

Received January 22, 2001 Accepted after resubmission February 27, 2001

Thromb Haemost 2001; 86: 715–6

Reassessment of the Correlation between the von Willebrand Factor Activity, the PFA-100®, and the Bleeding Time in Patients with von Willebrand Disease

Dear Sir,

We read with great interest the letter by Veyradier et al. (1). The authors compared the PFA-100® with the von Willebrand ristocetin cofactor activity (VWFRCo) in patients with von Willebrand disease (VWD) and controls. An excellent correlation was found between the VWFRCo levels and the closure time (CT) measured with both ADP (CT-ADP) ($r = -0.94$) and Epinephrine (CT-EPI) ($r = -0.89$) cartridges. Although these correlations seem powerful, they may be spuriously high because data from both patients and controls were analysed together, which could be statistically faulted (2).

To test this hypothesis we have evaluated to what extent the CT-ADP and the CT-EPI are determined by the VWF activity (VWF:AC) levels in 52 patients with VWD (Table 1). The VWF:AC was measured by an in-house ELISA assay (3). The normal range was established in a group of 20 normal controls (CT-ADP: 61-104 s, CT-EPI: 74-146s). Factors which can influence the CT, such as haematocrit, platelet count, the VWF:AC and the VWF antigen (VWF:Ag) levels were evaluated as independent variables by stepwise regression analysis. In 40/52 patients for whom a bleeding time (BT) was available, a similar analysis was performed using the BT as a dependent variable. CT values were analysed as a continuous variable [by assigning to every infinite CT (> 300s) a fixed value of 300s] and also as an ordinal variable (considering three categories for the CT values: normal, prolonged or infinite).

Three patients (6%) were found to have CT within the normal range. The VWF:AC emerged as the most significant determinant of the total variation of the CT measured with both cartridges, with a bigger effect on the CT-ADP than on the CT-EPI (Table 2). However, the VWF:AC accounted for only 34%, 20% and 35% of the total variation of the CT-ADP, CT-EPI and BT respectively. The small influence of the platelet count (6% of the variance) was only seen with the CT-ADP, reflecting the small number of patients with thrombocytopaenia included in the study.

In conclusion, although the VWF:AC had a significant influence on the CT, in patients with VWD we found a much weaker relation between these two parameters than those reported by Veyradier et al. (1) who studied a mixed population of patients and controls. Our findings reflect the fact that this relation was studied strictly in patients with

Correspondence to: Prof. Christine Lee, Haemophilia Centre and Haemostasis Unit, Royal Free and University College Medical School, Pond Street, London NW3 2QH, UK – Tel.: 0207 830 2068; Fax: 0207 830 2178; E-mail: lee@rfh.nthames.nhs.uk

Table 1 Laboratory characteristics of patients with VWD*

Type VWD	Number patients	CT-ADP sec	CT-EPI sec	BT min	VWF: Ag IU/dl	VWF: AC IU/dl	FVIII:C IU/dl
1	32	198 ± 76	246 ± 64	11 ± 7.4	31 ± 26	21 ± 14	51 ± 31
2A	6	281 ± 29	284 ± 24	16 ± 7.1	22 ± 10	9.6 ± 3.4	36 ± 10
2B	1	300	300	20	41	22	35
2M	12	250 ± 49	265 ± 51	16 ± 7.1	33 ± 17	16 ± 7.6	48.6 ± 11
3	1	300	300	20	4	1	3

* Values are given as arithmetic mean ± SD