Thrombosis and Haemostasis – © F. K. Schattauer Verlagsgesellschaft mbH (Stuttgart) 60 (3) 506–507 (1988)

A Study of the Effect of Ethamsylate (Dicynene) on the Bleeding Time, von Willebrand Factor Level and Fibrinolysis in Patients with von Willebrand's Disease

Ronald A. Hutton, Mary Hales, and Peter B. A. Kernoff

From the Katharine Dormandy Haemophilia Centre and Haemostasis Unit, Academic Department of Haematology, Royal Free Hospital, London, England

Key words

Bleeding time – von Willebrand factor – Fibrinolysis

Summary

Nine patients with clinically moderate or severe Type I von Willebrand's disease were treated for 2 weeks with ethamsylate (2 g/day in four equal doses) and with a matched placebo in a randomised double-blind trial. Template bleeding time, von Willebrand factor activity (ristocetin co-factor) and antigen, euglobulin lysis time and type I tissue plasminogen activator inhibitor were determined before and at the end of each treatment period. None of these parameters showed any significant change attributable to ethamsylate. Thus, despite the fact that five patients thought subjectively that their bleeding symptoms improved during ethamsylate treatment compared to only one while on placebo, we obtained no evidence that the drug was of benefit to patients with von Willebrand's disease.

Introduction

Ethamsylate (Dicynene, Delandale Laboratories) is a compound with anti-haemorrhagic properties which has been in clinical use for at least 20 years. It was originally thought to act by increasing capillary resistance, thereby shortening the bleeding time (1, 2). More recently, evidence has been accumulating that ethamsylate may inhibit the release from endothelial cells of inhibitory prostaglandins such as PGI_2 (3, 4). Although the precise mechanism of action has not been determined, ethamsylate continues to be used empirically as a haemostatic agent (5–7). We have recently shown (8) that in normal subjects, prolongation of the template bleeding time (TBT) by aspirin (600 mg orally) can be significantly blocked by ethamsylate. In the present study, we investigate the effect of ethamsylate in patients with Type I von Willebrand's disease (vWD), in whom a defect in platelet adhesion to the subendothelium results from decreased production of functional von Willebrand factor (vWF) by endothelial cells. The action of ethamsylate on the level of von Willebrand factor and on fibrinolysis were also monitored.

Patients, Materials, and Methods

Patients

Nine patients (6 male, 3 female, aged 18–48 years, mean 32.7 years) with moderate (7 patients) or severe (2 patients) Type I vWD, from whom written informed consent was obtained, were entered into a randomized, double-blind cross-over study consisting of two 2-weekly periods separated by a wash-out period of at least 4 weeks. Minimisation was used to avoid bias due to age, sex, severity of disease or baseline TBT.

In one period, the patients received ethamsylate in the conventional dose (2 g daily divided into 4 × 500 mg tablets taken approximately 6-hourly) for 2 weeks. In the other period, the patients received placebo under an identical regime. Patients were requested not to take any drugs known to influence haemostasis (other than those required for the treatment of their vWD) during the course of the study and to refrain from ingesting alcohol for at least 72 hours prior to each test. During the study, one patient received several doses of factor VIII concentrate and another received two doses of tranexamic acid but in neither case was treatment given within 72 hours of testing. At the conclusion of the study and prior to breaking the code, the patients were asked if they felt that their bleeding episodes had been modified during the trial.

Tests Performed

Individual patients were tested at the same time of the day on each occasion, either in the morning after a light breakfast or in the late afternoon at least 2 hours after their midday meal. Immediately prior to the start of each treatment period and again on the last day of each treatment period, a TBT (9) was performed, always by the same person, using the Simplate II device (General Diagnostics). Also, a sample of venous blood was collected by venepuncture into EDTA for a full blood count and into 1/9th volume of 3.2% tri-sodium citrate dihydrate for the measurement of von Willebrand factor antigen (vWF:ag) (10), ristocetin co-factor (RiCof) (11), euglobulin lysis time (ELT) (12) and the fast-acting inhibitor of tissue plasminogen activator (tPAI) (13).

With each bleeding time, the duration of bleeding was noted and the amount of blood lost was determined by spectrophotometry after eluting the blood from the filter paper into ammoniated water (8) and expressed in mg of haemoglobin, corrected for the patients haemoglobin concentration.

The results, expressed as medians and ranges, were analysed statistically using the paired Wilcoxon rank sum test.

Table 1 Effects of ethamsylate or placebo in von Willebrand's disease

Test performed	Placebo Pre	Placebo Post	Ethamsylate Pre	Ethamsylate Post
Hb (g/dl)	14.2 (11.0–18.3)	14.5 (11.0–18.0)	14.6 (11.2–17.3)	14.4 (11.2–16.6)
TBT (min)	17.5 (9.75–>40)	16.0* (7.0–>40)	15.0 (7.25–>40)	21.0 (6.25–>40)
Blood loss (mg Hb)	81.9 (9.3–261.9)	47.0 (2.0–406.6)	57.6 (2.1–214.3)	112.3 (4.2–419.9)
RiCof (u/dl)	8 (1–44)	8 (2–50)	4.5 (1.5–40)	10 (2–37)
vWF:ag (u/dl)	31 (<5–42)	24 (<5–50)	20 (<5–65)	29 (<5–52)
ELT (min)	195 (90–240)	210 (150–240)	210 (90–225)	195 (60–240)
tPAI (au/ml)	13 (1–24)	12 (0–21)	7 (0–28)	10 (0–34)

Results expressed as medians (n = 9) with ranges in parentheses. * p = <0.05. All other results are not significant.

Correspondence to: Dr. R. A. Hutton, Haemophilia Centre, Royal Free Hospital, London NW3 2QG, England

Results

Table 1 shows that Dicynene had no significant effect on any of the parameters measured. During the placebo phase, there was a slight decrease in the bleeding time, which just reached conventional statistical significance ($p \leq 0.05$).

Six of the nine patients stated that either the number or the duration of bleeding episodes (chiefly due to epistaxis and minor cuts) had improved during one or other of the trial periods (3 for stage 1 and 3 for stage 2). After breaking the code, the improvement occurred while on ethamsylate in five out of six cases. The three remaining patients expressed no preference.

Discussion

Because of the hazards of using blood products, there is current interest in alternative therapies for the treatment of minor bleeds in patients with mild bleeding disorders. Amongst the possible alternatives, ethamsylate is attractive since it can be administered orally, is free of any important adverse effects and has proven benefit in a number of clinical conditions associated with excess bleeding (5–8).

In the present study, 6/9 patients stated that their bleeding tendency improved while on ethamsylate, but this subjective evidence was not supported by the quantitative data gathered. In particular, no shortening of the TBT or fall in the amount of blood emerging from the bleeding time wounds was found after 2 weeks of ethamsylate therapy. The marginal, but just significant fall in TBT during the placebo period was presumably a chance observation. There was no increase in vWF:ag or Ricof during the study, which argues against any generalised action of ethamsylate on the endothelial cells. The ELT and tPAI assay were also unaffected by the drug, which supports our previous conclusion (8) that it does not influence fibrinolysis.

Thus, in this limited study carried out on a small number of patients with Type I vWD, despite the subjective impressions of some patients, there was no hard evidence that ethamsylate improved their haemostatic function. Whether or not ethamsylate might be of use in platelet disorders involving altered prostaglandin metabolism, remains to be established.

Acknowledgements

We wish to thank Dr. E A. Wickham and Mr J. V. Reed formerly of Delandale Laboratories Ltd., for their help in organising and analysing the results of this study and to the Company for financial support.

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Received May 26, 1988 Accepted after revision August 16, 1988