Thrombosis and Haemostasis – © F. K. Schattauer Verlagsgesellschaft mbH (Stuttgart) 58 (4) 1090–1091 (1987)

Effectiveness of a Heated Prothrombin Complex Concentrate in Hemophiliacs with Inhibitors

Dear Sir,

The clinical effectiveness of prothrombin complex concentrates (PCC) in the treatment of hemophiliacs with inhibitor was established by Lusher et al. (1) in a double-blind, randomized cross-over trial. Two commercial PCC (Konyne and Proplex) were significantly more effective than placebo in treating acute hemarthroses of the elbow, knee or ankle joint. Since 1984–1985, PCC have been heated in the attempt to inactivate the human immunodeficiency virus (HIV). Whether or not heating has decreased the effectiveness of PCC by destroying the putative moieties that by-pass factor VIII activity in the intrinsic coagulation system, is still a matter of uncertainty. A randomized double blind study comparing heated and unheated PCC is not feasible, because unheated PCC are no longer licensed since the demonstration that HIV is highly sensitive to thermal inactivation. Hence, the only realistic approach to assess whether or not heated PCC are still effective is that of historically comparing the results obtained for these PCC with those obtained by Lusher et al.

Table 1 Effect of Konyne HT on joint mobility

Patient	Site of hemarthroses	Changes in joint mobility before Konyne HT*	Changes in joint mobility after Konyne HT**
1	elbow, left	−50	30
	knee, left	−40	30
	knee, left	−10	0
	elbow, left	−60	30
2	knee, right	−40	30
	ankle, right	−20	10
	elbow, right	−110	80
	knee, left	−70	−20
	knee, left	−90	40
3	elbow, left	−70	30
	knee, left	−15	5
	elbow, left	−50	30
	elbow, left	−40	30
4	knee, right	−80	40
	knee, right	−60	0
	elbow, right	−150	40
	ankle, right	−20	0
5	knee, right	−55	−10
	elbow, right	−50	30
	knee, left	−25	20
6	knee, right	−35	−10
	elbow, left	−20	20
7	elbow, right	−100	40
	ankle, right	−20	0
	knee, right	−80	40
8	elbow, right	−105	35
	knee, right	−80	−10
	ankle, right	−20	10
	elbow, right	−105	40
9	knee, right	−50	30
	knee, left	−60	50

* Differences in values of joint mobility (expressed in degrees) between baseline values taken at a bleeding-free time and values taken before infusion of Konyne HT. Only patients with hemarthroses and a reduction of joint mobility of at least 10 degrees were evaluated.

** Differences in joint mobility between values taken 6 hours after and immediately before Konyne HT. Treatment was judged effective when there was an increase of joint mobility of at least 10 degrees.

We elected to do such a study in hemophiliacs with inhibitors treated by Konyne-HT (Cutter Biologicals, Berkeley, California), the PCC heated in a lyophilized state that replaced unheated Konyne. We adopted the same criteria as Lusher et al. for patient entry into the study and we gave to each patient the same dose of Konyne HT in a single infusion (75 IU/kg) after the same type of acute hemarthroses (elbow, knee and ankle). Since our study was open and without control group, we did not use the subjective criteria used by Lusher et al. for effectiveness evaluation (pain control and patient perceived effectiveness) and we restricted ourselves to the more objective criterion of measuring the degree of changes in joint mobility after PCC. We included in the evaluation of effectiveness only those hemarthroses that did reduce, by at least 10 degree, the joint mobility taken in each patient before the trial, when the target joints were free from bleeding.

Patients with hemophilia A and factor VIII inhibitors who needed treatment at home or in hospital for acute hemarthroses were enrolled in the study provided that they had an inhibitor titer greater than 2 Bethesda units. When the patient was treated in hospital, joint mobility was measured by the same physician throughout the study; when treatment was given at home, it was measured with a goniometer by the patient or by one of his associates, provided they had acquired proficiency with the procedure during specific training at the hemophilia center. Treatment was judged effective when, at 6 hour post-infusion, there was an improvement in joint mobility of 10 degree or more, in accordance with the endpoint of Lusher et al. When the first infusion was not effective in arresting bleeding, additional treatment with Konyne-HT or other therapy was given as judged necessary by the physician in charge for in-hospital infusions or by the patients or their associates for home infusions. However, evaluation of effectiveness of additional treatments was not included in this study. Of 16 patients considered elegible for entry into the study and evaluated in terms of baseline joint mobility, 9 bled into the target joints during the study period. They had a median age of 24 years (range 9–56) and their median anti-VIII:C titer was 15 (6–165) Bethesda unit. There were 35 hemarthroses in the target joints. However, only 31 hemarthroses were characterized by restriction in joint mobility of at least 10 degrees in comparison with baseline bleeding-free mobility. The Table shows that after Konyne-HT there was an improvement of mobility of at least 10 degrees in 22 hemarthroses (70%) whereas in the remaining 9 there was no change or deterioration. These results compare favourably with the results obtained by Lusher et al., who found an improvement of joint mobility in 34% of hemarthroses treated with unheated Konyne. Open and uncontrolled studies such as this, however, tend to give more favourable results than controlled double-blind studies. Moreover, there are other potential pitfalls inherent to our study design, such as the difficulty for the patients to use the goniometer, the awareness of the patients that there is hardly an alternative to heated PCC and the spontaneous recovery of hemarthroses.

These limitations notwithstanding, our findings indicate that the clinical efficacy of this heated PCC in controlling joint hemorrhages in patients with hemophilia A who have inhibitors is at least as good as that of the unheated product.

P. M. Mannucci
D. Mari
F. I. Pareti
A. Bianchi Bonomi
Hemophilia and Thrombosis Center
University of Milano, Italy

References

1 Lusher J M, Shapiro S S, Palascak J E, Rao A V, Levine P H, Blatt M P and the Hemophilia Study group. Efficacy of prothrombin-complex concentrates in hemophiliacs with antibodies to factor VIII. A multicenter therapeutic trial. N Engl J Med 1980; 303: 421–5.

Received May 13, 1987 Accepted after revision July 22, 1987