abnormality in the giant platelet syndrome of Bernard-Soulier[18] and also in von Willebrand's disease, in which the abnormality is probably secondary to a deficiency or defect of a plasma protein related to factor VIII—the factor VIII-related protein.[19] In our patient the defective ristocetin platelet aggregation seemed to be due to a plasma defect rather than to a primary platelet abnormality because aggregation was corrected partially or completely by the addition of normal plasma, cryoprecipitate, or a plasma fraction rich in factor VIII-related in protein. On the other hand the level of factor VIII-related protein in the infant's plasma was normal, which suggested that either there was a functional abnormality of this protein or the patient lacked another substance necessary for ristocetin platelet aggregation. This did not seem to be fibrinogen, which, it has been suggested, is a co-factor for ristocetin aggregation,[20] because the thrombin clotting times and fibrinogen levels were normal. The small volumes of blood obtainable from the infant precluded more detailed in-vitro studies, and it is possible that the vitamin E deficiency was directly responsible for the defective platelet ristocetin aggregation or that the deficiency resulted in the synthesis of an abnormal factor VIII-related protein. The normal bleeding time, the lack of family history, and the results of treatment, however, did not suggest that the infant was suffering from von Willebrand's disease.

The role of iron or folate deficiency in the pathogenesis of the patient's haematological status is difficult to assess. It has been suggested that folate deficiency may aggravate haemolysis in vitamin E deficiency,[21] but though the patient's folate status was not certain his marrow was normoblastic, a finding which suggested that he did not have severe folate deficiency. Iron treatment is also thought to aggravate vitamin E deficiency and enhance lipid peroxidation and haemolysis,[22 23] but the child was not on iron treatment when his peroxide lysis tests gave persistently abnormal results. This persisting abnormality, however, was not really surprising because the serum vitamin E levels were not fully corrected with treatment. Though a relation between vitamin E deficiency and the abnormal platelet function was not definitely proved the response of the platelets to vitamin E treatment was striking. This finding suggests a possible relation between vitamin E and ristocetin-induced platelet aggregation which warrants further studies in patients in severe tocopherol-deficient states.

This patient was admitted under the care of Professor O. P. Gray to whom we are indebted for helpful comments and advice. We also thank Dr. J. F. Pennock of the biochemistry department at the University of Liverpool for the vitamin E assays. Mr. J. Lari performed the laparotomy.

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SHORT REPORTS

Effect of ethamsylate and aminocaproic acid on menstrual blood loss in women using intrauterine devices

The effect of ethamsylate and aminocaproic acid (EACA) in reducing menstrual bleeding were studied in women using intrauterine contraceptive devices (IUDs). Ethamsylate is claimed to increase capillary resistance and reduce menorrhagia by counteracting a fall in capillary resistance that occurs in the premenstrual phase.[1 2] EACA is an antifibrinolytic agent which is believed to reduce menstrual blood loss by reducing the increase in endometrial fibrinolytic activity associated with menorrhagia.[3]

Patients, methods, and results

Twenty-five women complaining of excessive menstrual blood loss or volunteering for research while using IUDs were studied during six consecutive periods. The devices used were the Saf-T-Coil, Dalkon shield, Copper 7, and Lippes loop. By random allocation 12 patients received treatment during the third and fourth cycle with ethamsylate and 13 with EACA. One from each group did not complete the trial for personal reasons. A further patient from the EACA group dropped out after experiencing severe headache during treatment. Eleven women in each group completed the study. Blood loss was measured using the alkaline haematin method, which involved extracting iron pigment with 5% NaOH from all sanitary towels used and measuring the optical density of the resulting solution. The accuracy of this method was 97%. "Menstrual calendar" cards were also kept by each patient and all medicine taken was recorded. Ethamsylate was taken as tablets, 500 mg four times a day from the onset of menstruation until bleeding ceased. EACA was taken as a powder dissolved in water, 3 g four times a day from the onset to the end of menstruation.

The results for both groups are summarised in the table. The average menstrual loss of 94·6 ml in cycle 1 and 108·3 ml in cycle 2 in the ethamsylate-treated group did not seem to be influenced by ethamsylate treatment in cycles 3 and 4, while treatment with EACA reduced menstrual loss by almost 50%—a highly significant reduction ($P<0.001$).

Mean (± SD) blood loss (ml) in 11 women treated with ethamsylate and 11 treated with EACA in cycles 3 and 4

Period:	1	2	3	4	5	6	P Values (log values)*
Ethamsylate group ..	94·6 ± 73·6	108·3 ± 91·2	94·3 ± 89·6	100·9 ± 85·4	100·9 ± 85·4	109·5 ± 110·9	0·7
EACA group	132·3 ± 102·3	122·9 ± 91·3	59·8 ± 46·7	54·0 ± 28·7	121·0 ± 117·5	109·4 ± 106·4	0·001

*In view of the skewed distribution of data all results were converted to logarithms before applying Student's *t* test for significance.

Discussion

EACA was clearly effective in reducing menstrual blood loss in women using IUDs. Our results do not support previous claims,[4] based on subjective improvement and a reduction in tampon usage, that ethamsylate reduces menstrual loss. The patients treated by Gaudefroy and Debienne-Wibaux,[4] however, had various gynaecological conditions but were not using IUDs, and they received ethamsylate for five days before the onset of menstruation and during menstruation. Caution must also be expressed about accepting the accuracy of menstrual blood loss based entirely on counting tampons.

Enhanced fibrinolysis in the uterus seems to play a significant part in IUD menorrhagia,[5] and EACA, with its potent antifibrinolytic effect, seems to be a rational and effective way of reducing the excessive menstrual bleeding that occurs with the IUD.

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A Chromosome study of patients with uveitis treated with chlorambucil

A variety of nonmalignant conditions are being treated with immunosuppressive drugs which may have carcinogenic, teratogenic, or mutagenic effects. One way of estimating possible hazards is to monitor the patients for chromosomal damage. We have made chromosome studies of peripheral blood lymphocytes from patients treated with chlorambucil for various forms of uveitis.[1]

Methods and Results

Peripheral blood cultures were set up using a standard method and were ended after 48 hours (72 hours in one case). Cells were stained with Giemsa, but not banded since gaps are difficult to visualize in our standard Giemsa-banded preparations. Whenever possible at least 50 well-spread metaphases from each sample were examined for dicentrics, fragments, simple breaks, and gaps (gaps are non-staining regions in which there is no chromatid displacement). A dicentric chromosome was recorded as two breaks. Ten healthy laboratory personnel served as controls.

Twelve patients were studied and the results, arranged according to total dose of chlorambucil, are presented in the table. The overall breakage frequency in the control group was 1·2% (range 0-4%), including two dicentric chromosomes. Among the cases treated only with chlorambucil, seven had no chromosomal breaks at any time. Four patients had a breakage frequency of between 2% and 3%, and two (cases 9 and 11) each had one dicentric chromosome. The only patient (case 4) also treated with cyclophosphamide had a breakage frequency of 2·8% during treatment. The frequency of gaps in the controls was 0·6% overall, which was contributed by only one person. Among the patients treated with chlorambucil alone gaps (1%-4%) were seen in cells from seven patients. One patient (case 4) had 2·8% gaps in the first sample, and the overall aberration frequency (5·6%) was the highest in the series. One of the controls had a total aberration frequency of 5%. Apart from the dicentric chromosomes most lesions were of chromatid type.

Discussion

Damage, of predominantly chromatid type, is induced in the chromosomes of normal peripheral blood lymphocytes treated with chlorambucil in vitro.[2] There is, however, little information available on in-vivo effects in non-malignant conditions. In a group of patients being treated for systemic lupus erythematosus[3] no chromosomal damage attributable to chlorambucil was observed. A high incidence of gaps together with breaks has been noted in patients with gynaecological tumours who were receiving cyclophosphamide.[4] This observation is relevant to the findings in our patient who received cyclophosphamide.

With the exception of the dicentric chromosomes most aberrations found in the patients and controls were of chromatid type. Using the lymphocyte culture method we have been unable to show chromosome breakage in excess of control values in patients in whom the total dose of chlorambucil varied from 65 to 2940 mg. More chromosome gaps were seen in the lymphocytes of the patients than in those of controls. This finding cannot be regarded as unimportant and probably reflects an effect of the drug. The mechanism by which chlorambucil induces chromosomal lesions is at present unknown.

On balance we do not consider that our findings indicate a high level of chromosome damage to the lymphocytes of the patients

Clinical and Chromosome Data of Patients

Case No.	Age and Sex	Date of Chromosome Study	Lymphocyte Count ($\times 10^9$/l)	Total Dose at Time of Study (mg)	Date Drug Stopped	Total Dose (mg)	Chromosomes			
							No. of Cells Examined	No. of Breaks	No. of Fragments	No. of Gaps
1	46 M.	9 Jan. 75	2·75	2940	21 Feb. 74	2940	50	0	0	2
2	23 M.	20 Aug. 74	0·66	1520	7 Oct. 74	1670	50	0	0	0
		27 Jan. 75	2·61	1670	7 Oct. 74	1670	50	0	0	0
3	27 M.	20 Aug. 74	0·60	1140	3 Oct. 74	1395	0	0	0	0
		17 Dec. 74	1·20	1395	3 Oct. 74	1395	100	2	1	1
4	26 M.	14 Aug. 74	0·36	1120	9 Oct. 74	1260	250	4	3	7†
		16 Jan. 75	1·20	1260	9 Oct. 74	1260	50	0	0	0
5	26 M.	27 Aug. 74	1·04	1060	27 Aug. 74	1200	50	0	0	0
		17 Dec. 74	0 72	1200	22 Oct. 74	1200	50	0	0	2
6	19 F.	27 Aug. 74	1·56	415	28 Jan. 75	1180	50	0	0	1
		28 Jan. 75	1·00	1180	28 Jan. 75	1180	50	1	0	1
7	34 M.	27 Aug. 74	0·55	1160	30 Jun. 74	1160	50	0	0	0
8	38 F.	3 Oct. 74	1·75	1060	3 Sep. 73	1060	50	0	0	2
9	44 M.	24 Oct. 74	2·07	1000	12 Jul. 73	1000	100	2	0	1‡
		16 Jan. 75	1·70	1000	12 Jul. 73	1000	50	0	0	0
10	49 F.	3 Sep. 74	1·02	375	15 Oct. 74	560	2	0	0	0
		15 Oct. 74	0·70	560	15 Oct. 74	560	6	0	0	0
							50*	0	0	1
11	36 M.	22 Aug. 74		365	24 Oct. 73	365	50	0	0	0
		5 Feb. 75	2·24	365	24 Oct. 73	365	100	2	0	0
12	35 M.	11 Feb. 75	2·07	65	On treatment	65	50	0	0	0

* Blood cultures lasted 72 hours.
† Also treated with cyclophosphamide 17 350 mg Nov. 1971-March 1972.
‡ One endoreduplication.