Effects of manufacturing oral contraceptives on blood clotting

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Summary and conclusions

In monitoring the effects of industrial exposure resulting from the pharmaceutical manufacture of oestrogen-progestogen combinations by coagulation studies acceleration of some clotting tests was found. The most pronounced changes were in workers most closely associated with the industrial process. Less pronounced changes were found in women employees not closely concerned with the processing and may have been secondary to the postmenopausal bleeding to which they were prone. A safer work procedure elaborated by the Employment Medical Advisory Service was monitored by clotting studies for over a year but the three most highly exposed subjects showed no substantial improvement.

Introduction

The administration of oestrogen-progestogen oral contraceptives is associated with accelerated blood clotting tests, which is largely due to the oestrogen component of such preparations.¹⁻⁸ The possibility of undesirable effects on blood clotting was raised, therefore, when in 1975 a pharmaceutical manufacturer of oestrogen-progestogen oral contraceptives requested the help of the Government's Employment Medical Advisory Service (EMAS) because of clinical problems among their staff. A group of employees, who had been concerned in processing these hormones, were screened for adverse effects on clotting and monitored sequentially for over a year to see whether a safer work procedure elaborated by the Factory Inspectorate might reduce the adverse effects on blood clotting that the study subsequently disclosed.

Historical outline

A commercial pharmaceutical manufacturer had been preparing increasing amounts of oral contraceptive tablets for 15 years. The first sign of side effects was gynaecomastia in some men employed in a granulation process, and after taking advice the company decided to employ only postmenopausal women in this part of the manufacture and to introduce much

more stringent environmental control. The hormone preparations concerned were 12 brands of tablet made by the normal technique of dry blending, wet granulation using organic solvents, drying, sieving and final dry blending, followed by compression. Active agents include norethisterone, norgestrel, ethinyloestradiol, and mestranol in varying combinations and proportions. Dilution with inert excipients is of the order of one of oestrogen in 3000, and a full-scale batch is 300 kg. The active materials are dissolved in the granulating liquid and added to the mixed excipients. The work, after the initial stage, was carried out using space suits and airlines, and with the co-operation of the EMAS various modifications in procedures were adopted in an attempt to improve operator safety.

Subjects and methods

We studied two groups of subjects. Group A comprised one male inspector and two women employees who were both aged over 50 and had worked most closely with the manufacturing process. These subjects were monitored at intervals of about four to six weeks for one year after the safer working procedure devised by the EMAS was introduced. Group B comprised seven men and nine women who were concerned with the later stages of production, where the exposure to the product was less direct. Two of the women were excluded from the analysis as they were aged under 45 years. Most of the subjects in this group were tested only once. Their results were compared with baseline values obtained in 28 women of similar age participating in a parallel study of hormone replacement treatment for menopausal symptoms (conducted concurrently with but independently of this study).

We took a clinical history and performed a physical examination in all subjects. The following standardised measurements were made on each occasion⁹: prothrombin time; activated partial thromboplastin time (APTT); thrombin time; assays of factors VII and X; platelet aggregation (Chandler's tube); thromboelastography; platelet adhesion; fibrinogen estimation; euglobulin lysis time; fibrin degradation products; full blood count; and platelet count.

Results

CLINICAL FINDINGS

Group A—The two women, who had intermittent vaginal bleeding, had few climacteric symptoms. One had increased smoothness of the skin and the other increased breast size. Physical examination showed no abnormality. The man in this group was diabetic and had gynaecomastia. All subjects were normotensive, with no clinical manifestation of thromboembolic disease.

Group B—Four of the seven women in this group suffered from intermittent vaginal bleeding. Three were postmenopausal and the fourth thought to be menopausal. Two showed some increase in breast size. One of the seven men had mild hypertension.

LABORATORY RESULTS

The unpaired *t* test was used for analysis. The following results were obtained (see table). When the man in group A was compared with the seven men in group B the APTT ($P < 0.001$) and platelet aggregation (Chandler's tube) ($P < 0.025$) were accelerated while factor X ($P < 0.025$) and platelet adhesion ($P < 0.025$) were increased. When, in group A, the two women were compared with the man the following clotting parameters were significantly accelerated or increased: prothrombin time ($P < 0.001$), factor VII ($P < 0.001$), factor X ($P < 0.001$), platelet count ($P < 0.001$), and the *r* ($P < 0.05$)

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and k values ($P < 0.005$) on the thromboelastogram. The APTT ($P < 0.001$) and fibrinogen concentration ($P < 0.001$) were increased.

There was no significant difference in the results of the clotting test between the seven men and seven women in group B. The only differences between the women in group B and the 28 controls in the study of hormone replacement treatment were in the fibrinogen concentration ($P < 0.025$) and platelet count ($P < 0.05$), which were significantly increased in the industrial workers.

When the two women in group A were compared with the seven in group B the following clotting tests were significantly different. The prothrombin time was accelerated ($P < 0.005$), as were factor VII ($P < 0.001$) and factor X ($P < 0.025$). Platelet count ($P < 0.001$) and adhesion ($P < 0.025$) were increased in the two women in group A, whose haemoglobin concentration was significantly reduced ($P < 0.005$). When the two women in group A were compared with the 28 menopausal controls the prothrombin time ($P < 0.001$) and factor VII ($P < 0.001$) were significantly accelerated. The fibrinogen concentration ($P < 0.005$) and platelet count ($P < 0.001$) were also increased and the haemoglobin concentration significantly reduced ($P < 0.005$).

when detected, have been associated with other coagulation changes. The most likely explanation of this rise in platelet count is that it, in addition to the fall in haemoglobin concentration, was partly or wholly secondary to chronic bleeding. Four of the seven women in this group had a history of intermittent vaginal haemorrhage.

The coagulation response of the three employees with a high degree of oestrogen exposure (group A) to the protective measures introduced by the Health and Safety Executive was disappointing. They were followed up at regular intervals for over a year after the introduction of the safety measures, but the coagulation results were equivocal. The APTT tended to be prolonged, but the thromboelastograph r time, which measures some early stages of intrinsic clotting, was accelerated over a similar period. Factor X tended to be reduced, but platelet adhesion tended to increase. Most tests, which were grossly accelerated in this group, showed no correction after protective measures were introduced.

Mean ($\pm$ SD) results of clotting tests in different groups of subjects

	Group A		Group B		Female controls (n = 28)
	Men (n = 1)	Women (n = 2)	Men (n = 7)	Women (n = 7)	
Prothrombin time (s)	13.1 $\pm$ 0.59	11.5 $\pm$ 0.75	12.6 $\pm$ 0.80	12.4 $\pm$ 0.69	12.6 $\pm$ 0.68
Activated partial thromboplastin time (s) ..	38.6 $\pm$ 2.19	43.1 $\pm$ 3.21	42.9 $\pm$ 2.12	42.1 $\pm$ 3.11	
Factor VII (s)	12.7 $\pm$ 0.33	10.6 $\pm$ 0.43	12.8 $\pm$ 0.74	12.4 $\pm$ 1.03	12.2 $\pm$ 0.76
Factor X (s)	14.8 $\pm$ 0.92	13.3 $\pm$ 0.64	13.7 $\pm$ 0.39	14.0 $\pm$ 0.78	
Fibrinogen (g/l)	2.33 $\pm$ 0.35	2.98 $\pm$ 0.44	2.57 $\pm$ 1.05	2.89 $\pm$ 0.40	2.53 $\pm$ 0.40
Thromboelastography:					
r (mm)	11.8 $\pm$ 2.99	14.4 $\pm$ 2.21	16.5 $\pm$ 2.12	13.7 $\pm$ 3.50	14.4 $\pm$ 2.10
k (mm)	5.5 $\pm$ 1.60	8.2 $\pm$ 1.72	8.0 $\pm$ 0.0	7.3 $\pm$ 2.20	8.4 $\pm$ 1.37
ma (mm)	48.3 $\pm$ 8.34	43.5 $\pm$ 8.20	45.5 $\pm$ 3.54	48.9 $\pm$ 9.05	44.0 $\pm$ 7.40
Haemoglobin (g/dl)	15.1 $\pm$ 0.40	12.3 $\pm$ 0.56	14.8 $\pm$ 1.17	12.9 $\pm$ 0.35	13.2 $\pm$ 1.04
Platelet count ($\times 10^9$ /l)	294 $\pm$ 40.5	447 $\pm$ 82.9	267 $\pm$ 67.3	275 $\pm$ 47.0	230 $\pm$ 59.9
Platelet aggregation (Chandler's tube) (s) ..	467 $\pm$ 48.6	501 $\pm$ 71.4	659 $\pm$ 158.0	578 $\pm$ 131.5	508 $\pm$ 68.3
Platelet adhesion (%)	51.8 $\pm$ 8.86	44.4 $\pm$ 10.05	37.4 $\pm$ 5.22	34.7 $\pm$ 8.31	

PROGRESSIVE MONITORING

In the three subjects in group A the CUSUM technique, which detects any possible change of clotting test values, was used to monitor the effects of reducing atmospheric contamination by introducing the safer working procedure devised by the Health and Safety Executive. The only results that showed any significant changes were the following. In all three subjects the APTT tended to be prolonged, but this was significant in only one instance ($P < 0.05$); the factor X time decreased in all three subjects but significantly in only the man and one woman.

Discussion

This study provides evidence that industrial exposure in the pharmaceutical industry to hormone preparations used to manufacture combined oral contraceptive tablets results in accelerated blood clotting tests. The changes are similar to those induced by oral administration of the hormones. The subjects studied also had clinical signs and symptoms of exposure to oestrogen. The most pronounced clotting changes were found in the two women and one man with the greatest industrial exposure. The haemoglobin concentration was significantly low in these two women, presumably due to their postmenopausal bleeding associated with the process. Even the less exposed group of seven women, however, had significantly accelerated clotting tests compared with the control group of women of similar age attending the hospital for hormone replacement treatment. It is unlikely, however, that this difference could be accounted for by the diminishing endogenous oestrogen secretion in the control group.

One feature of this study differs from previous reports of findings with oral contraceptives. Rises in platelet count are not usually part of the haemostatic response to the administration of oral contraceptives, and rises in fibrinogen concentration,

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References

- Donayre, J, and Pincus, G, *Metabolism*, 1965, **14**, 418.
- Hougie, C, *et al*, *Metabolism*, 1965, **14**, 411.
- Miller, S P, Lee, S L, and Ritz, N, *Metabolism*, 1965, **14**, 398.
- Thomson, J M, and Poller, L, *British Medical Journal*, 1965, **2**, 270.
- Amris, G J, and Starup, J, *Acta Obstetrica et Gynaecologica Scandinavica*, 1967, **46**, 78.
- Nilsson, I M, and Kullander, S, *Acta Obstetrica et Gynaecologica Scandinavica*, 1969, **46**, 286.
- Poller, L, in *Recent Advances in Thrombosis*, ed L Poller, p 181. London, Churchill, 1973.
- Poller, L, *British Medical Bulletin*, 1978, **34**, 151.
- Thomson, J M, *Blood Coagulation and Haemostasis: A Practical Guide*, 2nd edn. Edinburgh, Churchill Livingstone. To be published.

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ONE HUNDRED YEARS AGO The Luton Club (composed of about thirty young men) lately handed over to Mr Horace Sworder, one of the medical officers of the Cottage Hospital, the sum of £21 to purchase surgical instruments for the hospital, being the surplus money of a theatrical entertainment given a month or two ago. With the money he has purchased a handsome brass-bound mahogany case, lined with silk velvet, with the words "Presented by the Luton Club to the Luton Cottage Hospital, April 1879" engraved on the outside. The case contains all the instruments necessary for ordinary surgical operations; and as the Cottage Hospital, of about ten beds, is situated some distance from the houses of the medical men, its value is apparent. (*British Medical Journal*, 1879.)