Ultrasound findings and oral contraceptive taken

Case No	Pill	Ovarian follicular appearances (maximum diameter (mm))		
		Day 21	Day 28	Day 7
1	Microgynon	None	Multiple (7)	None
2	Microgynon	None	Multiple (3)	None
3	Ovranette	None	Multiple (3)	None
4	Microgynon	None	Multiple (3)	None
5	Microgynon	20 mm cyst	Multiple (3) + 20 mm cyst	20 mm cyst
6	Eugynon 30	None	Multiple (7)	None
7	Marvelon	None	Multiple (5)	None
8	Trinordiol	None	Multiple (5)	None
9	Microgynon	25 mm cyst	Multiple (7) + 25 mm cyst	17 mm cyst
10	Trinordiol	None	Multiple (7)	None
11	Eugynon 30	None	Multiple (7)	None
12	Microgynon	None	Multiple (8)	5 mm follicle
13	Microgynon	None	Multiple (4)	None
14	BiNovum	None	Multiple (7)	None
15	Ovranette	None	Multiple (9)	None
16	Logynon	None	Multiple (5)	None
17	Ovranette	None	Multiple (5)	None
18	Microgynon	None	Multiple (10)	None
19	BiNovum	None	Multiple (6)	None

pearances had returned to the dormant condition shown by the first scan in all but one subject (case 12) and she showed reduction in follicular diameter.

No pills were missed by any subject during the study cycles. In two subjects (cases 5 and 9) small cysts were detected at the first scan and at the second and third examinations, unaffected by the development and regression of the other follicles. One subject (case 1) inadvertently missed a pill on day 5 of a cycle after completing the study. She was examined 24 hours later and a 10 mm follicle was seen. She was unable to attend for further examinations.

Comment

The demonstration of ovarian folliculogenesis in all 19 subjects, and to a significant degree in nine, on the seventh pill free day, means that during the early days of the subsequent pill cycle, some women harbour significantly developed follicles, ready to respond to any gonadotrophin surge which might occur if oestrogen suppression were to fail because of a missed pill. By the seventh day of pill use, in all but one subject, the follicles had disappeared. Missing a pill after this time would seem to be less important.

If a pill were missed during the first seven days of the pack and rebound gonadotrophin production continued to mature a partially developed follicle, then the normal practice of taking two pills the next day might theoretically add positive oestrogen feedback to the gonadotrophin production and make even more likely the risk of ovulation. This possibility has not been proved as it is difficult to find for study women taking the pill for reasons other than contraception.

To reduce the risk of missed pill conception a 28 day pack containing 23 pills and 5 blanks could be substituted for the current 21 day pack. This would still permit a withdrawal bleed without the risk of significant follicular development. The use of a 5 day pill free period with the current 21 day packs might cause confusion for some women but would be equally effective.

With the current 21 day pill pack we strongly recommend that alternative contraception be used when a pill is missed during the first seven days of a pack, even if the woman has been using oral contraception for some time. This is probably not necessary when a pill is omitted later in the course. Women using oral contraceptives should also be warned of the danger of delaying restarting treatment after the seven pill free days.

We thank the volunteers who made themselves available for examination when requested.

- 1 Rubinstein L, Moguilevsky J, Leiderman S. The effect of oral contraceptives on the gonadotrophin response to LHRH. *Obstet Gynecol* 1978;52:571-4.
- 2 O'Herlihy C, DeCrespigny LJCh, Robinson HP. Monitoring ovarian follicular development with real time ultrasound. *Br J Obstet Gynaecol* 1980;87:613-8.
- 3 Hodgen GD. The dominant ovarian follicle. *Fertility Sterility* 1982;38:281-300.

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Potential hazard of clotting during blood transfusion using a blood warming pack

It was recently reported to the regional blood transfusion centre that an anaesthetist at a district hospital had found blood clots in the blood warming bag at the end of a transfusion. All the equipment was returned for examination.

Equipment and investigations

The equipment consisted of an empty blood pack connected via a micro-aggregate blood filter to a standard Y recipient set, and a part pack of compound sodium lactate intravenous infusion BP (Hartmann's solution for injection; Ringer lactate solution for injection). The distal end of the recipient set was connected to a blood warming bag (Fenwal code 4C2416) (see figure).

Transfusion system with blood warming pack. (A Compound sodium lactate intravenous infusion. B Blood Pack. C Micro-aggregate filter. D Standard recipient set filter and drip chamber. E Blood warming pack.)

Blood clots were present in the filter chamber of the recipient set on both sides of the filter and along the entire length of the fluid pathway.

One ml aliquots of whole blood (420 ml blood collected into 63 ml of CPDA-1) and plasma reduced blood (whole blood from which 200 ml plasma had been removed) were added to 1, 2, 3, and 4 ml of compound sodium lactate. Four tubes of each were prepared. These were incubated in a water bath at 37°C for three minutes and examined at minute intervals for signs of clotting. The plasma reduced blood (1 to 1 dilution) did not clot at 20 minutes but the contents of the other tubes clotted within three to six minutes. Whole blood did not clot in 20 minutes in the 1 ml of whole blood to 1 and 2 ml of compound sodium lactate solution, but the other two dilutions clotted at eight and 11 minutes.

Comment

Compound sodium lactate intravenous infusion contains calcium chloride 0.27 g/l giving a calcium content of 2 mmol/l (8 mg/100 ml), just below the normal serum concentration of 2.30-2.65 mmol/l (9.2-10.6 mg/100 ml). The citrate in CPDA-1 acts as an anticoagulant by chelating calcium, but the amount required is much greater than if 1 mol of citrate firmly chelated one atom of ionised calcium. Plasma citrated with CPDA-1 has a final citrate concentration of about 25 mmol/l and a final calcium concentration of approximately 1.8 mmol/l (7.2 mg/100 ml), a molar ratio of about 12.5:1. Yet it takes only 500 mg of calcium chloride added to a unit of whole blood to provide sufficient calcium to "satisfy" all the citrate present.¹

The experiments show that 2 ml of compound sodium lactate intravenous infusion causes clotting with 1 ml of plasma reduced blood in five to six minutes and 3 ml causes clotting with 1 ml of whole blood in 10 to 11 minutes at a temperature of 37°C, the temperature at which the Fenwal blood warmer operates.

If the compound sodium lactate solution is run through the system after whole blood or plasma reduced blood a dilution gradient is produced through the system. When the dilution is 1/4 for whole blood, or 1/3 for plasma reduced blood, clotting occurs. Before the addition of the blood warmer, clotting takes longer in the system as the temperature is 15°C lower, about room temperature. Clotting may not clearly register in the recipient set because of slow formation, and diluent and streamlining effects of the sodium lactate solution. Initially the clots formed are soft and pass easily along the fluid pathway into the patient, the size and number depending on the rate of flow. If blood is then rapidly infused, using a pressure infusor, then probably all the clots formed in the system distal to the recipient filter pass into the patient.

This hazard is not mentioned in the *British Pharmacopoeia* 1980, the *European Pharmacopoeia* 1975, *Martindale: The Extra Pharmacopoeia* 1977, the *British Pharmaceutical Codex* 1973, or the data sheets issued with the product. The *British National Formulary*² does comment that if a giving set is not changed after transfusion, and is used for other infusion fluids, a precipitate of fibrin may form, which physically blocks the set and increases the likelihood of microbial growth. Printed on the back of the carton containing the blood warming bag under Notes is: a) "Use set only with fluids compatible with each other."

We do not know how common is the practice of giving compound sodium lactate through the same recipient system as blood, but, clearly, this could harm the patient. Although Fenwal equipment was used in this study, clotting would occur with any other similar equipment.

1 Mollison PL. *Blood transfusion in clinical medicine*. 7th ed. London: Blackwell Scientific Publications, 1983:34.

2 *British National Formulary*, No 8. London: British Medical Association and the Pharmaceutical Society of Great Britain, 1984:415.

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Symptomatic reaction to hepatitis B vaccine with abnormal liver function values

We report the first case of a systemic reaction with abnormal liver function values in a healthy person receiving hepatitis B vaccine. We used H-B-Vax (Thomas Morson Pharmaceuticals).

Case report

A 43 year old woman who had been offered hepatitis B vaccination as part of a prophylactic vaccination programme for staff working in hospital theatre, was admitted on 28 April after five days of malaise, shivering, anorexia, loss of taste for cigarettes, and discomfort in the right upper quadrant of the abdomen. She had received the standard dose of vaccine (1 ml containing 20 µg hepatitis B surface antigen) on 7 March and 4 April. She did not declare any history of excess alcohol consumption and she had never suffered from jaundice. Examination showed that she was anicteric and had no signs of chronic liver disease, although a tender liver edge was palpable on inspiration. The spleen was not enlarged.

Investigations showed that haemoglobin was 13.1 g/100 ml and white blood cell count was $13.6 \times 10^9/l$ (76% neutrophils, 8% eosinophils, absolute count $1.09 \times 10^9/l$); she was negative for antinuclear factor, smooth muscle, and antimitochondrial antibodies. The results of convalescent titres of complement fixing antibodies two months later were influenza A and B and *Coxiella burnetii*, all 1:4; psittacosis, lymphogranuloma venereum, *Mycoplasma pneumoniae*, and leptospirosis 1:4; adenovirus 1:8; and cytomegalovirus 1:16. Ultrasonographic scan of the abdomen indicated normal liver, bile ducts, gall bladder, and pancreas. The table shows the progressive changes in liver function values that occurred over the next five months.

At presentation she was negative for hepatitis B surface antigen with no antibodies by radioimmunoassay to hepatitis A. The patient had not formed antibodies to the surface antigen or the core antigen on 14 June, 9 August, or 27 September. She was symptomatically and biochemically normal five months after presentation and returned to work. A third dose of vaccine was not given. No relapse occurred in the subsequent year.

Comment

Hepatitis B vaccine, as currently available in the UK, is prepared from purified surface antigen using the plasma of chronically infected asymptomatic carriers of hepatitis B virus.¹ The manufacturing process comprises the purification of the surface antigen, the removal of extraneous material, and, finally, the destruction of the infectivity of hepatitis B and any other viruses which might be present.² Each batch of vaccine is tested for sterility, pyrogenicity, and innocuousness on animals in the laboratory. Each lot of vaccine is tested for safety in susceptible chimpanzees before being passed for human use. The safety of the vaccine has been confirmed in over 19 000 volunteers.³

Progressive changes in liver enzymes over five months. Normal values are given at the top of each column

	Alkaline phosphatase 20-95 IU/l	5 Nucleotidase 2-17 IU/l	Aspartate transaminase <35 IU/l	Alanine transaminase <35 IU/l
29 April 1983	243		45	66
3 May 1983	373	43.5	55	77
16 May 1983	318		28	47
3 June 1983	268		32	40
11 July 1983	182	27.7		
9 August 1983	91	8.1	25	22
27 September 1983	68		25	29

All values for serum bilirubin, albumin, and globulin remained within normal range at all times.

This vaccine is well tolerated except for occasional hypersensitivity reactions to any one of its components. Twenty five percent of the 2485 volunteers reported local soreness and erythema at the injection site with occasional low grade fever (<38°C). Other systemic complaints are malaise, fatigue, rash, headache, nausea, myalgia, and arthralgia, but these are rare (brochure on hepatitis B vaccine, Thomas Morson Pharmaceuticals).

Our patient was offered prophylactic hepatitis B vaccination in accordance with recently reviewed policy for use of the vaccine for medical personnel.² We do not consider that the abnormalities of liver function resulted from occupational exposure to halothane in the operating theatre. The temporal correlation between the two vaccine doses suggests the mechanism of cause and effect.

We do not know of a previous report of a systemic reaction accompanied by abnormal liver function values after hepatitis B vaccination. We reported the case to the Committee on Safety of Medicines and the manufacturers, neither of whom informed us of similar cases. The clinical picture was of an anicteric hepatitis episode, where the patient had a hypersensitive reaction. It is unlikely that any adjuvant or additive in the vaccine was the cause. Interestingly, the patient did not develop antibodies to either the surface antigen or the core antigen, even when tested at six months. Normally 90% of those given the first two of the three doses will have developed antibodies to the surface antigen, as is the intention of the proposed vaccination programme.¹

We thank Dr J M Graham, consultant microbiologist for his help, and Miss P A Farmer for preparing the manuscript.

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2 Zuckerman AJ. Who should be immunised against hepatitis B? *Br Med J* 1984;289:1243-4.

3 Intergroup group. Hepatitis B virus vaccine safety. *MMWR* 1982;31:464-7.

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Correction

Endoscopic Teflon injection for a refluxing ureteric stump after simple nephrectomy

In this report by K N Bullock and colleagues (13 April, p 1109) the cystogram was obtained before operation and not postoperatively as stated in the legend.