Hepatic Impairment During the Intake of Contraceptive Pills: Clinical Trial with Postmenopausal Women

Brit. med. J., 1964, **2**, 426–427

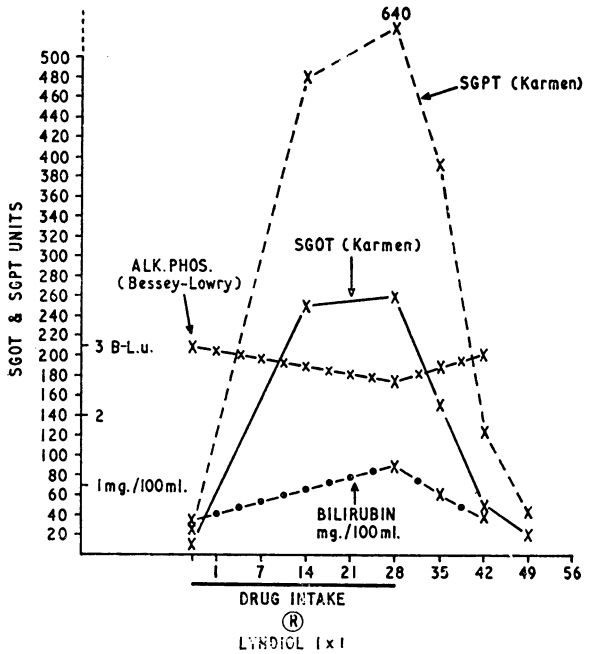
It is well known that hepatic dysfunction and jaundice occur in subjects treated with some oral anabolic steroids (for a review see Drill, 1963). Although oral contraception with modified steroids is widely practised, there have been no previous reports of any severe hepatic injury due to this treatment. But owing to the structural similarity between these two groups of drugs, it was thought necessary to make sure that these contraceptive pills are completely free of hepatotoxicity, because they are used nowadays for long periods almost without any medical supervision. We therefore tested one contraceptive drug and its separate progestogen and oestrogen components on postmenopausal women. Since treatment for as little as 28 days was enough to provoke hepatic injury, the preliminary results of the trials are reported here.

Subjects and Methods

The twelve postmenopausal patients were selected for the study because physical and laboratory examinations revealed no signs of hepatic damage and we did not wish to disturb the menstrual cycle of fertile women with steroid components having no contraceptive effect. After the basic examination Lyndiol (5 mg. 17α-ethynyloestrenol and 0.15 mg. 3-methoxy-17α-ethynyloestradiol) was given to seven women, Orgametril (5 mg. 17α-ethynyloestrenol ; lynoestrenol) to two women, and Mestranol (0.15 mg. 3-methoxy-17α-ethynyloestradiol) to three women for 28 consecutive days. The dosage is seen in the accompanying Table. The hepatic function was followed with determinations of S.G.O.T., S.G.P.T., alkaline phosphatase, and total bilirubin. Bromsulphthalein retention and clearance tests were performed, giving 5 mg./kg. of body weight intravenously, in three of the subjects receiving Lyndiol, one of those taking Orgametril, and in all the Mestranol subjects.

Results

The results of transaminase determinations before, during, and after the different types of treatment are shown in the Table.



Typical results of liver-function tests in the clinical trial (Case 6). One pill of Lyndiol was given daily for 28 days. On the 29th day after the start of treatment the bromsulphthalein retention was 39 mg./1,000 ml./120 min. and on the 49th day after the start of treatment 8.3 mg./1,000 ml./120 min. Normal values are below 4 mg./1,000 ml./60 min. The bromsulphthalein clearance was 2.6% and 7.7% respectively. Normal values are 11–18%/min.

Biochemical Data of Subjects Treated with 17α-ethynyloestrenol and/or 3-methoxy-17α-ethynyloestradiol for 28 Days

Case No. and Age (Years)	Drug and Daily Dose	Transaminase	Results and Day of Laboratory Investigations. Drug intake Between 1–28 days							Remarks
			0	14	21	29	36	43	49	
1 79	Lyndiol 2 pills	S.G.O.T.	29	570	—	385	230	90	53	On 29th day
		S.G.P.T.	37	940	—	520	340	140	67	B.S.P.$_r$ 33·6, B.S.P.$_{cl.}$ 4·8
2 80	Lyndiol 2 pills	S.G.O.T.	19	800	800	700	470	365	—	On 29th day total
		S.G.P.T.	22	1,720	1,900	1,440	1,350	1,210		bilirubin 2·4
3 80	Lyndiol 2 pills	S.G.O.T.	21	—	490	440	410	—	—	On 29th day
		S.G.P.T.	18	—	720	—	—	—	—	B.S.P.$_r$ 23·4, B.S.P.$_{cl.}$ 5.1
4 78	Lyndiol 2 pills	S.G.O.T.	24	210	250	500	—	—	—	Alkaline phosphatase
		S.G.P.T.	42	740	550	680	—	—	—	14th day 3·8, 29th 5·0
5 62	Lyndiol 2 pills	S.G.O.T.	35	80	140	—	—	—	—	
		S.G.P.T.	—	—	260	—	—	—	—	
6 74	Lyndiol 1 pill	S.G.O.T.	15	250	—	260	150	50	19	On 29th day
		S.G.P.T.	23	480	—	640	395	126	42	B.S.P.$_r$ 39, B.S.P.$_{cl.}$ 2·6
7 72	Lyndiol 1 pill	S.G.O.T.	20	37	100	400	—	—	—	
		S.G.P.T.	26	49	—	680	—	—	—	
8 59	Orgametril 1 pill	S.G.O.T.	26	28	—	23	22	—	—	
		S.G.P.T.	34	50	—	33	31	—	—	
9 69	Orgametril 2 pills	S.G.O.T.	30	21	—	30	—	—	—	
		S.G.P.T.	57	48	—	59	—	—	—	
10 52	Mestranol 1 pill	S.G.O.T.	16	25	27	130	55	—	—	On 29th day
		S.G.P.T.	20	37	42	318	142	—	—	B.S.P.$_r$ 21·3, B.S.P.$_{cl.}$ 5·3
11 60	Mestranol 1 pill	S.G.O.T.	24	18	14	16	—	—	—	
		S.G.P.T.	22	38	32	23	—	—	—	
12 60	Mestranol 1 pill	S.G.O.T.	30	32	28	26	—	—	—	
		S.G.P.T.	33	29	29	32	—	—	—	

One pill of the drugs contained:—Lyndiol: 5 mg. of 17α-ethynyloestrenol and 0·15 mg. of 3-methoxy-17α-ethynyloestradiol. Orgametril: 5 mg. of 17α-ethynylestrenol; Mestranol: 0·15 mg. of 3-methoxy-17α-ethynyloestradiol. Serum transaminases: S.G.O.T. and S.G.P.T., normal values below 40 units. Bromsulphthalein retention (B.S.P.$_r$) normal values below 4 mg./1,000 ml./60 min., bromsulphthalein clearance (B.S.P.$_{cl.}$) normal range 11–18%/min. Alkaline phosphatase Bessey–Lowry units, normal range 0·8–2·9.

In every one of the group of patients treated with Lyndiol it can be seen that the transaminase levels in the serum were clearly elevated after 20 days. In most cases this rise could already be observed on the fourteenth day after the start of treatment. The serum transaminase levels of the four patients who were kept in hospital after the treatment decreased when the drug intake was discontinued. Bromsulphthalein retention and clearance showed highly pathological values in three patients who were tested on the day following the drug intake (Cases 1, 3, and 6 in Table). The total bilirubin was elevated in only one patient (Case 2), and alkaline phosphatase was above the normal level in one patient (Case 4) on the day following the treatment. These changes in the tests could be observed even with a daily dose of one pill of Lyndiol. A typical example of the change of the liver-function tests (Case 6) due to Lyndiol intake is graphically illustrated in the accompanying Chart.

Orgametril, the progestogen component of Lyndiol, did not seem to result in elevation of the serum transaminase levels of the two patients studied, and the other tests also revealed normal values during and after the treatment (Cases 8 and 9).

The oestrogen component of Lyndiol (mestranol) was given to three patients, using the same daily dose as is contained in one Lyndiol pill. The serum transaminase levels were raised and the bromsulphthalein retention and clearance were pathological in one patient (Case 10). The transaminase levels and other tests were normal in the remaining two cases treated with this common synthetic oestrogen.

Discussion

The average age of the patients in this series was very high; but it must be borne in mind that treatment for as little as two weeks altered the hepatic condition as judged by the transaminase levels of most of the patients in the series.

The synthetic oestrogen component, 3-methoxy-17α-ethynyl-oestradiol, of the drug tested had the same hepatotoxic effect as the whole contraceptive pill, while the progestogen component was without effect. This may indicate that only the oestrogen component is responsible for the effect. However, the number of patients on whom the components were tested separately was small, and only one patient out of three showed signs of hepatic injury in the series given mestranol. Therefore, the uniform results in every patient tested with the whole drug may reflect a synergistic action of the two components.

It was evident that this type of hepatic injury cannot be discovered with total bilirubin or alkaline phosphatase determinations alone, because they were normal, although S.G.O.T., S.G.P.T., and B.S.P. retention clearly revealed the hepatic impairment. The very high values of the serum transaminases found in all the cases treated with Lyndiol seem to indicate that the liver damage was of hepatocellular type, but the observed high-degree retention and the decreased clearance of bromsulphthalein is more likely to be found in "canalicular" jaundice, so it might be "mixed" in type.

Further investigations are in progress to clarify how often hepatic dysfunction has been or can be provoked with contraceptive drugs in younger subjects and to study in larger series which of the components of the oral contraceptive are responsible for the side-effects found.

Summary

Seven postmenopausal women were treated for 28 days with a contraceptive drug. This clearly resulted in hepatic dysfunction in every patient, as judged by elevation of serum transaminase levels. The progestogen component of the drug was without effect in the two patients studied, and in one out of three cases treated with the oestrogen component of the drug changes in hepatic function similar to those produced by the whole drug were observed.

We would like to thank the Sigrid Juselius Foundation for a grant. Lyndiol and its components were generously supplied by Organon, Oss, Netherland.

ANTTI EISALO, M.D.,
Third Medical Clinic, University of Helsinki, Finland.
PENTTI A. JÄRVINEN, M.D.,
TAPANI LUUKKAINEN, M.D.,
Second Department of Obstetrics and Gynaecology, University Central Hospital, Helsinki, Finland.

Reference

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Medical Memoranda

Stokes-Adams Attacks Precipitated by Hypokalaemia

Brit. med. J., 1964, **2**, 427–428

I have been unable to find any previously recorded case of heart-block precipitated by hypokalaemia, though Bettinger *et al.* (1956) describe two cases with heart-block in which sinus rhythm was temporarily restored by intravenous infusion of potassium chloride. In the patient described here hypokalaemia occurred during the treatment of diabetic acidosis; heart-block supervened and responded only to potassium therapy.

Case History

A married woman aged 65 years was admitted with diabetic ketosis on 15 February 1960. Diabetes mellitus had been diagnosed four years previously. This had been controlled by a mixture of lente and semilente insulin, the daily doses averaging 48 units and 28 units respectively. Before this admission she had suffered from foot sepsis, and had complained of thirst and polyuria. Examination revealed that she was dehydrated. She was quite rational. Her blood-pressure was 100/70 mm. Hg, rising to 170/90 mm. Hg after rehydration. Her pulse rate was regular at 84 per minute.

She had heavy ketonuria; her initial blood-sugar was 320 mg.%. The serum electrolytes were as follows: potassium 3.0 mEq/l., sodium 137 mEq/l., chlorides 104 mEq/l., alkali reserve 43 vol.%, blood urea 44 mg.%.

Forty-five minutes after her admission her pulse became impalpable while being recorded by a nurse. It remained so for 30 seconds and then returned. Many similar episodes followed during the next 36 hours, and were variably accompanied by unconsciousness, incontinence, epileptiform movements, and flushing during recovery. The attacks persisted in spite of treatment with ephedrine, subcutaneous adrenaline, and intravenous infusion of molar lactate. The periods of ventricular asystole were most commonly of the order of two minutes, but on one occasion four minutes and eight seconds passed without any electrocardiographic evidence of ventricular activity.