Clinical Significance of Estrogens in Chronic Aggressive Hepatitis

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In eight patients with chronic aggressive hepatitis during menopause after bilateral ovariectomy, the excretion of estrogens in the urine decreased; gonadotropin, especially follicular stimulating hormone, in the blood serum increased; and the maximum excretion of estrogen in urine after trial medication of estrone sodium sulfonate came on the following day and the excretion lasted 8 days with a tendency toward gradual decrease. In these patients, the inflammatory process came to a standstill both clinically and histologically after therapeutic medication of medicinal estriol for 6-9 weeks.

In six patients during menopause after physiological climacterium, the excretion of estrogens in the urine decreased, except for estrogen excretions of 10 μg a day several times a month. Follicular stimulating hormone in the blood serum increased in these patients, except for several times a month which were within the normal range. The excretion of estrogen in the urine after trial medication of estrone sodium sulfonate showed a similar pattern to that of the former group but the maximum excretion was lower. In these patients, the inflammatory process tended to come to a standstill clinically as well as histologically after therapeutic medication of medicinal estriol for 6-9 weeks.

The PHA-test for estrogens and immunological investigations showed no pathological findings in either group. From these findings, it can be said that estrogen deficiencies influence pathogenesis and the clinical course of chronic aggressive hepatitis.

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Since it has been known that the liver plays an important role in estrogen metabolism (1, 2), the idea that stagnation of active

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Fig. 1 Excretion of estrogen in urine in patient with chronic aggressive hepatitis during menopause.

Estrogen in the blood gives rise to liver injury seems to be gaining ground. The fact that women are three or four times more susceptible to chronic aggressive hepatitis than men, is also interpreted as a basis for such a view. It seems plausible that estrogens can not be produced in bilaterally ovariectomized women, but the author has occasionally encountered patients with chronic aggressive hepatitis among women after bilateral ovariectomy. Therefore, the author attempted to clarify this contradiction and to determine the pathogenetical and clinical significance of estrogens in chronic aggressive hepatitis.

Methods

In fourteen patients with chronic aggressive hepatitis, eight of which were previously ovariectomized because of gynecological diseases and the remaining six of which were in a state of physiological climacteric menopause, the level of gonadotropin, especially the follicular stimulating hormone (abbreviated as FSH), in the blood was estimated according to the McCann-Igarashi method and the excretion of estrogen in urine with or without prior administration of 20 mg of estrone sodium sulfonate was estimated by the Brown-Kohbegawa method. Then, the clinical course after medication of medicinal estriol was observed and a laparoscopic examination of the liver with or without needle biopsy was performed with respect to administration of medicinal estrogen. To
ascertain the immunological predisposition of these patients to medicinal estrogen, the phytohemagglutinin (abbrev. PHA)-test was performed along with certain other immunological tests.

Results

In eight patients with chronic aggressive hepatitis during menopause after bilateral ovariectomy, the disease of the onset was assumed to be serum hepatitis. Excretion of estrogens in the urine amounted to less than 2 μg daily. This value was not clinically significant, which might be interpreted as a technical error (Fig. 1). Gonadotropin, especially FSH in blood serum, increased to more than 2500 μg/dl a day. This indicates that the ovary does not act as a receptor of FSH, while the production of gonadotropic hormone remains well within the hypophysis. The maximum excretion of estrogens in the urine after trial medication of 20 mg of estrone sodium sulfonate came to 1700 μg on the following day and excretion continued for 8 days with a tendency to decrease gradually (Fig. 2). Fig. 3 shows the excretion of the estrogen in the urine after trial medication of 20 mg of estrone sodium sulfonate in the control group which consisted of two young women with chronic persistent hepatitis, one preclimacteric patient with cirrhosis of the liver and four middle-aged men with liver cirrhosis. The excretion of estrogens in the urine after trial medication showed similar tendencies not only in the group of patients with chronic aggressive hepatitis but also in the control group. In other words, the excretion of previously administered medicinal estrogen was not hindered in these patients. Therefore, it can be assumed that the decreasing excretion of endogenous estrogen in the urine and the lack of excretory hindrance of previously administered estrogen justify administering estrogen to patients with chronic aggressive hepatitis. The clinical course of a patient with chronic aggressive hepatitis in this group is shown as an example in Fig. 4. The inflammatory process came to a standstill clinically as well as histologically after therapeutic medication of 200–300 μg of medicinal estriol a day for 6–9 weeks (Fig. 5-a, b).

In six patients during physiologic climacteric menopause, the onset of the disease was characterized by the symptoms of infectious hepatitis. The excretion of estrogens in the urine generally decreased to the same degree in these patients as in the former group, except that 10 μg of estrogen a day was excreted several times a month (Fig. 1). FSH in the blood serum increased mostly above 2500 μg/dl a day and several times a month in the range of 1500 and 2500 μg/dl a day. This means that the FSH-level in the blood reflects the dysfunction of the climacteric ovary. The excretion of estrogens in the urine after trial medication of 20 mg of estrone sodium sulfonate showed a similar pattern to that of the former group, but the maximum excretion reached 1000 μg. In these patients, the inflammatory process had a tendency to reach a clinical standstill about 4 weeks after therapeutic medication of 200–300 μg of medicinal estriol a day (Fig. 6). Thereafter, the laboratory findings of the clinical course, especially transaminase-activity in blood serum, sometimes became unstable. Histologically, a standstill tendency in the liver
Fig. 2  Trial medication of estrone sodium sulfonate in patient with chronic aggressive hepatitis.

was occasionally seen 6–9 weeks after treatment (Fig. 7-a, b), while laboratory findings sometimes became unstable.

The PHA-test for medicinal estrogens showed the normal range of results. The results of immunological tests including the characteristic finding of markedly increased IgG are shown in Figs. 4 and 6.

Discussion

The liver plays an important role in the intermediate metabolism of estrogens. It has been demonstrated that estrogens are removed from systemic circulation and it is generally believed that they undergo prompt inactivation in this organ (3, 4, 5). It was recognized early that this inactivation of estrogens by the liver is due to an enzymatic process.
Fig. 3 Excretion of estrogen in urine after trial medication of estrone sodium sulfonate.

The exact nature of the enzyme system involved is not known but it is probable that the process of inactivation involves conversion of the original estrogen in part to biologically inactive substances and in part to estrogens of lower activity (1, 2, 6, 7). The observation that subclinical hepatic changes become manifest clinically after a long-term administration of overdoses of estrogen (8) and that, in animal experiments, estradiol gives rise to liver injury, sets us to thinking that liver injury is due to stagnation of active estrogen (9). It considered that these facts indicate the reasons for severe clinical course of hepatitis in women (10, 11, 12) and during pregnancy (13, 14, 15).

The author has already pointed out, however, that the excretion of estrogen in urine as well as the estrogen level in the blood was so small in patients during menopause with chronic aggressive hepatitis after bilateral ovariectomy that it might be due to an inadvertent
Fig. 4 Chronic aggressive hepatitis during menopause after bilateral ovariectomy.

technical error (16). Based on our own clinical experience and reports by hepatological experts, it can be said that chronic aggressive hepatitis occurs three or four times more in female than in male patients and that chronic aggressive hepatitis affects chiefly women after menopause. Therefore, it might not always be true that stagnation of active estrogens gives rise to liver injury and causes a severe inflammatory process in the liver as well as affecting the clinical course of chronic aggressive hepatitis in women and during pregnancy (17, 18, 19). These facts suggest that in women, estrogens exert some form of liver-protecting
influence against infection as well as the protracting factors (11, 16, 20, 21, 22, 23).

Fourteen patients with chronic aggressive hepatitis showed normal excretion of estrogen in urine after prior administration of a trial medication of 20 mg of estrone sodium sulfonate and negative PHA-tests for estrogens. Therefore, it can not be assumed that the administration of estrogens to these patients brings on stagnation of estrogens in the systemic circulation and that it gives rise to liver injury. In patients
with chronic aggressive hepatitis during menopause after bilateral ovariectomy, the inflammatory process came to a standstill clinically as well as histologically after therapeutic medication of 200–300 µg of estriol/day for 6–9 weeks, while patients after physiological climacteric menopause showed a tendency to clinical and histological standstill after therapeutic medication of 200–300 µg of estriol per day for 6–9 weeks in spite of unstable blood-chemical findings thereafter. The differences in the clinical course (including gonadotropin) in both groups and the significance of progesterone should be thought of separately.

In conclusion, it can be stressed, based upon these findings, that there are some differences in hormonal aspects between patients with chronic aggressive hepatitis after physiological climacteric menopause or after bilateral ovariectomy, and that these findings suggest an interrelationship between sex-hormones and chronic aggressive hepatitis, i.e. a
a. Before treatment

b. Seven weeks after treatment

Fig. 7 Histologic findings of the liver by needle biopsy (100X).

type of liver-protecting influence of estrogens against infection as well as the protracting factors of hepatitis.
References


