CHANGES IN THE FUNCTIONAL STATE OF THE LIVER IN THYROTOXICOSIS PATIENTS

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Clinical manifestations of hepatic damage in thyrotoxicosis are rearely observed. Nevertheless, functional, biochemical and pathoanatomical studies of the liver show that overactivity of the thyroid gland leads to considerable disorders in its functions (1, 2, 3, 4, 7, 8, 11, 16). The metabolism of lipids in the liver is disturbed (10, 17), the glycogen content of hepatocytes (5) and of adenosine 3'-phosphate as well (2) is reduced, whilst the content of serum-glutamic oxalacetic transaminase (aspartate-aminotransferase) (13), alkaline and acid phosphatase (12) is increased. It is supposed that the listed changes are due to the effect exerted by thyroid hormones on mitochondria (12).

Parallel to changes in the content of some enzymes within the hepatic tissue, changes in their serum level are also established (9, 12). Kubacki et al (cited by 12) state that the increase in serum alkaline phosphatase is due to the latter's rise in the tissues, and to the modified tissues to serum transport. Liver ferments and their changes in the serum of thyrotoxicosis patients are still insufficiently studied (7).

The dynamics of hepatic changes in thyrotoxicosis under the influence of thyrostatic therapy is likewise scarcely explored. Actually, the most widely employed thyrostatics — mercaptoimidazoles — rank first in the list of hepatotoxic drugs (6), while experimental studies by M. Oprescu et al (1974) have demonstrated their hepatoprotective action.

We made it our aim to study the changes in the functional state of liver in patients affected with thyrotoxicosis prior to and in the course of treatment with thymidazole (1-methyl-2-mercaptoimidazole).

Material and Method

A series of twenty patients with recently discovered thyrotoxicosis of medium-heavy degree were subjected to study. Diagnosis was established on the basis of clinical picture, radioactive iodine intake by the thyroid, and protein-bound iodine level in the serum. A hepatic affection in the past history was recorded in none of the patients.

To assay the functional state of the liver the Bromsulphalein test was investigated as well as the enzymes: serum glutamic-oxalacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), leucine aminopeptidase (LAP), aldolase and alkaline phosphatase in the serum. Enzyme studies were made with the Boehringer firm tests.

Thymidazole treatment of the patients was carried out according to a common scheme with slight individual variations. Initially, 40—60 mg daily

were given, and within twenty days of the beginning of treatment, the dose was reduced to 30 mg, and maintained till the end of the second month. There after, the treatment proceeded with a supporting dose of 10—15 mg by the end of the 12th month. The patients were investigated befcre the beginning of therapy, and at the end of the 2nd and 12th month.

Results

The results of our studies are submitted in Table 1 and 2. The Bromsulphalein test (sodium sulfobromphthalein test) which was positive in eighteen

Table 1

Number of Patients with Pathological Bromsulphalein Test Values and Increased Level of Some Serum Enzymes

Indicator	Before treatment	After 2-month treatment	After 12-month treatment
Bromsulphalein test	18	15	9
Leucine aminopeptidase	9	7	3
Alkaline phosphatase	4	9	2
Aldolase	3	1	0
SGPT	1	0	0
SGOT	0	0	0

Table 2

Mean Values of Brosulphalein Test and Some Enzymes in the Serum of Patients with Thyrotoxicosis Before and in the Course of Thymidazole Treatment

Indicator	Before treatment	After 2-month treatment	$P_{1, 2}$	After 12-month treatment	$P_{2, 3}$	$P_{1, 3}$
Bromsulphalein test mg %	0,56± 0,007	0,3± 0,02	<0,01	0,23± 0,01	<0,01	<0,01
Leucine aminopeptidase IU	20,4± 0,43	16,2± 0,56	<0,05	14,2± 0,88	<0,05	<0,05
Alkaline phosphatase IU	34,5± 2,0	46,5± 2,9	<0,01	30,9± 2,4	<0,01	<0,05
Aldolase IU	3,3± 0,28	3,0± 0,12	<0,02	2,11± 0,27	<0,01	<0,01
SGPT IU	6,0± 0,67	6,3± 0,44	>0,05	5,6± 1,03	>0,05	>0,05
SGOT IU	6,6± 0,63	7,9± 0,69	>0,05	7,2± 1,27	>0,05	>0,05

patients prior to treatment was the one yielding pathological results most frequently. Within two months of treatment, it was still positive in most of the patients, although in a lower degree. The one-year-long treatment failed

to bring about normalization of this particular test in practically half of the patients.

Of the enzymes studied LAP was increased most frequently. Alkaline phosphatase and aldolase were increased rather rarely, whilst both transaminases were almost invariably within normal limits. In the course of treatment, the number of patients with augmented enzymes in the serum decreased, while the mean values of the Bromsulphalein test, LAP and aldolase displayed a regular fall. Alkaline phosphatase was an exception since on the second month it increased in a greater number of patients, and its mean value showed a reliable increase, exceeding the pre-treatment level. However, at the end of the 12 th month, it fell below the starting level similarly to the other enzymes. SGOT and SGPT did not undergo noteworthy changes in the course of thymidazole treatment.

Discussion

Our results demonstrate the high incidence of hepatic lesion in thyrotoxicosis. The Bromsulphalein test which reflects the overall functional state of the liver, and proves to be pathologically altered in virtually all patients, is particularly indicative. The studied enzymes show a rise in the serum much more rarely, and could hardly serve as a routine test in the assessment of hepatic damage in thyrotoxicosis. The possibility of enzyme increase in the serum as the result of damage to other organs and tissues should be by no means overlooked. LAP rise is noted in lesion of the pancreas, increased aldolase — in muscular dystrophy such as thyrotoxic myopathy, and increased alkaline phosphatase — in enhanced activity of osteoblasts (14). Nevertheless, the combined increase of these enzymes in the serum in conjunction with the pathological Bromsulphalein test render most verisimilar the hypothesis about the hepatic origin of their rise.

Adequate thyrostatic treatment according to the scheme outlined above leads to a gradual lowering and normalization of the pathological Bromsulphalein test, and of the elevated serum enzymes as well. At the end of the second month when the patients are already clinically euthyroid, but the thymidazole dosage is still high, a judgement with a certain degree of reservation could be made about its medicamentous effect on the hepatic function. Our results show that both Bromsulphalein test and enzymes, except for alkaline phosphatase, are improved already at this early stage. Hence, the assumption is warranted that thymidazole at the doses employed does not interfere with the hepatic function in thyrotoxicosis patients.

Alkaline phosphatase rise at the end of the second month of treatment might be an expression of a discrete, drug-induced hepatic lesion, e. g. intrahepatic cholestasis. Anyway, the latter conjecture is less likely because of the improvement recorded in all the other indicators, and the lack of clinical manifestations pointing to an eventual cholestasis. We feel that the explanation of the transitory increase in alkaline phosphatase should be sought for in the restorative processes, occurring in the convalescence of the disease. It is a well known fact that in thyrotoxicosis a great amount of calcium is eliminated via urine with ensuing osteoporosis. In the recovery period, a restoration of the calcium content in bones is begun, most likely in connexion with the en-

hanced osteoblastic activity. The enhanced activity of osteoblasts augments the level of alkaline phosphatase in the serum (14). This is an explanation requiring further verification.

At the end of the 12-month-long treatment, when the doses of thymidazole were reduced to a minimum, and when the patients were practically permanently euthyroid, a substantial improvement in the functional state of the liver was also established. The Bromsulphalein test was considerably reduced, and its mean value was closer to the uppermost normal limit. Enzymes were likewise appreciably reduced. Nevertheless, the Bromsulphalein test, although lowered, as compared to the starting values, was pathological in almost half of the patients, while LAP and alkaline phosphatase were sustained slightly augmented in sporadic cases. The reported data demonstrate that the reparative processes in the liver are rather delayed, and do not run a parallel course to the clinical improvement of patients. Apparently, they are much slower, and the persistence of permanent hepatic lesions in isolated patients is by no means ruled out. There are literature reports on liver cirrhosis, developing against the background of thyrotoxicosis (3, 8). The above facts oblige us to follow with greater attention the hepatic function of thyrotoxicosis patients covered by the outpatient network, to spare the liver during drug prescriptions, and to conduct hepatoprotective therapy in instances of persisting pathological Bromsulphalein test.

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ИЗМЕНЕНИЯ ФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ПЕЧЕНИ У БОЛЬНЫХ ТИРЕОТОКСИКОЗОМ

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РЕЗЮМЕ

Исследованы бромсульфалеиновая проба и энзимы: глютамат-оксалуксусная трансаминаза (СГОТ), глютамат-пируватная трансаминаза (СГПТ), левцинаминопептидаза (ЛАП), алдолаза и щелочная фосфатаза в сыворотке у 20 больных тиреотоксикозом при лечении тимидазолом (1-метил-2-меркаптоимидазол) в течении года. Патологическая бромсульфалеиновая проба установлена у 18 больных, в то время как энзимы в сыворотке повышаются у значительно меньшего числа больных. В конце второго месяца лечения определяется тенденция к нормализации исследуемых показателей за исключением щелочной фосфатазы, уровень которой повышается. После лечения в течении года тенденция к нормализации показателей еще более сильно выражена, но у 9 больных бромсульфалеиновая проба все еще не достигла границ нормы. Щелочная фосфатаза и ЛАП тоже остаются повышенными у отдельных больных.

Указывают необходимость динамического наблюдения за функциональным состоянием печени при тиреотоксикозе и проведения гепатопротективного лечения у отдельных больных.