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Original Article

Exploration and analysis of the effect of thiamazole and propylthiouracil on serum glutamic pyruvic transaminase and serum bilirubin level as well as liver damage incidence in patients with hyperthyroidism

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Abstract: Objective: To explore and expound the effect of thiamazole and propylthiouracil on serum glutamic pyruvic transaminase (ALT) and serum total bilirubin (TBIL) levels as well as liver damage incidence in patients with hyperthyroidism and to evaluate clinical medication safety and satisfaction degree of the two drugs. Methods: A total of 120 patients with hyperthyroidism who received initial treatment in our hospital from May 2015 to May 2016 were selected and divided into thiamazole group and propylthiouracil group by random and double-blind method. Patients in thiamazole group were treated with thiamazole, and patients in propylthiouracil group were received propylthiouracil treatment. With the remission of patients' condition, drug dose was adjusted according to the concentration of thyroid stimulating hormone (TSH), tyroxine (T4) and triiodothyronine (T3). Maintenance treatment was given for one year after reaching the minimum dose. The analysis and comparison of the increased rate of ALT and serum TBIL as well as the liver damage incidence and other adverse reactions in the two groups were carried out. Results: The liver damage incidence in thiamazole group was 11.7%, which was significantly lower than that in propylthiouracil group (26.67%, P=0.031). There were more patients with increased ALT in propylthiouracil group than that in thiamazole group (P=0.006). While there were more patients with increased serum TBIL in thiamazole group than that in propylthiouracil group (P=0.013). Meanwhile, the patient satisfaction in both groups was investigated and the results were statistically analyzed; it was significantly higher in thiamazole group than that in propylthiouracil group, which were 93.3% and 68.3% respectively (P=0.001). Conclusion: By comparing the efficacy of the two therapeutic drugs of hyperthyroidism, we found that the impact of thiamazole on liver function and liver damage incidence were relatively lower than that of propylthiouracil, and the adverse reaction of thiamazole mainly was serum TBIL increase. Therefore, thiamazole is safer with higher patient satisfaction.

Keywords: Thiamazole, propylthiouracil, liver damage

Introduction

Hyperthyroidism is a clinical common and frequently-occurring disease. It is a kind of autoimmune disease caused by excessive secretion of thyroid hormone, resulting in organic metabolic syndrome. Anti-thyroid drug (ATD) has become an important cornerstone for the treatment of hyperthyroidism [1, 2]. Currently, thiamazole and propylthiouracil were two ATDs that widely used in China [3-5]. However, retrospective studies showed that they would induce granulocytopenia, rash and other adverse reactions in the course of clinical treatment [6-9], and the most common one was hepatocyte damage.

In order to explore and analyze the safety of thiamazole and propylthiouracil in the course of treatment and the features of its impact on liver function in patients with hyperthyroidism as well as to provide a reference for clinical rational drug use and for the prevention and treatment of hyperthyroidism, a total of 120

Table 1. General information of patients in two groups

	Sex		Age (years)	Average (years)
	Male	Female		
Thiamazole group (n=60)	24	36	17-67	30.86±6.81
Propylthiouracil group (n=60)	25	35	19-66	31.16±10.27
χ^2	0.034			0.189
P	0.500			0.851

patients with hyperthyroidism who received initial treatment in our hospital from May 2015 to May 2016 were selected as subjects of the study. The reports were as follows.

Materials and methods

Subjects

Hyperthyroidism patients received treatment in our hospital during May 2015 to May 2016 were recruited. This clinical trial was reviewed and approved by the medical Ethics Committee of our hospital, and informed consents were signed by all patients and their family members.

Inclusion criteria: Hyperthyroidism patients who took initial standard treatment; patients and their family members knew about the study and signed informed consents voluntarily; patients who could complete relevant inspections.

Exclusion criteria: Patients with severe self-diseases, such as hepatic cirrhosis and renal failure; patients with mental diseases; patients who were suffering from other illnesses and receiving long-term drug treatment; patients who did not cooperate with medical staff; patients with drug use contraindication.

Grouping and general data

A total of 120 patients with hyperthyroidism were divided into methimazole group and propylthiouracil group by random and double-blind method, with 60 patients in each group. Patients in methimazole group received methimazole treatment, and patients in propylthiouracil group received propylthiouracil treatment. Laboratory examinations were carried out for the detection of liver and thyroid function before treatment.

Therapeutic method

Methimazole group received oral methimazole (produced by Shanghai Huanghai Pharmaceutical Co., Ltd.) treatment with an initial dose of 40 mg/d. Then, after the clinical symptoms of patients improving significantly (about 4-8 weeks), reexamination of thyroid function was performed every 4 weeks. According to the level of thyroid stimulating hormone (TSH), tyroxine (T4) and triiodothyronine (T3), the dose was gradually reduced every 2-4 weeks based on demand. At last, maintenance treatment was given for one year with minimum dose (between 2.5-10 mg/d). Propylthiouracil group received oral propylthiouracil (produced by Nanjing Bai Jingyu Pharmaceutical Co., Ltd.) treatment with an initial dose of 400 mg/d. Then, after the clinical symptoms of patients improving significantly (about 4-8 months), reexamination of thyroid function was performed every 4 weeks. According to the level of TSH, T4 and T3, the dose was gradually reduced every 2-4 weeks based on demand. At last, maintenance treatment was given for one year with minimum dose (between 25-150 mg/d).

Monitoring indexes

The reexamination of liver function and blood routine was performed every 2 weeks in initial treatment stage, and every 4 weeks in maintenance therapy stage. The indexes including liver function indexes (such as ALT and serum TBIL), the liver damage incidence, and occurrence time of liver damage and other adverse reactions of the two groups were monitored.

The evaluation standards on drug-induced liver injury: Firstly, patients not suffered from non-viral hepatitis or autoimmune liver disease, whose liver function was normal before treatment, but damaged after taking medicine indicated by biochemical indexes, those including ALT and serum TBIL (at least one of them) should rise to 2 times or more than normal upper limit, and liver damage caused by taking other medicines should be excluded; secondly, patients suffered from autoimmune liver disease or non-viral hepatitis, whose liver function was abnormal before treatment, and durative exacerbation after taking medicine. Drug-induced liver injury just needed to meet one

Table 2. Comparison of laboratory findings before treatment in both groups

Group	T4 (nmol/L)	T3 (nmol/L)	TSH (nmol/L)	ALT (U/L)	Serum TBIL (μmol/L)
Thiamazole group (n=60)	264.56±18.67	23.57±8.48	17.56±1.34	32.86±19.56	12.62±7.81
Propylthiouracil group (n=60)	269.32±17.82	24.21±8.65	17.48±1.42	31.51±21.45	11.57±8.29
t	1.429	0.409	0.317	0.360	0.714
P	0.156	0.683	0.752	0.719	0.477

Note: T4, tyroxine; T3, triiodothyronine; TSH, thyroid stimulating hormone; ALT, glutamic pyruvic transaminase; TBIL, total bilirubin.

Table 3. Comparison of incidence and occurrence time of liver damage in two groups after treatment

Group	Liver injury incidence (n/%)	Occurrence time of liver damage (d, $\bar{x}$ ± sd)
Thiamazole group (n=60)	7/11.7	17.47±8.56
Propylthiouracil group (n=60)	16/26.67	41.56±8.34
χ^2	4.357	15.614
P	0.031	0.000

of the above two. For patients with abnormal liver function, liver protecting therapy or adjusting dosage should be given.

Patient satisfaction survey: The two groups of patients were given follow-up visit after a year, and they were asked to evaluate the drug therapy from great satisfaction, general satisfaction and dissatisfaction. Then, the results were counted.

Statistical analysis

The analysis of test results was performed with statistical software SPSS 20.0. The enumeration data were expressed by rate, and the differences of independent samples of two groups were carried out with χ^2 test. The measurement data were expressed by mean ± standard deviation ($\bar{x}$ ± sd), and the comparison of those in the two groups was performed with independent-sample t-test. The difference was statistically significant when P<0.05.

Results

General information

There were 120 patients enrolled in the study, including 60 patients in thiamazole group and 60 patients in propylthiouracil group. There was no statistically significant difference of the general conditions and the laboratory examination results between the two groups before the treatment (P>0.05). See **Tables 1** and **2**.

Comparison of incidence and occurrence time of liver damage in the two groups after treatment

Both groups had lesions in the liver. The incidence of hepatic injury was significantly higher in propylthiouracil group than that in thiamazole group with significant difference (P=0.031). The occurrence time of hepatic injury in propylthiouracil group was significantly later than that in thiamazole group, and the difference was statistically significant (P=0.000). See **Table 3**.

Comparison of laboratory test indexes between the two groups after treatment

After 15-week treatment, the thyroid function and liver function of patients were detected, and the differences of TSH, T4 and T3 between the two groups were analyzed, which were not statistically significant (all P>0.05). But ALT and serum TBIL in the two groups showed different characteristics. The serum ALT increased significantly in thiamazole group, however, in propylthiouracil group, the serum TBIL increased significantly, and the comparison of the differences between the two groups was statistically significant (all P<0.05). See **Tables 4** and **5**.

Comparison of other adverse reactions after treatment in the two groups

There were adverse reactions, such as granulocytopenia/agranulocytosis, hypothyroidism, pruritus (rash) showed during the treatment period. The adverse reactions in the two groups were counted and compared without statistically significant difference (P>0.05). See **Table 6**.

Comparison of patient satisfaction degrees of the two groups

The patient satisfaction in the two groups were investigated and statistically analyzed.

Table 4. Comparison of laboratory examination indexes after treatment in both groups

Group	T4 (nmol/L)	T3 (nmol/L)	TSH (nmol/L)	ALT (U/L)	Serum TBIL (μmol/L)
Thiamazole group (n=60)	153.45±16.56	1.91±0.41	4.34±1.23	54.49±35.54	12.46±10.72
Propylthiouracil group (n=60)	158.21±15.89	1.95±0.38	4.47±1.31	38.75±24.47	17.55±11.34
t	1.607	0.554	0.560	2.826	2.526
P	0.111	0.580	0.576	0.006	0.013

Note: T4, tyroxine; T3, triiodothyronine; TSH, thyroid stimulating hormone; ALT, glutamic pyruvic transaminase; TBIL, total bilirubin.

Table 5. Comparison of abnormal liver function incidences between two groups after treatment

Group	Increase of serum ALT (n/%)	Increase of serum TBIL (n/%)
Thiamazole group (n=60)	2/3.33	5/8.33
Propylthiouracil group (n=60)	16/26.67	0/0
χ^2	12.810	5.217
P	0.000	0.029

Note: ALT, glutamic pyruvic transaminase; TBIL, total bilirubin.

Table 6. Adverse reactions after the treatment in the two groups

Group	Granulocytopenia/ agranulocytosis (n/%)	Hypothyroidism (n/%)	Pruritus/ rash (n/%)
Thiamazole group (n=60)	0/0	2/3.33	4/6.67
Propylthiouracil group (n=60)	1/1.67	3/5.00	5/8.33
χ^2	1.008	0.209	0.086
P	0.500	0.500	0.522

The satisfaction degree in thiamazole group was higher than that in propylthiouracil group with statistically significant difference (P=0.001). See **Table 7**.

Discussion

Thioureas and imidazoles are the main drugs used in clinical treatment for hyperthyroidism [9]. At present, thiamazole and propylthiouracil are commonly used in China, so the safety of them is the focus of this study. Liver damage is a common adverse reaction of ATDs [10, 11]. Study indicates that it is related to the drug-induced idiosyncratic reactions of organism, which include allergic reactions and immune-mediated liver function impairment [12]. Besides, "drug poisoning" theory suggested that bioactive metabolite of propylthiouracil presented hepatotoxicity in organism, which could easily cause liver damage [13, 14]. Most of ALTs are in hepatocytes, which concentration is thousands of times more than that in serum. Thus, when a small number of hepatocytes are damaged, ALT level in serum, as one of the most sensitive indexes in detecting liver function impairment, would still increase [15]. The main manifestation of the adverse reaction of thiamazole is cholestatic hepatic injury, resulting in the increase of serum TBIL [16-18]. This experiment found that liver function indexes of patients in two groups increased after treatment. In addition, the incidence of liver damage in propylthiouracil group is significantly higher than that in thiamazole group, which indicated that in medicinal treatment on hyperthyroidism, patients received propylthiouracil were easier to present liver function impairment than patients received thiamazole. However, in thiamazole group, the occurrence time of liver damage was obviously earlier than that in propylthiouracil group, which suggested that compared with propylthiouracil, thiamazole caused earlier liver function impairment. Apart from that, there were more patients with increased serum TBIL in thiamazole group, however, there were more patients with increased ALT in propylthiouracil group. These results indicated that thiamazole mainly caused the increase of serum TBIL while propylthiouracil mainly led to the increase of ALT.

In the safety research of the two treatments, adverse reactions such as granulocytopenia/ agranulocytosis, hypothyroidism and pruritus/ rash appeared but relatively rare [19, 20]. It

Table 7. Comparison of patient satisfaction degree after treatment in both groups

Group	Great satisfaction	General satisfaction	Dissatisfaction	Satisfaction degree
Thiamazole group (n=60)	49	7	4	93.3%
Propylthiouracil group (n=60)	38	3	19	68.3%
χ^2				11.531
P				0.001

indicates that the safety in thiamazole and propylthiouracil groups is relatively reliable in this aspect.

From the investigation and statistical analysis of patient satisfaction in two groups, thiamazole group showed a greater degree of patient satisfaction. It may relate to the features such as lower incidence of liver damage, lighter damage to liver and more significant curative effect of orally taking thiamazole [21]. In addition, thiamazole can increase thiol level in blood plasma, and reduce the activity of antioxidant enzyme *in vivo*, thus the activity of extracellular free radical scavenging system is reduced [17].

But there are some limitations in this study such as simple experimental design, relatively fewer subjects and short observation time. Besides, the safety of ATDs in groups such as children, gravida and the aged as well as the features of impact on liver function need to be further explored.

In conclusion, thiamazole exerted lesser influence on liver function and lower incidence of liver damage when compared with propylthiouracil in medicinal treatments for hyperthyroidism patients. It mainly caused the increase of serum TBIL and had higher medication safety and patient satisfaction. However, in propylthiouracil treatment, the incidence of liver damage was higher. It mainly caused the increase of ALT. These results are of great reference significance for the guidance of clinical medication as well as the prevention and treatment for liver damage.

Disclosure of conflict of interest

None.

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