

PLASMAPHERESIS IN THE MANAGEMENT OF PROPYLTHIOURACIL TOXICITY

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SUMMARY : *Thyroidectomy is an alternate mode of therapy in the treatment of toxic nodular goitre. Thionamides are widely used to provide an euthyroid state before surgery. Toxic hepatitis due to thionamide is an extremely rare situation that requires withdrawal of the drug. We report a 50-year-old male patient with toxic nodular goitre who developed hepatotoxicity against thionamide and in whom an euthyroid state could only be obtained with the use of plasmapheresis preoperatively. In a 14-day-period, totally 17.5 L plasma was removed and replaced without any complications in seven sessions on alternate days. We suggest that therapeutic plasmapheresis is an alternative and effective way to provide an euthyroid state before surgery in situations when other therapies are ineffective or contraindicated and emergency exists.*

Key Words : *Hyperthyroidism, Thiocarbamates Toxicity, Plasmapheresis.*

INTRODUCTION

Toxic nodular goitre is a common cause of hyperthyroidism. Because malignancy incidence of scintigraphically hypoactive nodules in diffuse hyperactive thyroid tissue is high (1), surgery is preferred in these circumstances. Thionamides are widely used as antithyroid agents. A well known side effect of the drug is agranulocytosis due to its allergic reaction.

Cholestatic jaundice is another rare side effect that may require withdrawal of the drug (2). When the drug must be withdrawn for any reason, other choices of treatment such as β -blockers, iopanoic acid, lithium, or glucocorticoids can be used. But if the hyperthyroid state is severe and a rapid response is needed, these choices may not answer to the requirements. In such cases, plasmapheresis is suggested as an alternative way in reducing the

circulating thyroid hormones and immune factors (3).

CASE REPORT

I.C., a 50-year-old male patient was admitted to hospital with irritability, weight loss, exhaustion, emotional instability, poor appetite, and tremor. He was 170 cm tall and weighed 67 kg. Blood pressure measured 170/80 mm Hg, and heart rate was 112/min and regular. Body temperature was 36,8°C. The skin was hyperhydrotic and there was mild exophthalmos. Two nodules sized 5x2 cm and 3.5x2 cm were palpated in each thyroid lobes. Biochemical measurements were all normal with the exception of mild elevations in AST, ALT, and GGT. Serum free T3 and free T4 levels were elevated; TSH level was decreased. Ultrasound and scintigraphy of the thyroid gland revealed hyperfunctional multinodular goitre. Thyroid fine

needle aspiration biopsy revealed class III cytology, and surgery was chosen for the ultimate treatment. To provide an euthyroid state before surgery, propranolol 20 mg twice a day, propylthiouracil 50 mg three times a day, and amitriptyline 25 mg a day were started orally. Serum liver enzymes levels started to rise (AST from 40U/L to 147 U/L, ALT from 89 U/L to 265U/L, ALP from 144 U/L to 230 U/L, GGT from 281 U/L to 789U/L and bilirubine from 1.04 mg/dL to 5.24 mg/dL) gradually in three weeks after administration of amitriptyline. Viral hepatitis serologic markers were negative. Drug induced toxic hepatitis was suggested and confirmed by liver needle biopsy. Propylthiouracil and amitriptyline were withdrawn. Antithyroid therapy was continued with propranolol 40 mg four times a day and iopanoic acid 500 mg a day only. Liver enzymes began to decrease with fluctuations. after withdrawal of propylthiouracil and amitriptyline while thyroid hormones stayed at the same high levels. Thus, to prepare the patient for thyroidectomy, plasmapheresis (Fresenius AS104 PL 1 plasma exchange Set) was planned. 2.5 L plasma was removed with substitution of 1L 5 % albumin and 1.5 L fresh frozen plasma in each session. At least 10 mEq Ca gluconate was given iv bolus. Plasma fibrinogen, FDP, Na⁺, K⁺, Ca⁺⁺ levels were followed during the procedure with 30 minutes' intervals. In a 14 day-period, totally 17.5 L plasma have been removed and replaced without any complications in 7 session on alternate days. In this period, propranolol was continued with the same dose and Lugol solution was added with the dose of 10 drops per day. Serum FT3 was 14.66 pg/ml and FT4 was 7.25 ng/ml before the procedure, and decreased to 3.32 pg/ml and 2.19 ng/ml, respectively after plasmapheresis. Change in TSH level was not significant (0.18 IU/ml to 0.23 IU/ml). Serum antithyroglobulin and antimicrosomal antibody levels changed from 19.34 IU/ml to 44.94 IU/ml, and from 89.07 IU/ml to 9.94 IU/ml respectively. Near total thyroidectomy was performed without any hyperthyroid attack or other serious complications. Six months' follow-up of the patient showed that all thyroid hormones and blood counts were normal, THS level was still depressed and liver functions returned to normal.

DISCUSSION

Hyperthyroidism is widely treated with

conventional antithyroid therapy that includes thionamides and propranolol. Side effects of thionamides such as agranulocytosis or cholestatic jaundice are very rare, but when they occur, the drug should be discontinued. Jaundice due to propylthiouracil usually develops after four to six weeks of treatment (4, 5). A case of fulminant hepatitis has been reported by Milton in 1953 only after 300 mg of propylthiouracil and was suggested to be an hypersensitivity reaction of the drug (6). In fact, thyrotoxicosis itself may cause hepatic changes on biopsy and elevations in liver enzyme and bilirubin levels. But, hepatic changes are usually minimal and bilirubin levels generally stay below 2 mg/dL (7). Liver biopsy in our case revealed a typical drug-induced cholestatic hepatitis with severe enlargement of portal canals, mononuclear cell infiltration, destruction of ductal epithelium, bile plugs in canalicules, and striking cholestasis at portal areas. Whether or not the cause of hepatotoxicity is amytriptilin is not clear and needs to be answered. In general, the tricyclic antidepressants are known not to form hepatotoxicity with the exception of a reported imipramine-induced jaundice (8). Because thyroid fine needle biopsy suggested a doubt of malignancy and because antithyroid therapy other than propylthiouracil failed to provide an euthyroid state, we decided to perform plasmapheresis to the patient. Plasma exchange techniques have been tried to the patients with severe hyperthyroidism, thyroid storm, or infiltrative Graves' ophthalmopathy. It has not been found effective in iodine-induced hyperthyroidism (9). In another study, measured thyroid hormones were not significantly different immediately after the procedure in patients to whom the plasmapheresis performed for any other reason (10). On the other hand, in the cases of emergencies like thyroid storm or unresponsive Graves' ophthalmopathies and especially when thionamides are contraindicated, many studies confirmed the usefulness of plasmapheresis (11-15).

As a result, we conclude that plasmapheresis is an easy and safe way to remove the high levels of circulating thyroid hormones in a short period. It could be beneficial in patients in whom sufficient response cannot be obtained with conventional antithyroid therapy and in cases with contraindications for thiocarbamides are present.

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