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PERSPECTIVE

PROPYLTHIOURACIL IS AN OLD BUT STILL USEFUL DRUG

Propylthiouracil (6-propyl-2-thiouracil, PTU) is probably one of the oldest drugs on the market in the Western world. Its use as an antithyroid drug has been well established for nearly 70 years (1). It was originally developed in the search for taste-changing substances (2). Its goitrogenic effect in laboratory animals led to the detection of its antithyroid effect. In the United States it is currently used as a second-line agent for control of hyperthyroidism and as a first-line agent in pregnancy and routinely by some practitioners.

PTU is rapidly absorbed from the gastrointestinal tract, peaking in serum within 1 to 2 hours after drug ingestion. Its half-life in serum is 75 minutes. Approximately 75% of PTU is bound to albumin. Serum levels have, however, little to do with its antithyroid effect, which typically lasts from 12 to 24 hours. PTU is actively transported into the thyroid, where it inhibits both the organification of iodine into tyrosine residues in thyroglobulin and the coupling of iodotyrosines. In contrast to methimazole (MMI), it has an important extrathyroidal action: it inhibits peripheral conversion of thyroxine (T_4) into the biologically more active (3,5,3¢-triiodothyronine (T_3) by inhibiting the enzyme 5 ¢-deiodinase type 1.

The pharmacokinetics are not altered in patients with hyperthyroidism or in chronic renal failure (3). They are, however, strongly influenced by iodine. In the presence of low intrathyroidal iodine concentration, PTU and/or its metabolites remain in the thyroid for a much longer time than in serum. With an iodide load (and high intrathyroidal iodine concentrations), PTU is more rapidly metabolized, and during long-term iodine contamination its uptake is also decreased (4). Patients with iodine-induced hyperthyroidism therefore need higher doses to control their thyrotoxicosis.

PTU like MMI, can cause rash, urticaria, arthralgias, arthritis, fever, nausea, or vomiting in approximately 14 to 20% of patients (3). PTU can also leave a bitter or metallic taste. Most of these side effects are considered to be allergic reactions. In one large study, the median duration of these side effects was 1.5 months. They were mostly controllable so that treatment could be continued in half of the affected patients, although at a lower dose (5). If one drug is not tolerated, then it can usually be substituted by the other drug. Some patients, however, experience cross-reactivity.

More severe, sometimes life-threatening, side effects such as agranulocytosis and hepatotoxicity were reported more than 60 years ago (6). Agranulocytosis

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is a rare but serious complication of treatment with PTU as well as with MMI. Its prevalence in patients treated with PTU is in the range of 0.1 to 0.5%. The prevalence seems to be independent of the age of the patient and of the dose used (3). Most—but by far not all—cases of agranulocytosis occur within 3 months after starting treatment. The utility of monitoring the white-count regularly during treatment has been challenged because of the usually very sudden onset of PTU-induced agranulocytosis. Patients taking PTU in whom fever or a sore throat develops should, however, immediately have a white-cell count with differential and discontinue the medication until the result is available. Recovery from agranulocytosis usually takes a few days, but morbidity and death from serious infections can occur, especially if agranulocytosis is prolonged (7).

Hepatic toxicity is also a rare, but especially in PTU-treated patients, sometimes life-threatening complication of thionamide therapy. This well-known phenomenon has recently raised much concern in the United States. PTU-induced hepatitis was first reported 4 years after the introduction of PTU (6). The results of baseline liver-function tests are, however, often abnormal in hyperthyroidism, and have not been found to be predictive for PTU-associated hepatotoxicity. Transient elevations in transaminases may occur during the first 2 months in up to one third of patients taking PTU and usually resolve with no intervention.

The first case of fulminant hepatic failure attributed to PTU was reported in 1953 by Eisen (8). Today, severe PTU-induced hepatotoxicity is postulated to be a dose-independent, idiosyncratic hypersensitivity reaction. It can occur any time over the course of therapy. The onset is sudden and the course is rapidly progressive. Its estimated incidence seems to be less than 0.5% in 35 patients with PTU-induced severe hepatic failure well-documented in the literature (9). Based on the assumption that 15,000 adults are treated with PTU per year in the United States and that the incidence of PTU-induced severe liver injury is approximately 0.1%, it has been calculated that this complication will develop in 15 adults annually. Of these 15 adults 10% will progress to acute liver failure requiring liver transplantation. Therefore, one can estimate that 1 of 10,000 adult patients treated with PTU will have severe acute liver failure requiring transplantation. The situation seems to be even worse for children, which has raised concern; the calculated risk to develop severe hepatotoxicity is in the range of 1 of 2000 children treated with PTU. This calculation is essentially based on data provided by the United Network for Organ Sharing (UNOS). These data from the United States, unfortunately, cannot be compared with data from Europe, since the European Liver Transplant Registry (ELTR) does not specify routinely which drug—except for acetaminophen—is responsible for their cases of drug-induced hepatic failure requiring liver transplantation.

In view of the data presented above and the very small but possible risk of MMI-induced embryopathy, a Task Force of the American Thyroid Association together with the American Association of Clinical Endocrinologists and the Food and Drug Administration has recently published the following recommendations regarding the use of PTU (10): 1) PTU should not be prescribed as a first-line agent in children or adults; 2) PTU is recommended when an antithyroid drug is to be started during the first trimester of pregnancy (until more is known about possible teratogenic effects of MMI); 3) PTU is recommended in preference to MMI in life-threatening thyrotoxicosis because of its ability to inhibit peripheral conversion of T_4 to T_3; 4) PTU should be used in patients with adverse reactions to MMI other than agranulocytosis and for whom radioiodine or surgery are not treatment options; 5) routine monitoring of the white-cell count and of liver function is not useful but should be performed in symptomatic patients.

My personal additional recommendation is that PTU should be used in preference to MMI also in lactating mothers, since its secretion in the milk is less than that of MMI (11).

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