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Commentary

A comparison of potency differences among thyroid peroxidase (TPO) inhibitors to induce developmental toxicity and other thyroid gland-linked toxicities in humans and rats

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ABSTRACT

The potencies of resorcinol, 6-propylthiouracil (PTU) and methimazole (MMI) for inducing developmental toxicity and neurotoxicity were compared in pregnant rats, regarded as valid model for human thyroid toxicity. Profound differences on maternal thyroid hormone levels (THs), maternal toxicity as well as developmental and neurotoxicity sequelae occurred. Resorcinol affected none of those end points. PTU and MMI caused significant effects. Therapy with either PTU or MMI during the first trimester of human pregnancy can cause reductions of maternal THs, accompanied by disruptions of prenatal development. Clinical MMI studies show sporadic evidence of teratogenic effects, with equivocal relation to thyroid peroxidase (TPO) inhibition. In recent decades no MMI associated prenatal toxicity has been reported, an outcome possibly related to carefully managed therapy. Orally administered resorcinol was rapidly absorbed, metabolized and excreted and was undetectable in the thyroid. In contrast, PTU or MMI accumulated. Resorcinol's potency to inhibit TPO was profoundly lower than that of PTU or MMI. Quantum chemical calculations may explain low resorcinol reactivity with TPO. Thus, distinctions in the target organ and the TPO inhibitory potency between these chemicals are likely contributing to different reductions of maternal THs levels and affecting the potency to cause developmental toxicity and neurotoxicity.

1. Introduction

This review article offers a historical perspective on the use of three chemicals well known to inhibit the biosynthesis of thyroid hormones. All publications cited, related to resorcinol, PTU and MMI, are almost exclusively focused on pregnancy and developmentally toxic consequences in the offspring if such information is available. Animal studies reviewed derive entirely from rats. PTU and MMI are anti-thyroid drugs widely used in humans to treat hyperthyroidism such as Graves' disease. The data available from human studies during pregnancy refer only to the therapeutic use of PTU and MMI. Resorcinol has a very long history of medicinal use in dermatology in humans. Thyroid gland toxicities in both male and female patients are well documented. There is, however, no mentioning in the medical histories as to whether any of the female subjects were pregnant. Our review includes mechanistic considerations as to the scientific evidence that help explain drastic potency differences among the three chemicals on blood thyroid hormone levels and their ability to cause adverse developmental outcomes upon maternal exposure during pregnancy. Included in this review is an assessment of the present use of resorcinol in formulations intended for human therapeutic applications and for cosmetic indications. The quantities incorporated into such products are trivial compared to large-scale applications of resorcinol in industrial production processes. The evidence from measurements of occupational exposure levels indicates that exposures are quite low and below the detection limits, especially in the rubber industries (IPCS, 2006).

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1.1. Maternal thyroid homeostasis and pregnancy in human subjects

Maintenance of maternal euthyroidism during pregnancy is important for normal development, in particular during neurological development of the fetus. In the first trimester of human gestation, the embryo/fetus depends entirely on the maternal thyroid hormones (THs): thyroxine (T4) and/or triiodothyronine (T3). Later in pregnancy and during lactation, maternal THs still contribute significantly to fetal and neonatal thyroid homeostasis (Hartoft-Nielsen et al., 2011).

Thyroid peroxidase (TPO) is a heme-containing multifunctional enzyme located in the apical membrane of follicular thyroid cells and is essential for the synthesis of THs. TPO catalyzes several reactions, including the oxidation of iodide, iodination of tyrosyl residues of thyroglobulin (Tg), and the coupling of iodotyrosyls to produce Tg-bound THs (Ehrenshaft and Mason, 2006). Crofton (2012) and Paul et al. (2014) pointed out that inhibition of such TPO functions may cause a reduction of blood THs levels, resulting in two kinds of adverse outcomes: one is developmental abnormalities or neurological dysfunction; the other is thyroid hyperplasia or thyroid tumors as shown (Fig. 1).

For this review of the scientific evidence and to elucidate crucial factors contributing to such severe adverse outcomes, we examined the open literature regarding three prototypical TPO inhibitors: 6-propylthiouracil (PTU; CAS No. 51-52-5), methimazole (MMI; CAS No. 60-56-0) and resorcinol (1,3-dihydroxybenzene; CAS No. 108-46-3). There is some published information available that PTU and MMI can cause thyroid hyperplasia or thyroid tumors. Hackmon et al. (2012) reported, however, that no thyroid tumors were induced by PTU and MMI in humans. In regard to resorcinol, both human clinical case studies and animal experimental data indicate that the possibility of thyroid tumor induction appears to be negligible (RTF, 2014; US-NTP, 1992). Thus, for the survey at hand, we focused on developmental toxicity and neurotoxicity. Such adverse outcomes are presently of ever growing concern (Crofton, 2012). In our literature analyses we compared the potencies of the three agents to cause prenatal toxicity and establish relationships to blood THs levels. We then explored the main sources of the observed differences in rats from several perspectives.

1.2. Anti-thyroid drug treatment in human subjects

The anti-thyroid drugs, PTU and MMI, are TPO inhibitors, and PTU also acts by inhibiting the enzyme deiodinase type 1 (D1), which converts T4 to its active form T3 (Rijntjes et al., 2013; Zoeller and Crofton, 2005). These drugs have been used therapeutically in human subjects to treat hyperthyroidism for more than six decades (Cooper, 2005; Rivkees and Mattison, 2009). Pregnant women were among those patients. The therapeutic objective was to maintain free THs concentrations in maternal serum within a physiological range. However, these drugs are known to readily cross the placenta (Mortimer et al., 1997). Prenatal/developmental toxicity caused by MMI in the earlier years of its use has been associated with characteristic teratogenic effects. They include aplasia cutis congenita, choanal atresia, tracheoesophageal fistulas and other less common abnormalities (Earl et al., 2010). In contrast to MMI, few PTU developmental toxicity studies in humans have been published. During the last two decades a growing number of reports have raised concerns about PTU-induced hepatotoxicity (Hackmon et al., 2012), which seems to be unrelated to TPO inhibition. The US Food and Drug Administration (US-FDA, 2016) designates both drugs as “Pregnancy Category D (There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.)”. The complete bases for this designation are not easily accessible to the public. This classification indicates that a human embryo/fetal risk may exist based on adverse reaction reports from investigational or clinical patient experience. The therapeutic benefits and lack of alternative drugs, however, may warrant use of the drugs in pregnant women despite the potential risk.

1.3. Therapeutic use of resorcinol in humans

It is well documented that resorcinol is a TPO inhibitor (Divi and Doerge, 1994; Fraser et al., 1955; Lindsay et al., 1992; Paul et al.,

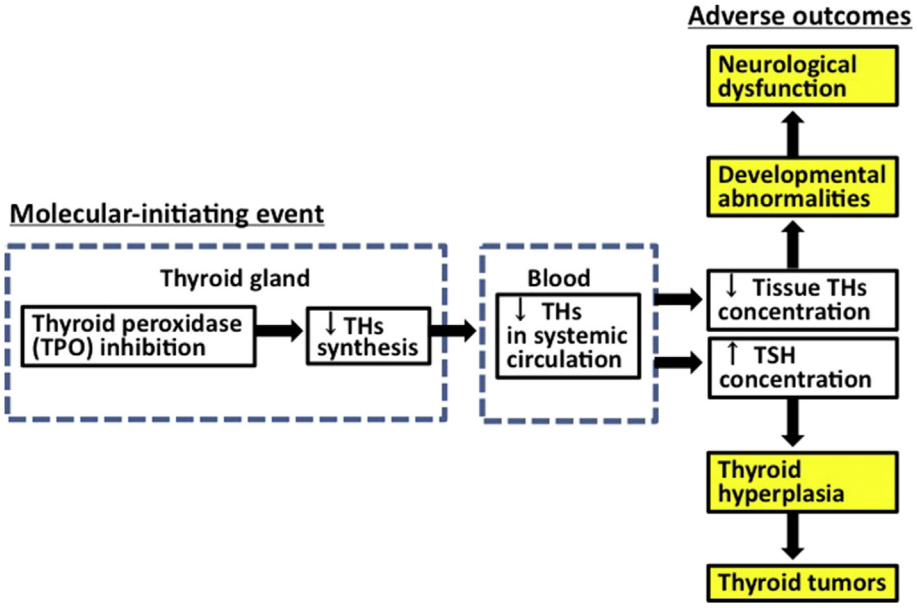

Fig. 1. Adverse outcome pathway (AOP) initiated by TPO inhibition. Modified from Crofton (2012) and Paul et al. (2014).