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Breastfeeding and Antithyroid Drugs: A View from Within

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Antithyroid drugs · Breastfeeding · Graves' disease · Hyperthyroidism · Propylthiouracil · Carbimazole · Methimazole

Abstract
The aim of this communication is to provide information regarding the use of antithyroid drugs (ATD) during lactation. Three ATD are used today: propylthiouracil (PTU), methimazole (MMI) and carbimazole (CMZ). The latter is a prodrug which is bioactivated to MMI. PTU is transferred in small amounts (0.025%) into milk. These amounts were considered nonsignificant for inducing adverse effects for the suckling infant. The amount of MMI excreted in milk is equal to MMI levels in serum. Due to its lower concentrations in milk, PTU was used for decades as the treatment of choice during breastfeeding. Recent studies have demonstrated that physical development, intelligence scores and thyroid status of children whose mothers had received MMI while breastfeeding were similar to those of healthy children. These new data offered clinicians an alternative drug approach. Several hepatic dysfunction studies have been published so far. Clinical manifestations varied from mild to severe hepatic failure, liver transplantation or death. Most PTU cases were more severe, idiosyncratic and not dose related. We recommend that PTU should not be prescribed for thyrotoxicosis during lactation. MMI should be used instead, in doses up to 30 mg/day, while PTU should be used in special cases for a restricted time period.

Introduction

Breastfeeding is considered the optimal way of newborn and infant feeding by clinicians and social workers [1, 2].

It provides multiple advantages for the mental and physical development of the infant and is also implicated in the reduction of the development of several diseases in adulthood [3]. Breastfeeding period comprises a critical time frame during which a newly diagnosed disease or the relapse of a chronic autoimmune disease in a new mother could encumber her physical status, hindering the breastfeeding process in several aspects. Moreover, drug treatment of such clinical entities during this period raises safety issues regarding the excretion of pharmaceutical agents used by the mother into human milk, and the manifestation of potential toxicological manifestations in the neonate [4].

The vast majority of thyroid abnormalities are chronic autoimmune diseases, which are found in approximately 5% of new mothers in the general population [5]. Hyperthyroidism due to Graves' disease (GD) can occur during the postpartum period, as a relapse of previous GD or a newly diagnosed case with no apparent thyroid disease background. In this case, antithyroid drugs (ATD) are considered the treatment of choice by most endocrinologists for Graves' hyperthyroidism (GH). The same applies for cases of postpartum thyrotoxicosis.

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Pharmacokinetics of ATD

ATD which are used today include propylthiouracil (PTU), carbimazole (CMZ) and methimazole (MMI) [6]. CMZ is a prodrug which is rapidly and totally bioactivated to MMI. PTU is about 80% protein bound, while MMI is non-protein bound and more lipid soluble [7]. The pharmakokinetic properties of all ATD have been extensively evaluated in previous studies. The half-life of MMI is 4–6 h, while PTU has a half-life of about 75 min [8]. MMI has a minimal plasma protein binding, longer plasma half-life and is more lipid soluble compared to PTU. These characteristics favor the increased passage of MMI over PTU into the human milk. Moreover, PTU is more easily ionized in serum than in human milk, a phenomenon which inhibits its transfer into human milk [9].

Excretion of ATD into Human Milk – Experimental and Clinical Data

Previous experimental studies assessed the excretion of ATD into human milk [10, 11]. In most of these studies, the mean serum PTU concentration after oral ingestion in thyrotoxic lactating women was compared with the mean total amount of PTU excreted in human milk. Data showed that PTU is transferred in small amounts into human milk. Approximately only 0.025% of the administered PTU dose was transferred, suggesting that PTU is minimally concentrated in breastmilk [10]. These amounts were considered nonsignificant for inducing adverse effects for the suckling infant. Similar studies evaluated the excretion of MMI into human milk. It was demonstrated that the amount of MMI excreted in milk was equal to MMI levels in serum, with a total of 70.0 μg MMI excreted in the milk of normal lactating subjects, 8 h following oral administration of 40 mg of MMI. The authors hypothesized that these levels of MMI could have a potentially harmful effect on the infant [12, 13].

Based on the above experimental studies regarding ATD use during lactation, it was suggested that PTU should be preferred over MMI, due to its lower concentration in milk [14]. In 1989, the American Academy of Paediatrics listed PTU as a lactation-compatible treatment [15]. At that time, PTU had already been considered as the first-line treatment in postpartum GH. This approach has been deeply established in the clinical practice of physicians for decades. However, in vitro models are often differentiated from in vivo circumstances [4]. In the case of drug transfer from maternal plasma to milk, the physiochemical properties and concentrations of a pharmaceutical agent are not always translated into clinically significant consequences affecting the newborn. Several additional parameters are of major importance in the occurrence of epiphenomena that could predispose breastfeeding children to drug toxicity related to maternal drug exposure [16]. Factors such as the frequency and quantity of meals of the newborn, relation of meals to drug ingestion, peak drug levels in human milk, and infant's hepatic and renal function are significant parameters in determining the risk of drug exposure in this case. Hence, a compound that is considered minimally excreted in breast milk compared to another could be harmful in certain circumstances. These additional parameters are not easily incorporated into existing in vitro risk-predicting models. New models that offer a more holistic approach of these issues are under investigation, but further studies are still required for their validation in the general population [4].

With that in mind, clinical studies are of paramount importance in confirming previous experimental data which proposed that the increased amount of MMI could predispose to toxicological manifestations in the infant. This critical gap between experimental data and the potential clinical consequences was clarified by later studies that assessed the possible effects of MMI on physical development, intelligence scores and thyroid status of children whose mothers received MMI postpartum while breastfeeding [17, 18]. No differences compared to healthy children of the same age group were found. Moreover, in mothers with iatrogenic hypothyroidism due to MMI, no harmful effects of the above parameters were found in their offspring [19]. These data have established a new era in the medical treatment of thyrotoxicosis during lactation. As initially suggested by pioneer researchers [20], although MMI is excreted at higher levels in human milk compared to PTU, no clinically significant effects were evident in those studies. Of note, similar data for PTU are lacking. These new data offered clinicians an alternative drug approach. As a result of the above scientific findings, the Endocrine Society in 2007 recommended [21] that ATD therapy (PTU <300 mg/day, MMI <20 mg/day) may be considered during lactation, although some reservations still exist due to the small number of infants investigated so far. It is advisable that until more studies are available, monitoring the thyroid function of infants may be an option.

Hepatoxicity after ATD Use

Several reports of severe hepatic dysfunction for both ATD, but especially for PTU, were published in the past [22, 23]. Clinical manifestations varied from mild and reversible hepatic injury to severe hepatic failure, liver transplantation or death. Most PTU cases were more severe, idiosyncratic and not dose related. Fatal outcome was observed in PTU-treated children in the vast majority of cases [24, 25].

Based on these data, in July 2009, the Hyperthyroidism Guidelines Task Force of the American Thyroid Association recommended that PTU should not be prescribed as the first-line agent in children or adults except in special clinical situations such as the first trimester of pregnancy [26], severe life-threatening thyrotoxicosis or in patients exhibiting adverse reactions to previous MMI treatment [27]. The US Food and Drug Administration followed with the same recommendations in 2010 [28]. Recent reviews on the general use of ATD in lactation consider both ATD drugs compatible for the treatment of hyperthyroidism during lactation [29, 30]. In July 2011, the American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum recommended the use of moderate doses (MMI in doses up to 20–30 mg/day and PTU less than 300 mg/day) of ATD during breastfeeding as a safe approach during breastfeeding [31]. It is currently recommended that breastfeeding infants of mothers taking ATD should be screened using thyroid function tests. According to the Task Force, PTU at doses of up to 300 mg/day is a second-line agent due to concerns about its severe hepatotoxicity.

Recommendation

In conclusion, in our opinion and in the light of these new data regarding PTU hepatoxicity, PTU should not be prescribed for thyrotoxicosis in breastfeeding women. MMI should be used instead, at the minimal effective doses of up to 30 mg/day, while PTU should be used only in women with previous allergic manifestations to MMI for a restricted time period. Permanent treatment of thyrotoxicosis, such as ablation with radioactive iodine or thyroidectomy, should be considered in such cases when an euthyroid stage will need to be secured. Continuation of breastfeeding under ATD should be encouraged by clinicians as long as the proven benefits of breastfeeding and the risks are discussed extensively with the new mother in order to provide an integrated therapeutic approach.

Disclosure Statement

The authors have no conflicts of interest.

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