NOVA

University of Newcastle Research Online

nova.newcastle.edu.au

Goel, Himanshu; Dudding, Tracy (2015) Carbimazole/methimazole embryopathy in siblings: a possible genetic susceptibility. Originally published in Birth Defects Research Part A: Clinical and Molecular Teratology Vol. 97, Issue 11, p. 755-758

Available from:

<http://dx.doi.org/10.1002/bdra.23200>

This is the peer reviewed version of the following article: Goel, H. and Dudding, T. (2013), Carbimazole/methimazole embryopathy in siblings: A possible genetic susceptibility. Birth Defects Research Part A: Clinical and Molecular Teratology, 97: 755–758, which has been published in final form at doi:10.1002/bdra.23200. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving

Accessed from: <http://hdl.handle.net/1959.13/1318720>

Carbimazole/methimazole embryopathy in siblings: a possible genetic susceptibility.

Corresponding author

Dr Himanshu Goel

Postal address: Hunter Genetics, P O Box 84, Waratah, NSW 2298, Australia
Hunter Genetics, PO Box 84, Waratah, NSW 2298, Australia
University of Newcastle, Callaghan, NSW
Phone: +61-2-49853100, fax: +61-2-49853105,
Email: himanshu.goel@hnehealth.nsw.gov.au

Co-author

Dr Tracy Dudding

Postal address: Hunter Genetics, P O Box 84, Waratah, NSW 2298, Australia
Hunter Genetics, PO Box 84, Waratah, NSW 2298, Australia
University of Newcastle, Callaghan, NSW
Phone: +61-2-49853100, fax: +61-2-49853105,
Email: tracy.dudding@hnehealth.nsw.gov.au

Running title: Carbimazole/methimazole embryopathy.

ABSTRACT

Background: The teratogenic effects of antenatal exposure of antithyroid drugs, carbimazole and methimazole have been well reported in the literature. These comprise of typical facial features and a wide variety of malformations such as choanal atresia, tracheo-oesophageal anomalies, congenital heart disease and ectodermal defects. However, the longitudinal studies have failed to establish the consistent teratogenicity of these drugs.

Cases: we report here two siblings with physical features consistent with carbimazole/methimazole embryopathy. We also describe previously unreported minor dental anomalies in these siblings with antenatal exposure of carbimazole.

Conclusions: Generally, only a small proportion of prenatally exposed children have the typical manifestations, and the presence in siblings supports a possible hereditary susceptibility to carbimazole/methimazole embryopathy. This highlights the importance of recognising this diagnosis prior to a subsequent pregnancy.

Key words: carbimazole, methimazole, choanal atresia, dysmorphism, congenital abnormalities, embryopathy

INTRODUCTION

As all antithyroid medications are potential teratogens, their use during pregnancy presents a challenging balance between optimal control of hyperthyroidism and their possible harmful foetal effects. Carbimazole/methimazole embryopathy is characterised by typical facial features including broad forehead, arched and flared eyebrows, broad nasal bridge, hypoplastic alae nasi and ear abnormalities. A wide variety of malformations such as choanal atresia, aplasia cutis, tracheo-oesophageal anomalies, congenital heart disease, omphalocele, patent vitellointestinal duct and nipple anomalies (Bowman and Vaidya, 2011). The teratogenic risk of carbimazole/methimazole appears to be limited to early gestation (Barbero et al., 2004). It remains insignificant in some studies (Di Gianantonio et al., 2001), and very small in others (between 1 in 1000 and 1 in 10,000) (Karlsson et al., 2002). The concept of genetic susceptibility to drug teratogenicity has been proposed in a few studies (Koenig et al., 2010), and the occurrence of embryopathy in siblings supports this hypothesis. There are only two previously published reports of siblings affected with carbimazole/methimazole embryopathy (Barbero et al., 2008; Gripp et al., 2011). Dental anomalies are not a recognised association with carbimazole/methimazole embryopathy. We describe two siblings with carbimazole/methimazole embryopathy in addition to previously undescribed dental anomalies.

CASE REPORT

Patient 1

Patient 1 was a 12-year-old girl born to non-consanguineous Caucasian parents. Her mother had a corneal graft for keratoconus. The proband's mother was diagnosed with Graves' disease at time of conception and was commenced on carbimazole 30mgs daily. She was rendered euthyroid, and the dose was gradually reduced to 15mgs by the third trimester. Her other medications were folic acid and multivitamins. The pregnancy was otherwise uncomplicated, and her regular prenatal sonograms were normal. Patient 1 was born vaginally at term with a birth weight of 3.5 kg (50th percentile). Apgar scores were 7, 9 and 10 at 1, 5 and 10 minutes respectively. . At birth, she was noted to have right sided choanal atresia, hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and a small left ear. She also had a subaortic ventriculo-septal defect that resolved by age 4 years. At 12 years of age, she had normal growth and development (figure 1a and 1b). She did not

have coloboma, developmental delay or aplasia cutis. She had generalised dental spacing and was missing 1 premolar and 1 molar tooth (figure 2a). Her molecular karyotype using the BlueGnome 60k oligonucleotide array was normal, 46XX. One older sibling was a boy who was in good health without any evidence of carbimazole embryopathy or dental anomaly (figure 3).

Patient 2

During her third pregnancy, the mother's hyperthyroidism remained well controlled with carbimazole 15mg daily. Antenatal scans were normal. A male baby was delivered vaginally at term with a birth weight of 4.6 kg (90th-98th centile). His Apgar scores were 9, 10 and 10 at 1, 5 and 10 minutes.. He had mild hypospadias for which he underwent a meatoplasty soon after birth. His facial features were remarkably similar to his sister but different to their unaffected brother. He had hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and small ears (figure 1c and 1d). He also had generalised dental spacing, microdontia and was missing 2 premolars (figure 2b). He did not have choanal atresia or a congenital heart defect. At 8 years of age, he had normal growth and development.

DISCUSSION

Carbimazole, used for the treatment of hyperthyroidism, is a pro-drug that is converted to its active form, methimazole, after absorption. Methimazole inhibits the production of the thyroid hormones T3 and T4 (thyroxine). Carbimazole/methimazole embryopathy was first reported when an increased incidence of cutis aplasia was noted following the prenatal exposure to methimazole (Milham and Elledge, 1972). Several authors have subsequently reported a characteristic combination of facial features and other malformations including oesophageal atresia with or without TE fistula (Clementi et al., 1999; Ramirez et al., 1992), and choanal atresia (Barbero et al., 2004; Barwell et al., 2002), following prenatal exposure to methimazole. Similar observations were noticed after prenatal exposure to carbimazole, which is fully metabolized to methimazole (Jansson et al., 1983). Therefore, the syndrome resulting from prenatal exposure to either drug is best referred to as carbimazole/ methimazole embryopathy (Foulds et al., 2005). The teratogenicity of carbimazole/methimazole remains controversial. Although a number of case reports and case-studies report a teratogenic effect of carbimazole/methimazole, a prospective cohort study (Momotani et al., 1984) and more recently a population-based matched case-control study do not show a significant association between carbimazole/methimazole and adverse pregnancy outcome (Chen et al., 2011). The possibility that maternal hyperthyroidism might be the risk factor rather than methimazole exposure has also been raised (Barwell et al., 2002). Recently, Bowman et al has published an extensive

review on this subject (Bowman et al., 2011). The authors concluded that carbimazole has a teratogenic potential and they advised prescribing physicians to be aware of the potential association of carbimazole with the congenital anomalies.

Both siblings had facial features previously reported in other children exposed to carbimazole/methimazole during pregnancy. These include hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and small ears (Bowman et al., 2011). These facial features were not seen in the unaffected sibling or the parents. In addition to the characteristic facial features, patient 1 had a ventriculo-septal defect and choanal atresia; and patient 2 had mild hypospadias, all of which have been previously reported in children with intrauterine exposure to carbimazole/methimazole (Mujtaba and Burrow, 1975). Based on overlapping characteristic features, we believe that both siblings have a diagnosis of carbimazole/methimazole embryopathy. These siblings, in addition to the two previously reported affected sib pairs in the literature (Barbero et al., 2008; Gripp et al., 2011), suggest a genetic susceptibility to the teratogenicity of carbimazole/methimazole in a small proportion of exposed children. Underlying aetiological factors may include genetic polymorphisms influencing drug metabolism in the mother or foetus.

We also considered a dosage effect of carbimazole on the fetus. Patient 1 was exposed to a larger dose (30 mg) than Patient 2 (15 mg) during the first two trimesters. The published literature does not give any indication of a dosage effect or gender predisposition to carbimazole or methimazole (Clementi et al., 1999). Although dental defects have not been previously reported, there are several reports of other ectodermal anomalies like aplasia cutis, (Clementi et al., 1999; Foulds et al., 2005; Gripp et al., 2011; Rodriguez-Garcia et al., 2011), dystrophic nails (Martin-Denavit et al., 2000), and nipple anomalies (Foulds et al., 2005; Gripp et al., 2011; Martin-Denavit et al., 2000). The underlying mechanism of these defects is still unknown.

This report extends the phenotype of carbimazole/methimazole embryopathy to include dental anomalies, and highlights the importance of recognising this uncommon but potentially preventable condition prior to a subsequent pregnancy.

ACKNOWLEDGEMENTS

The authors thank the family for their participation.

REFERENCES

Barbero P, Ricagni C, Mercado G, Bronberg R, Torrado M. 2004. Choanal atresia associated

- with prenatal methimazole exposure: three new patients. *Am J Med Genet A* 129A(1):83-86.
- Barbero P, Valdez R, Rodriguez H, Tiscornia C, Mansilla E, Allons A, Coll S, Liascovich R. 2008. Choanal atresia associated with maternal hyperthyroidism treated with methimazole: a case-control study. *Am J Med Genet A* 146A(18):2390-2395.
- Barwell J, Fox GF, Round J, Berg J. 2002. Choanal atresia: the result of maternal thyrotoxicosis or fetal carbimazole? *Am J Med Genet* 111(1):55-56; discussion 54.
- Bowman P, Osborne NJ, Sturley R, Vaidya B. 2011. Carbimazole embryopathy: implications for the choice of antithyroid drugs in pregnancy. *Qjm*.
- Bowman P, Vaidya B. 2011. Suspected Spontaneous Reports of Birth Defects in the UK Associated with the Use of Carbimazole and Propylthiouracil in Pregnancy. *J Thyroid Res* 2011:235130.
- Chen CH, Xirasagar S, Lin CC, Wang LH, Kou YR, Lin HC. 2011. Risk of adverse perinatal outcomes with antithyroid treatment during pregnancy: a nationwide population-based study. *Bjog* 118(11):1365-1373.
- Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT, Tenconi R. 1999. Methimazole embryopathy: delineation of the phenotype. *Am J Med Genet* 83(1):43-46.
- Di Gianantonio E, Schaefer C, Mastroiacovo PP, Cournot MP, Benedicenti F, Reuvers M, Occupati B, Robert E, Bellemin B, Addis A, Arnon J, Clementi M. 2001. Adverse effects of prenatal methimazole exposure. *Teratology* 64(5):262-266.
- Foulds N, Walpole I, Elmslie F, Mansour S. 2005. Carbimazole embryopathy: an emerging phenotype. [Review] [28 refs]. *American Journal of Medical Genetics Part A* 132A 2:130-135.
- Gripp KW, Kuryan R, Schnur RE, Kothawala M, Davey LR, Antunes MJ, Reichard KW, Schneider A, Hall BD. 2011. Grade 1 microtia, wide anterior fontanel and novel type tracheo-esophageal fistula in methimazole embryopathy. *Am J Med Genet A* 155A(3):526-533.
- Jansson R, Dahlberg PA, Lindstrom B. 1983. Comparative bioavailability of carbimazole and methimazole. *Int J Clin Pharmacol Ther Toxicol* 21(10):505-510.
- Karlsson FA, Axelsson O, Melhus H, Cooper DS, Mandel S. 2002. Severe embryopathy and exposure to methimazole in early pregnancy [3] (multiple letters). *Journal of Clinical Endocrinology and Metabolism* 87 (2):947-949.
- Koenig D, Spreux A, Hieronimus S, Chichmanian RM, Bastiani F, Fenichel P, Brucker-Davis F. 2010. Birth defects observed with maternal carbimazole treatment: Six cases reported to Nice's Pharmacovigilance Center. [French]. *Ann Endocrinol (Paris)* 71 (6):535-542.
- Martin-Denavit T, Edery P, Plauchu H, Attia-Sobol J, Raudrant D, Aurand JM, Thomas L. 2000. Ectodermal abnormalities associated with methimazole intrauterine exposure. *Am J Med Genet* 94(4):338-340.
- Milham S, Elledge W. 1972. Maternal Methimazole and Congenital Defects in Children. *Teratology* 5(1):125.
- Momotani N, Ito K, Hamada N, Ban Y, Nishikawa Y, Mimura T. 1984. Maternal hyperthyroidism and congenital malformation in the offspring. *Clin Endocrinol (Oxf)* 20(6):695-700.
- Mujtaba Q, Burrow GN. 1975. Treatment of hyperthyroidism in pregnancy with propylthiouracil and methimazole. *Obstet Gynecol* 46(3):282-286.
- Ramirez A, Espinosa de los Monteros A, Parra A, De Leon B. 1992. Esophageal atresia and

tracheoesophageal fistula in two infants born to hyperthyroid women receiving methimazole (Tapazol) during pregnancy. *Am J Med Genet* 44(2):200-202.

Rodriguez-Garcia C, Gonzalez-Hernandez S, Hernandez-Martin A, Perez-Robayna N, Sanchez R, Torrelo A. 2011. Aplasia cutis congenita and other anomalies associated with methimazole exposure during pregnancy. *Pediatr Dermatol* 28(6):743-745.

Figure legends:

Figure 1

(a and b) Female patient at 12 years of age with hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and a small left ear. (c and d) 8-year-old brother had hypoplastic alae nasi, upslanting palpebral fissures, arched eyebrows, broad nasal bridge, bulbous nose, telecanthus and small ears.

Figure 2

(a) Sister had generalised dental spacing and was missing 1 premolar and 1 molar tooth. (b) Brother had generalised dental spacing, microdontia and was missing 2 premolars.

Figure 3

16-year-old unaffected brother