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DISCLOSURE STATEMENT

Speaker: John C. Carey

Dr. Carey has documented that he has nothing to disclose.

Rational Approaches to the Assessment of Clinical Evidence in the Determination of Teratogenicity: Methimazole as an Illustration

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Rational Approaches to Clinical Evidence: Methimazole

Purpose of Presentation

- To review 3 approaches to the case report/series methodology

- To illustrate the approaches in analyzing the evidence for methimazole

Examples of Established Human Teratogens Recognized by Astute Observer and Confirmed by Epidemiological Methods/Animal Models

- Alcohol
- Valproic acid
- Isotretinoin
- Warfarin
- Methotrexate

Jones & Carey, 2011

Examples of Human Teratogens Based on Clinical Evidence

- D-Penicillamine
- Fluconazole
- MMF

Carey et al., 2009

Jones & Carey, 2011

Proof of Causation in Teratology

- Epidemiological studies
- Clinical Evidence
- Biologic Plausibility - supportive
  - Animal Models
  - Pharmacology

Brent, Shepard, Holmes and others

Astute Clinician Method

- "Rare malformation/rare exposure method"
  - "Alert clinician", case report
- Criteria:
  - Critical time
  - Rare exposure/rare outcome
  - 3 or more cases
- Biologic plausibility - supportive

Shepard, 1994
Carey et al., 2009

Clinical Evidence

The Astute (Alert) Clinician Model:

Rare Exposure, Distinctive Outcome

Carey, *AJMG* 111:54, 2002

Carey et al., *BDR* 85:63, 2009

Rational Approaches to Clinical Evidence: Methimazole

Methods

- Review of literature in PubMed
- Perusal of Table of Contents of *BDRA* 2010 - 2021

Results

Three Approaches:

- Syntropy index – product of prevalences
  - Opitz, 1982
  - Carey et al., 2009
- Case – Series Approach- pattern recognition
  - Petersen et al., 2008
- Disproportionality analysis
  - Hyoun et al., 2012, methotrexate

Application to Methimazole

Birth Defects Research (Part A) 85:63–68 (2009)

Review Article

Determination of Human Teratogenicity by the Astute Clinician Method: Review of Illustrative Agents and a Proposal of Guidelines

John C. Carey,[1,2*] Lynn Martinez,[2] Elizabeth Balken,[2] Marsha Leen-Mitchell,[2] and Julia Robertson[2]

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Received 19 May 2008; Revised 4 September 2008; Accepted 6 September 2008

Rare exposure-Rare outcome

Astute Clinician Method

- Rare exposure – prevalence < 1 in 1,000

- Rare outcome – prevalence < 1 in 1,000

  * Multiple defects and/or

  distinctive outcome, a pattern

  increase likelihood of causal inference

Carey et al., 2009

MMF As A Potential Teratogen

- Prevalence of OFCs – 1/500
- Prevalence of microtia – 1/5000

Combined occurrence = ~1 in 2.5 million

- Usage of MMF in pregnancy < < 1/1000

American Journal of Medical Genetics 131A:287–298 (2004)

Rapid Publication

Mechanistic and Epidemiologic Considerations in the Evaluation of Adverse Birth Outcomes Following Gestational Exposure to Statins

Robin J. Edison and Maximilian Muenke*

Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

American Journal of Medical Genetics Part A 146A:2701–2705 (2008)

Research Letter

Maternal Exposure to Statins and Risk for Birth Defects: A Case-Series Approach

Emily E. Petersen,[1,2] Allen A. Mitchell,[3] John C. Carey,[4] Martha M. Werler,[3] Carol Louik,[3] Sonja A. Rasmussen,[1]* and the National Birth Defects Prevention Study

[1]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia
[2]The CDC Experience Fellowship, Atlanta, Georgia
[3]Slone Epidemiology Center at Boston University, Boston, Massachusetts
[4]Department of Pediatrics, University of Utah Health Sciences Center, Salt Lake City, Utah

N = 21 cases

"no distinctive pattern"

Results 1

Three Approaches:

- Syntropy index – product of prevalences
  - Opitz, 1982
  - Carey et al., 2009
- Case – Series Approach- pattern recognition
  - Petersen et al., 2008
- Disproportionality analysis
  - Hyoun et al., 2012, methotrexate

Application to Methimazole

Birth Defects Research (Part A) 94:187–207 (2012)

Teratogen Update: Methotrexate

Sara C. Hyoun,[1] Sarah G. Običan,[2] and Anthony R. Scialli[2,3]*

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Received 9 December 2011; Revised 9 January 2012; Accepted 13 January 2012

Apply **disproportionality analysis**

Risk of Cleft Lip and/or Palate Associated With Antiepileptic Drugs: Postmarketing Safety Signal Detection and Evaluation of Information Presented to Prescribers and Patients

Bita Rezaallah DMD, MAS, David John Lewis PhD, Hans-Florian Zeilhofer Prof. Dr. med., Dr. med. dent. & Britt-Isabelle Berg Dr. med., Dr. med. dent.

Therapeutic Innovation & Regulatory Science **53**, 110–119 (2019) | Cite this article

Results 2

Disproportionality Analysis - Methotrexate:

Compared to the proportion of all malformations in total case reports with some proportion derived from MACDP

e.g. Terminal transverse defects

- Mtx – 6.4%
- MACDP – 0.8%

Hyoun et al., 2012

Results

Three Approaches:

- Syntropy index – product of prevalences
  - Opitz, 1982
  - Carey et al., 2009
- Case – Series Approach
  - Petersen et al., 2008
- Disproportionality analysis
  - Hyoun et al., 2012

Application to Methimazole

Results 3

Methimazole (MMI):

- Treatment of hyperthyroidism
  (0.2% of pregnancies)
- Carbimazole converted to MMI
- MMI – < ½ of pregnancies with hyperthyroid
- Concerns about teratogenicity, 1972
  cutis aplasia

- Late 1980s – present: reports (>100) of choanal atresia, TEF, hypoplastic nipples, omphalocoele, facial features, hearing loss

- Controlled studies: 6 (including case-control)

Is MMI a Human Teratogen?

- Diav-Citrin and Ornoy, 2002
- Bowman (2011), Ting et al. (2013), "MMI embryopathy"
- Reprotox, 2022

Pattern:

choanal atresia, TEF, cutis aplasia
hypoplastic nipples, facial features

Is MMI a Human Teratogen? Clinical evidence

- The pattern: combination of TEF and choanal atresia- 4 case reports, 1 in US product of prevalences = 1 in 24 Mill,

  -1 case by chance every 6 years

  (Gripp et al., 2011)

- Recognizable pattern after rare exposure,

  < < 1/1000

  rare outcome; in ~30% of reports, MCA

Results 4

Disproportionality Analysis – Methimazole:

Compared to the proportion of specific malformations among all case reports of MMI (N = 102) with proportions among cases of malformations in UBDN,

2003 – 2007 (N = 4,674) *BDRA*, 2010

2012 - 2016 (N= 5,625) *BDRA*, 2019

Results 5

MMI

Disproportionality Analysis

	MMI Cases (109)	UBDN (4,674)	UBDN (5625)
TEF	5.5 (6)	1.5%	1.4%
CA	27.5 (30)	0.7%	0.7%
Omphalo	3.6 (4)	1.3%	1.3%

Results 6

MMI

Disproportionality Analysis

	UK Cases (72)	UBDN (4,674)
TEF	2.7 (2)	1.5%
CA	6.9 (5)	0.7%
Omphalocele	5.5 (4)	1.3%

Bowman et al., 2011

Rational Approaches to the Assessment of Clinical Evidence in the Determination of Teratogenicity: Methimazole

Discussion

- Limitations of Case Report/Series Method, publication bias, no denominator, chance

- Some established (e.g., MMF) teratogens based on distinctive pattern & biologic plausibility

- From controlled studies risk of pattern, few %, but clinical evidence for teratogenicity persuasive

Rational Approaches to the Assessment of Clinical Evidence in the Determination of Teratogenicity: Methimazole

Conclusions

- There is a need for systematized, critical, thoughtful approaches to clinical evidence
- Comprehensive phenotype analysis and precise documentation of observations crucial step