

Oxytocin Treatment May Improve Infant Feeding and Social Skills in Prader-Willi Syndrome

Nancie J. MacIver, MD, PhD

Prader-Willi syndrome (PWS) is a common neurogenetic obesity syndrome that is complicated by hypotonia, poor feeding, and failure to thrive in early infancy, followed by hyperphagia, obesity, and profound social defects later in life.¹ Autopsy studies have shown a significant reduction in the number and volume of oxytocin-producing neurons in the paraventricular nucleus of the hypothalamus in individuals with PWS.² Given the importance of oxytocin in regulating social interactions and mother-infant bonding, it has been postulated that treatment of PWS with oxytocin may improve poor feeding and social behaviors in infants. This was tested in the study presented by Tauber et al³ in this issue of *Pediatrics*.

PWS results from lack of expression of paternally inherited genes on chromosome 15q11-q13, due to deletion of the paternally inherited region, to maternal uniparental disomy (ie, both copies inherited from the mother), or to an imprinting defect. *Magel2* is one of the affected genes located on 15q11-q13, and *Magel2* mutations have been found in individuals with autism spectrum disorder, intellectual disability, and some features of PWS.⁴ *Magel2*-deficient mice have been shown to reproduce some of the phenotype of PWS, and have 50% mortality from impaired suckling activity.⁵ Interestingly, the hypothalamus of *Magel2*-deficient newborns shows reduced oxytocin, and administration

of a single dose of oxytocin within the first 5 hours of life rescued abnormal feeding behaviors by restoring normal suckling and preventing early death.⁵ In a separate study, *Magel2*-deficient mice displayed abnormal social recognition and social interactions that improved after 1 week of oxytocin treatment in the first week of life.⁶

In the phase 2 study presented by Tauber et al³ in this issue of *Pediatrics*, 18 human infants <6 months old were treated with intranasal oxytocin for 7 days in 1 of 3 treatment groups: group 1 received oxytocin every other day, group 2 received oxytocin once daily, and group 3 received oxytocin twice daily. Importantly, there were no adverse events, and there were no differences in outcomes among the 3 treatment groups. Overall, the authors observed 88% of subjects (16 of 18 studied) had normalization of sucking and improved swallowing studies immediately after treatment. Treated infants also had increased alertness, less fatigability, increased facial expressions, and less social withdrawal. One very interesting finding of this study was in the long-term observational data, in which it was reported that 81% of oxytocin-treated subjects with PWS were able to crawl as toddlers, compared with 13% of untreated age-matched controls with PWS. This improvement in gross motor skills was presumed secondary to improved muscle tone and motor coordination. As the treatment was given for only 1 week during infancy, this finding implies that a short course



Division of Pediatric Endocrinology, Duke University School of Medicine, Durham, North Carolina

DOI: 10.1542/peds.2016-3833

Accepted for publication Nov 17, 2016

Address correspondence to Nancie J. MacIver, MD, PhD, Department of Pediatrics, Duke University School of Medicine, 3000 Erwin Rd, Ste 200, DUMC Box 102820, Durham, NC 27710. E-mail: nancie.maciver@duke.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2017 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The author has indicated she has no financial relationships relevant to this article to disclose.

FUNDING: This work was supported by National Institutes of Health grant R01-DK106090. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The author has indicated she has no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this paper can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2016-2976.

To cite: MacIver NJ. Oxytocin Treatment May Improve Infant Feeding and Social Skills in Prader-Willi Syndrome. *Pediatrics*. 2017;139(2):e20163833

of oxytocin during infancy may have potential long-term benefits. The authors suggest a positive feedback loop may explain these interesting results, whereby exogenous oxytocin promotes the continued secretion of endogenous hormones, leading to long-term benefits. Moreover, the authors observed increased connectivity of the right superior orbitofrontal network after treatment with oxytocin and suggest that this increased connectivity may also mediate long-term effects. Increased circulating acyl-ghrelin (the active form of ghrelin) was observed at day 2 and day 4 after treatment with oxytocin. As ghrelin is a well-described “hunger” hormone, the influence of oxytocin on acyl-ghrelin levels may explain, in part, the improvement in feeding behavior seen in this study.

Other studies also have examined the use of oxytocin in humans with PWS. In an earlier study by Tauber et al,⁷ adults with PWS were treated with intranasal oxytocin or placebo. Subjects who received oxytocin had improved behaviors, including increased trust in others, decreased sadness, and less disruptive behavior shortly after receiving the medication.⁷ This study did not, however, discern any difference in social skills between the treated and untreated groups.⁷ A more recent double-blind randomized placebo-controlled crossover study of subjects with PWS age 12 to 30 years examined intranasal oxytocin on behavioral outcomes and found little effect.⁸ In yet another double-blind, placebo-controlled crossover study, intranasal oxytocin given

to 25 children with PWS aged 6 to 14 years resulted in no significant effect of oxytocin on social behaviors overall; however, children younger than 11 experienced less anger, sadness, conflict, and food-related behavior, along with a generalized improvement in social behavior.⁹ Altogether, these results suggest that oxytocin may have a greater benefit in PWS when given earlier in life. In that regard, this new study by Tauber et al³ is important, as it is the first to examine the effect of oxytocin on human infants with PWS.

In summary, early administration of oxytocin to infants with PWS shows promise as potential treatment of poor social behavior and feeding in infancy. Larger clinical trials are needed to confirm this result and determine long-term effects and safety. These findings are important, as the results of this study may be applicable to autism spectrum disorder and to other disorders in which early feeding dysfunction, abnormal musculoskeletal function, or depressed social interactions threaten well-being.

ABBREVIATION

PWS: Prader-Willi syndrome

REFERENCES

1. Irizarry KA, Miller M, Freemark M, Haqq AM. Prader Willi syndrome: genetics, metabolomics, hormonal function, and new approaches to therapy. *Adv Pediatr.* 2016;63(1):47–77
2. Swaab DF, Purba JS, Hofman MA. Alterations in the hypothalamic

paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases. *J Clin Endocrinol Metab.* 1995;80(2):573–579

3. Tauber M, Boulanouar K, Diene G, et al. The use of oxytocin to improve feeding and social skills in infants with Prader-Willi syndrome. *Pediatrics.* 2016;139(2):e20162976
4. Schaaf CP, Gonzalez-Garay ML, Xia F, et al. Truncating mutations of MAGEL2 cause Prader-Willi phenotypes and autism. *Nat Genet.* 2013;45(11):1405–1408
5. Schaller F, Watrin F, Sturny R, Massacrier A, Szeppetowski P, Muscatelli F. A single postnatal injection of oxytocin rescues the lethal feeding behaviour in mouse newborns deficient for the imprinted Magel2 gene. *Hum Mol Genet.* 2010;19(24):4895–4905
6. Meziane H, Schaller F, Bauer S, et al. An early postnatal oxytocin treatment prevents social and learning deficits in adult mice deficient for Magel2, a gene involved in Prader-Willi syndrome and autism. *Biol Psychiatry.* 2015;78(2):85–94
7. Tauber M, Mantoulan C, Copet P, et al. Oxytocin may be useful to increase trust in others and decrease disruptive behaviours in patients with Prader-Willi syndrome: a randomised placebo-controlled trial in 24 patients. *Orphanet J Rare Dis.* 2011;6:47
8. Einfeld SL, Smith E, McGregor IS, et al. A double-blind randomized controlled trial of oxytocin nasal spray in Prader-Willi syndrome. *Am J Med Genet A.* 2014;164A(9):2232–2239
9. Kuppens RJ, Donze SH, Hokken-Koelega AC. Promising effects of oxytocin on social and food-related behaviour in young children with Prader-Willi syndrome: a randomized, double-blind, controlled crossover trial. *Clin Endocrinol (Oxf).* 2016;85(6):979–987

Oxytocin Treatment May Improve Infant Feeding and Social Skills in Prader-Willi Syndrome

Nancie J. MacIver

Pediatrics 2017;139;

DOI: 10.1542/peds.2016-3833 originally published online January 18, 2017;

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/139/2/e20163833>

References

This article cites 9 articles, 0 of which you can access for free at:
<http://pediatrics.aappublications.org/content/139/2/e20163833#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Endocrinology
http://www.aappublications.org/cgi/collection/endocrinology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Oxytocin Treatment May Improve Infant Feeding and Social Skills in Prader-Willi Syndrome

Nancie J. MacIver

Pediatrics 2017;139;

DOI: 10.1542/peds.2016-3833 originally published online January 18, 2017;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/139/2/e20163833>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2017 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

