Drug for preterm labor may cause neuronal damage

Nearly a decade ago, Beth Crowell—a mother of autistic triplets—raised the possibility that the drug terbutaline, used to stop premature labor, played a role in her children's autism. New evidence strongly supports this theory, by showing that terbutaline is a potent developmental neurotoxin.

Melissa Rhodes and colleagues recently administered terbutaline to neonatal rats at a developmental stage similar to that of late fetal development in humans. The researchers report that the drug "elicited neurochemical changes indicative of neuronal injury and reactive gliosis," and that further evaluation revealed structural abnormalities in the cerebellum, hippocampus, and somatosensory cortex. Particularly notable was a reduced number of Purkinje cells and thinning of the granular and molecular layers in the cerebellum, a region strongly implicated in autism.

> Their findings, Mellisa Rhodes and colleagues say, "point to a causal relationship between fetal terbutaline exposure and the higher incidence of cognitive and neuropsychiatric disorders reported for the offspring of women receiving terbutaline therapy for preterm labor."

"These effects," Rhodes et al. say, "point to a causal relationship between fetal terbutaline exposure and the higher incidence of cognitive and neuropsychiatric disorders reported for the offspring of women receiving terbutaline therapy for preterm labor."

In related research, Rhodes et al. found that rats exposed to terbutaline during the neonatal period experienced brain changes that made them abnormally susceptible later in life to the harmful effects of the organophosphate insecticide chlorpyrifos (CPF). "You could see the biochemical evidence of the damage [from the combination of terbutaline and CPF] early on," says Theodore Slotkin, a member of the research team. "The functional and structural changes emerged or were evidenced in adolescence or adulthood."

This finding, the research team concludes, suggests that "terbulatine, like chlorpyrifos, is a developmental neurotoxicant, and that its use in the therapy of preterm labor may create a subpopulation that is sensitized to the adverse neural effects of a subsequent exposure to organophosphate insecticides."

Additional studies by the same researchers found that rats given terbutaline before birth showed decreased DNA synthesis in several brain regions, with results depending on gender and the timing of exposure; and that prenatal terbutaline exposure appears to alter the development of noradrenergic projections to the cerebellum.

Terbutaline, an asthma medication, is not approved by the Food and Drug Administration for use as a treatment for preterm labor, and the drug has never been formally tested for this purpose. In 1997, the FDA issued a letter cautioning doctors against prescribing terbutaline to pregnant women for extended periods, noting that the drug had been shown to be effective only at delaying premature labor for 48 hours or less, and warning that its effects on fetal development were largely unknown. However, the drug—frequently administered by subcutaneous pump—is currently being used as a long-term treatment for up to a quarter of a million pregnant women annually.

Editor's note: Our thanks to Audrius Plioplys, M.D., for bringing the issue of terbutaline's potential dangers to our attention.

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"Terbutaline is a developmental neurotoxicant: effects on neuroproteins and morphology in cerebellum, hippocampus, and somatosensory cortex," M. C. Rhodes, F. J. Seidler, A. Abdel-Rahman, C. A. Tate, A. Nyska, H. L. Rincavag, and T. A. Slotkin, *Journal of Pharmacology and Experimental Therapeutics*, Vol. 308, No. 2, February 2004, 529-37 (Epub ahead of schedule November 10, 2003). Address: Melissa Rhodes, Department of Pharmacology, Duke University Medical Center, Durham, NC 27710.

—and—

"Does pharmacotherapy for preterm labor sensitize the developing brain to environmental neurotoxicants? Cellular and synaptic effects of sequential exposure to terbutaline and chlorpyrifos in neonatal rats," M. C. Rhodes, F. J. Seidler, D. Qiao, C. A. Tate, M. M. Cousins, and T. A. Slotkin, *Toxicology and Applied Pharmacology*, Vol. 195, No. 2, March 2004, 203-17. See address above.

—and—

"Developmental toxicity of terbutaline: critical periods for sex-selective effects on macromolecules and DNA synthesis in rat brain, heart, and liver," M. C. Garofolo, F. J. Seidler, M. M. Cousins, C. A. Tate, D. Qiao, and T. A. Slotkin, *Brain Research Bulletin*, Vol. 59, No. 4, January 2003, 319-29. M. C. Garolofo, Department of Pharmacology, Duke University Medical Center, Durham, NC 27710.

—and—

"Prenatal terbutaline exposure in the rat: selective effects on development of noradrenergic projections to cerebellum," T. A. Slotkin, F. E. Baker, S. S. Dobbins, J. P. Eylers, S. E. Lappi, and F. J. Seidler. *Brain Research Bulletin*, Vol. 23, No. 4-5, 1989, 263-5. Address: Theodore Slotkin, Department of Pharmacology, Duke University Medical Center, Durham, NC 27710.

—and—

"Doctors weigh risks of drugs in pregnancy," Erika Niedowski, *The Morning News* (Fayetteville), April 27, 2004.

—and—

"Prenatal use of terbutaline and autism," Beth Crowell and Adam Kerzner, *ICPA Newsletter*, Nov./Dec. 1997.

FDA approves "black box" antidepressant warning

(continued from page 2)

The new analysis, which used different methods and different statistics than Mosholder's study, concluded that there is a "consistent link" between the use of any type of antidepressant drugs and suicidal tendencies in children. FDA analyst Tarek Hammad, who coauthored the review, said the data revealed that two to three percent of children treated with antidepressants developed suicidal thoughts or behavior as a result of treatment. While children taking antidepressants are sometimes suicidal to begin with, Hammad noted that the increased risk detected by the study is "beyond the suicidality as a result of the disease being treated."

While some research has suggested that Prozac is less dangerous than other antidepressants, the new FDA statement concludes that "the finding of an increased risk of suicidality in pediatric patients applied to all the drugs studied (Prozac, Zoloft, Remeron, Paxil, Effexor, Celexa, Wellbutrin, Luvox, and Serzone) in controlled studies." The agency is calling for black box warnings to be placed on all antidepressants, including those not yet clinically tested on pediatric patients.

However, the FDA stopped short of banning the use of antidepressants for pediatric patients, an action already taken in Great Britain where most antidepressants can no longer be prescribed for children.

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"FDA statement on recommendations of the Psychopharmacologic Drugs and Pediatric Advisory Committees," September 16, 2004, www.fda.gov.

—and—

"FDA panel urges black box warnings for antidepressants on child suicide risk," *Medical News Today*, September 16, 2004.

—and—

"Antidepressant study seen to back expert," Gardiner Harris, *New York Times*, Aug. 20, 2004.

LETTER TO THE EDITOR

To the Editor:

Re vaccine injury lawsuits:

I am an attorney, and the mother of a vaccine-injured autistic son. I have prepared, for the benefit of other parents, a "how-to-do-it" book titled "Vaccine Victims: A Guide to Bringing Your Vaccine Injury Claim." The book is for educational purposes, and is not intended to constitute legal advice.

The book consists of about 250 pages of detailed information and will be individually printed in response to orders. To purchase a copy, send a check or money order for $49 payable to Sandra Styka,Law Office of Sandra Styka, 383 Ontario Street, Buffalo, NY 14207.

Sandra Styka