Biomedical Update:

Caution warranted over generic seizure drug

Physicians who treat seizure disorders are often hesitant to switch patients from brand-name anticonvulsant drugs to generic brands. A new study of phenytoin supports these cautions, showing that the brand-name version (Dilantin) can have very different effects than the generic version.

Researcher B. J. Wilder notes, "Unlike many other drugs, phenytoin does not respond in the body in a linear fashion. For example, a 6 percent change in the rate at which the drug is absorbed by the body, or bioavailability, can result in a 25 percent increase in the amount of phenytoin in the blood."

Wilder gave 24 volunteers a single dose of one version of the drug (either generic or brand) during a meal, and two weeks later administered the other version of the drug. He reports that the bioavailability of the generic drug was 13 percent lower than that of the brand-name drug, which would translate into a 37 percent decrease in the concentration of phenytoin in the blood. For nearly half of individuals taking the drug, he says, "that would mean they no longer have enough of the drug in their bodies to control their seizures."

Conversely, Wilder says, switching from generic phenytoin to Dilantin could increase the blood concentration of the drug by an average of 102 percent, which "would likely cause 84 percent of the patients to have too much of the drug in their bodies, which could lead to serious side effects" such as confusion or drowsiness.

Wilder notes that generic forms of seizure drugs, while less expensive, are likely to cost medical plans more money because patients will require more intensive monitoring.

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"Substitution of generic drugs may cause problems for epilepsy patients," press release, American Academy of Neurology, August 28, 2001.

Tuberous sclerosis study: clues about autism's roots?

Tuberous sclerosis (TS) is a genetic disorder that causes benign tumors to grow in various organs, including the brain. While previous studies suggested that tumors (known as "tubers") in the brain greatly increase the risk of autism in children with tuberous sclerosis, a new study casts doubt on this finding. In addition, the new study reports no evidence that tubers in any single brain region can trigger autism.

Diane Chugani and colleagues evaluated 26 children with tuberous sclerosis, dividing them into three groups: autistic subjects, non-autistic but mentally retarded subjects, and subjects with relatively normal intelligence and no evidence of autism. All of the subjects had intractable epilepsy.

Using MRI and PET scans to evaluate brain structure and function, the researchers found that tubers increased a child's risk of being autistic only slightly, with eighty-three percent of children in the non-autistic group exhibiting at least one temporal-lobe tuber. "We found that in these children, autism results from a complex combination of events in different parts of the brain, rather than from one single source," Chugani says. In particular, the researchers found that abnormal biochemical patterns in the cortex were linked to impaired communication skills, while abnormalities in subcortical regions were associated with stereotypical behaviors and lack of social interaction.

The researchers say their findings may be relevant to researchers studying autistic children who do not have tuberous sclerosis.

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"Autism in tuberous sclerosis complex is related to both cortical and subcortical dysfunction," E. Asano, D. C. Chugani, O. Muzik, M. Behen, J. Janisse, R. Rothermel, T. J. Mangner, P. K. Chakraborty, and H. T. Chugani, *Neurology*, Vol. 57, No. 7, October 9, 2001, 1269-77. Address: Diane Chugani, Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, MI 48201.

Williams: MRI scans show opposite defect of that seen in autism

Children with Williams syndrome, a genetic disorder that causes motor and cognitive disabilities and elfin features, differ from autistic children in a very significant way: most are extraordinarily sociable. In fact, the disorder has been dubbed "cocktail party syndrome," because children with Williams syndrome are loquacious, outgoing, and verbally expressive.

In a recent study, J. E. Schmitt et al. studied the size of the cerebellum in 20 individuals with Williams syndrome and 20 non-disabled control subjects. The researchers found that in the cerebellar vermis, lobules VI-VII and VIII-X were significantly larger in the Williams syndrome group than in the controls. The researchers note that their finding is interesting in light of the fact that autistic individuals—who generally are aloof and have poor social and conversational skills—have reduced size of the cerebellar vermis.

Schmitt and colleagues say, "Given that reductions in posterior vermis size have been implicated in flattened affect and autistic features, increased vermis size in subjects with Williams syndrome may be related to the hypersociality and heightened affective expression characteristic of individuals with this condition."

Editor's note: While Williams syndrome and autism would seem to be very different, four cases in which the two conditions co-occurred were reported by Christopher Gillberg and colleagues. Also, individuals with Williams syndrome share some features with autistic individuals, including obsessiveness, ritualistic behaviors, hyperactivity, hypersensitive hearing, and (frequently) savant-like musical skills. Williams syndrome is caused by the deletion of two genes on chromosome 7, a chromosome also linked to autism and language disorders.

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"Enlarged cerebellar vermis in Williams syndrome," J. E. Schmitt, S. Eliez, I. S. Warsofsky, U. Bellugi, and A. L. Reiss, *Psychiatric Research*, Vol. 35, No. 4, July-August 2001, 225-9. Address J. E. Schmitt, Stanford Psychiatry Neuroimaging Laboratory, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 401 Quarry Road, Stanford, CA 94305-5719.

Growth factor levels low in autistic children

Substances called growth factors play a key role in brain development before birth. One of these substances, insulin-like growth factor-I (IGF-I), can affect brain size, myelination (the coating of neurons with an insulating covering), and the development of neurons in particular brain areas.

In a recent study, Finnish researchers measured IGF-I levels in 11 young autistic children and 11 non-autistic control subjects. R. Vanhala and colleagues found that cerebrospinal fluid levels of IGF-I were significantly lower in the autistic subjects than in the controls.

"IGF[I may play a role in pathogenetic mechanisms of autism," the researchers say, "and the role of neurotrophinc factors in autism and other neurodevelopmental diseases should be studied further."

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"Low levels of insulin-like growth factor-I in cerebrospinal fluid in children with autism," R. Vanhala, U. Turpeinen, and R. Riikonen, *Developmental Medicine and Child Neurology*, Vol. 43, No. 9, September 2001, 614-6. Address: R. Vanhala, Unit of Child Neurology, Hospital for Children and Adolescents, Helsinki, Finlind, raija.vanhala@huch.fi.