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Phase I trial of a novel anticonvulsant for infantile spasms: Safety and hormonal effects of a corticotropin releasing hormone antagonist in humans

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Abstracts

3. Phase I Trial of a Novel Anticonvulsant for Infantile Spasms: Safety and Hormonal Effects of a Corticotropin Releasing Hormone Antagonist in Humans

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Corticotropin releasing hormone (CRH) is a neurotransmit-ter in cortical, limbic, and autonomic brain regions and the primary modulator of the release of ACTH from the pitu-itary in response to stress. Dysfunction of CRH-mediated neurotransmission is emerging as a critical mechanism in sev-
eral human disorders such as anxiety, depression, and infan-tile spasms. Therefore, limiting the peptide's availability at its receptor sites is a potentially powerful means of therapy for these disorders. Inhibitory analogues of CRH have been tested in rodents and nonhuman primates. The safety and the hormonal effects of these compounds in humans are un-
known. We report on the administration of a CRH-antago-nist, α-helical-CRH-(9-41) to 6 adult humans. Each received two intravenous infusions: 50 μg/kg on the first morning and 100 μg/kg on the second. These doses block both endo-crine and central effects of CRH in experimental animals. ACTH, cortisol, electrolytes, glucose, and autonomic param-eters were measured before and after infusions and at selected subsequent time-points. Control samples, were obtained on a third morning when no antagonist was infused. Infusion of α-helical-CRH-(9-41) did not alter heart rate, blood pres-sure, temperature, or plasma electrolytes and glucose. Prein-fusion levels of plasma ACTH averaged 26.8 ± 6.7 pg/ml on the first day and 29.0 ± 5.8 pg/ ml on the second. Postin-fusion values were 11.8 ± 2 and 11.5 ± 2.4 pg/ml, signifi-cantly lower than preinfusion levels. Plasma cortisol levels, which averaged 21.4 ± 4 μg/dl on the first morning and 22.9 ± 4.2 on the second, were also significantly decreased at the end of helical-CRH infusions (to 14.0 ± 2.9 μg/dl on the first day and 13.9 ± 3.0 μg/dl on the second). The effect was transient, and circadian variability of these hor-mones was not affected. Though not measured formally,

euphoria, anxiety, or somnolence were not observed. In conclu-sion, the first human trial of CRH antagonist is reported. No side-effects were encoun tered, and inhibition of pituitary and adrenal hormone secretion was documented.

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