Opioid-induced endocrinopathy in a toddler with chronic codeine intoxication

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Background
Several studies in adults have provided evidence for opioid-induced hypofunction of the hypothalamo-pituitary-adrenal & GH-IGF-1 axis after chronic (oral and intrathecal) administration (1,2,3). Opioids act primarily at the pituitary level and also have effects on the peripheral glands, such as the adrenals (4). This so-called opioid endocrinopathy has not been reported in children.

Objective and hypothesis
We report the occurrence of delayed growth with low serum IGF-1 levels and recurrent hypoglycemia due to central hypocorticism in a toddler after a presumably intentional chronic codeine administration by her parents.

Method
In a healthy 12 months old girl, admitted for coma related to a benzodiazepine and codeine intoxication, a symptomatic hypoglycemia (glucose < 45 mg/dl), responding to glucose administration, was documented when excessive sleepiness reoccurred at the third day of hospitalization. Subsequent glucose monitoring showed several asymptomatic hypoglycemic episodes during the next day. Poor growth and previous episodes of excessive sleepiness were evidenced during the 4 months preceding the hospitalization.

Results
A critical sample analysis documented a ACTH level of 10 pg/mL and a cortisol of 1.7 µg/dL, which increased up to 13.9 µg/dL after a low dose ACTH test. Basal serum PRL and TSH were normal, but IGF-1 was low (26 µg/L) and DHEAS not measurable. A normal pituitary and hypothalamus were seen on MR imaging of the brain. After the instauration of hydrocortisone therapy, glucose levels remained normal and hydrocortisone was stopped after 6 weeks.

Four weeks after stopping therapy, a normal basal cortisol, but a weak response to ACTH was documented. A normal GH and cortisol response at glucagon testing was found after 6 weeks.

At the age of 2 years 11 months, her height (-1.4 SD) and weight (-0.4 SD) are normal. Her neuromotor development is normal.

Conclusion
In contrast with hyperglycemia seen in toddlers with acute codeine intoxication, recurrent hypoglycemia due to a transient central hypocorticism can be observed in chronic codeine ingestion. Genetic differences in opioid receptor binding and metabolizing properties might be responsible for the induction and recovery of the endocrine dysfunction after opioid administration in children.

Critical sample
ACTH : 10 pg/mL ( <46 )
Cortisol : 1.7 µg/dL ( 5.15 - 23.6 morning )

Low dose ACTH test
Cortisol 0' : 4.18 µg/dL
Cortisol 10' : 11.2 µg/dL
Cortisol 20' : 13.07 µg/dL
Cortisol 30' : 13.99 µg/dL

Glucagon stimulation test
Glucose 0' 0.69 g/L 2.85 µg/L 1.9 mU/L 10.06 µg/dL
30' 1.21 g/L 13.6 µg/L 82 mU/L
60' 0.95 g/L 16.7 µg/L 13 mU/L
90' 0.51 g/L 11.2 µg/L 9.67 µg/dL
120' 0.44 g/L 3.50 µg/L 16.18 µg/dL
150' 0.5 g/L 1.65 µg/L 16.93 µg/dL
180' 0.51 g/L 2.01 µg/L 12.86 µg/dL

Basal hormonology
TSH : 1.6 mU/L (0.70-6.0)
FT4 : 1.3 ng/dL (1.0 - 1.8)
Prolactin : 3.62 µg/L (6 - 30)
GH : 4.6 µg/L (<8)
IGF-1 : 26 (Z-Score:-3.61) ng/mL (66-328)
DHEAS : <5 µg/dL (0.47-19.4)

References
4. The effects of opioids and opioid analogs on animal and human endocrine systems. C. Vuong, Endocrine Reviews feb 2010, 31(1):98-132