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Letter to the Editor

The antiepileptic drug carbamazepine can cause adrenal insufficiency in patients under hormone replacement therapy for congenital adrenal hyperplasia

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Dear Sir,

Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-OH CAH) is treated with both glucocorticoids (to suppress pituitary ACTH and adrenal androgen production) and mineralocorticoids (to reduce angiotensin II concentrations).

A 25-year-old man affected by 21-OH CAH and followed at our endocrine clinic since the age of 2 months, after achievement of skeletal maturity, was treated with constant steroid doses of dexamethasone (DEX) 0.50 mg/day and fludrocortisone up to 0.1 mg/day, achieving good clinical and biochemical control of the disease. After a long period without follow-up visits the patient returned to us complaining of excessive fatigue and difficulty in concentrating. Serum ACTH, 17-OHPG, androstenedione and renin were all increased, suggesting hypoadrenalism. This condition persisted despite the progressive increase in replacement therapy dose. An effect of carbamazepine, started 3 years earlier because of epilepsy, on exogenous steroid metabolism was hypothesized.

Carbamazepine (200 mg TID) was then discontinued and substituted with levetiracetam (500 mg TID), an antiepileptic drug with different pharmacokinetics characteristics. Hormone levels gradually normalized and at 45 days were all within the normal range (Table 1). The patient reported a clear improvement of his symptoms within 5 weeks after drug switch.

This case highlights the importance of the interaction between steroid medications and drugs that increase cytochrome CYP3A4 activity. Carbamazepine, one of the most widely used and effective drugs for the treatment of epilepsy, is a potent inducer of the hepatic CYP3A4 enzyme activity with the consequence that the metabolism of many xenobiotics, such as DEX and fludrocortisone, is accelerated, lowering their serum

Table 1. Hormone measurements under carbamazepine (Basal) and after its discontinuation and substitution with levetiracetam. Reference values in parentheses.

	Basal	15 days	30 days	45 days
ACTH (10-60 pg/mL)	105.7	120.9	41.7	24.1
17-OHPG (0.5-2.4 ng/mL)	206.2	231.0	5.2	0.9
Androstenedione (0.3-3.1 ng/mL)	28.2	14.7	4.5	1.6
Renin (5.4-34.5 pg/mL)	120.8	182.5	73.9	53.8

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concentration. In our patient with 21-OH CAH, the treatment with antiepileptic carbamazepine induced a condition of adrenal insufficiency in spite of increased exogenous steroid dosage. Failure to recognize this interaction may expose treated patients to serious clinical consequences of adrenal insufficiency in the face of trauma, severe illness, surgery, and infectious or neoplastic disease.

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