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Usefulness of ethomidate in patients with Cushing syndrome with severe arterial hypertension and hypopotassemia☆

Utilidad de etomidato en paciente con síndrome de Cushing con hipertensión arterial e hipopotasemia graves

Cushing syndrome (CS) has a low prevalence in children and is rarely a cause for admission to the Pediatric Intensive Care Unit (PICU). However, it may manifest with severe and potentially life-threatening electrolytic disorders and arterial hypertension. We present the case of a nursing infant with CS admitted to the PICU due to severe arterial hypertension and hypopotassemia, in which etomidate was used to counter cortisol synthesis.

A 14-month-old infant girl was referred to our hospital due to suspected CS. The parents described hypotonus from 8 months of age, weight gain in the last four months, and recent rejection of food intake. The patient presented physical features consistent with CS, hypotonus, irritability and disconnection from the surroundings. The blood pressure was above percentile 99 for her age and size (200/120 mmHg). The brain CT and MRI scans revealed alteration of the supratentorial white matter in relation to edema. In the context of severe arterial hypertension, this was consistent with posterior reversible encephalopathy syndrome (PRES), with left thalamic hemorrhage. Echocardiography showed left ventricular hypertrophy. Maximum dose labetalol (3 mg/kg/h) was administered to control the blood pressure, followed by the combination of captopril, amlodipine and diuretics. Severe hypopotassemia was recorded (2.3 mEq/l) and was seen to persist despite high intravenous replacement doses (12 mEq/kg/day).

The endocrine study confirmed the suspicion of primary CS (urinary free cortisol 7578 $\mu g/m^2/24$ h, plasma cortisol 1665 ng/ml). The measurement of ACTH (<5 pg/ml) showed CS to be independent of the hormone. The abdominal ultrasound and brain and adrenal gland CT and MRI studies revealed no tumor disease. Somatostatin receptor scintigraphic assessment revealed no pathological uptake. In view of the persistence of arterial hypertension and hypopotassemia, we introduced ketoconazole at increasing doses (200 mg/24 h), with scant clinical and laboratory test response (plasma cortisol 1548 ng/ml after 72 h of treatment). No liver toxicity was observed. We then added etomidate 0.03 mg/kg/h, which resulted in partial adrenal axis suppression, with a reduction of the cortisol levels to 309 ng/ml as determined 24 hours after the start of perfusion. Improved blood pressure control was thus achieved, allowing the suspension of labetalol. The potassium values also normalized, making it possible to reduce intravenous administration. Etomidate was continued during 5 days, with plasma cortisol control values maintained between 331 and 300 ng/ml. However, in the last 48 hours the patient developed septic shock secondary to central venous catheter-related *E. coli* bacteremia that proved refractory to vasoactive support and corticosteroid replacement therapy, leading to the death of the patient.

The necropsy study revealed cortical nodular hyperplasia of both adrenal glands. The PRKAR1A gene, associated to pigmented nodular adrenocortical disease,[1] and the only known gene associated to infant CS, proved negative.

Cushing syndrome is infrequent in infancy. Once plasma cortisol elevation is confirmed, the underlying cause must be investigated. The determination of plasma ACTH allows differentiation between ACTH-independent CS (<5 pg/ml) and ACTH-dependent CS (>15 pg/ml). Computed

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tomography and MRI are the imaging techniques of choice for identifying the possible tumor.[2,3]

Surgery is the first treatment option. Medical management is required under circumstances that prove life-threatening for the patient, with the need to quickly lower the cortisol levels, such as severe water-electrolyte disturbances (hypopotassemia), severe arterial hypertension, immune suppression, or mental alterations.[5] The main drug treatment options are based on adrenal steroid synthesis enzyme inhibition with ketoconazole or metyrapone (the most widely used agents), though ACTH receptor antagonists or ACTH suppressor drugs can also be used.[4,5]

Ketoconazole is an imidazole derivative that blocks cortisol synthesis, and represents the most commonly used drug. Its main side effect is liver toxicity.

Etomidate is another imidazole agent used for the induction of anesthesia and in the rapid intubation sequence. Some authors have described increased mortality among septic patients in which the drug was used during intubation, though the purported causal relationship is subject to debate and has not been confirmed in later studies.[6] Etomidate inhibits the P450 cytochrome-dependent enzymes implicated in steroidogenesis–a fact that makes it useful in the treatment of CS. It is used in persistent hypercortisolism refractory to usual treatment, particularly in unstable patients (hypertensive crises or psychosis), in order to improve the conditions with a view to allowing surgical treatment,[7] and can be maintained for days or weeks if necessary. It is the only drug administered via the intravenous route, and is therefore the agent of choice in patients with oral intolerance. Etomidate is also an alternative in cases of liver disease secondary to ketoconazole.[8] Considerable experience has been gained with the use of etomidate in adult CS, though few cases involving pediatric patients can be found in the literature. Mettauer and Brierley[8] and Chan et al.[9] used etomidate in two patients aged 14 and 6 years of age with acute psychosis and scant response to oral treatment, respectively–the drug being found to be safe and effective in reducing the cortisol levels before definitive surgery. Our patient was a nursing infant, and very few data referred to this age range are available in the literature.

The dose achieving adrenal gland arrest[10] is 0.04–0.05 mg/kg/h. The effect is titrated against the plasma cortisol levels, with the control of potassium and glucose. Partial block is considered to be represented by cortisol levels of 300–800 nmol/l, while complete block corresponds to levels of <150 nmol/l. In cases of complete block, we must always combine hydrocortisone replacement therapy in order to avoid acute adrenal gland insufficiency. In cases of partial block, hydrocortisone replacement therapy is not an absolute indication, but is nevertheless advisable.

Our patient presented CS with clinical instability, characterized by both hemodynamic and water-electrolyte alterations. Ketoconazole was not effective in reducing the cortisol concentrations, though reduction and consequent clinical stabilization was achieved with etomidate. Cortisol reduction was obtained with doses somewhat lower than those described in the literature (0.02–0.03 mg/kg/h). However, although cortisol normalization was achieved, the situation of septic shock led to the death of the patient.

High glucocorticoid levels alter the immune system and increase the risk of infections. As a result, patients with hypercortisolism are more susceptible to systemic infections and sepsis caused by both bacteria and opportunistic organisms. In our patient, the existing immune suppression, combined with drug-induced adrenal response inhibition, could have contributed to the fatal outcome of the infection.

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