

Hair Analysis Differentiates Chronic From Acute Carbamazepine Intoxication

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This is a report of a 12-year-old epileptic child undergoing chronic treatment with carbamazepine who was found comatose. He was considered to have acute severe drug toxicity. Measurement of carbamazepine concentration in the patient's hair segments together with the carbamazepine blood levels were both important in determining the chronic nature of the patient's intoxication. © 2004 by Elsevier Inc. All rights reserved.

Mantzouranis EC, Bertsias GK, Pallis EG, Tsatsakis AM. Hair analysis differentiates chronic from acute carbamazepine intoxication. *Pediatr Neurol* 2004;31:73-75.

Introduction

Carbamazepine (carbamazepine) is a lipid-soluble iminostilbene derivative widely used for pediatric seizure disorders. Therapeutic plasma levels range from 25 to 42 $\mu\text{mol/L}$ (6-10 $\mu\text{g/mL}$), whereas levels $>51 \mu\text{mol/L}$ (12 $\mu\text{g/mL}$) cause dose-related adverse effects including dizziness, diplopia, ataxia, and gastric distress [1]. Carbamazepine is metabolized in the liver by the enzymes CYP3A4 and CYP2C8 to pharmacologically active carbamazepine-10,11-epoxide (carbamazepine E), accounting for 22-45% of plasma carbamazepine concentration and further metabolized into inactive trans-10,11-dihydro-

carbamazepine (carbamazepine-diol) [1]. Thus therapeutic and toxic drug effects correlate with carbamazepine and carbamazepine E levels better than with carbamazepine level alone. However, for patients on monotherapy, measurement of carbamazepine E levels is not currently recommended [2].

Monitoring blood carbamazepine levels is necessary for carbamazepine users and reflects recent drug administration. Carbamazepine levels in hair segments, used in forensic science and clinical pharmacology, can provide a long-term picture of drug use, because carbamazepine is incorporated and retained in hair for long time periods [3].

This study describes a patient chronically receiving carbamazepine who presented with symptoms of acute severe drug toxicity, and demonstrates how the clinical laboratory data and the sectional hair analysis facilitated our understanding of drug toxicity.

Case Report

A 12-year-old female was found unresponsive by her mother, 1½ hours after going to bed and was immediately transported to the emergency department. The patient was diagnosed with an epileptic disorder 6 years ago. She had been continuously receiving 400 mg of carbamazepine daily (16 mg/kg body weight) for 15 months. During the last 6 months the dosage was increased to 600 mg/day (20 mg/kg) at night, owing to a breakthrough seizure and an abnormal electroencephalogram. She was compliant to the treatment and had regular neurology follow-up visits and carbamazepine blood level measurements. Her last carbamazepine level, approximately 3 months before the emergency department visit, was within therapeutic range (21.6 $\mu\text{mol/L}$ [5.1 $\mu\text{g/mL}$]). The patient's mother, who provided the medical history, confirmed her daughter's compliance to the treatment; she denied any recent illness, concomitant use of other drugs, or knowledge of possible acute drug overdosage.

On physical examination, the patient had body temperature 36.5°C, blood pressure 98/48 mm Hg, respiratory rate 17 breaths/min, and heart rate 88 beats/min. She had a Glasgow Coma Scale score of 8 ($E_2V_1M_3$) and was minimally responsive to pain. She had recurrent, brisk myoclonic jerks of upper and lower limbs. The pupils were equally dilated and reactive to light. Fundi were normal. The rest of the system examination was unremarkable for abnormal findings.

The laboratory data indicated the following: arterial blood gases: pH: 7.38; oxygen pressure: 114 mm Hg (fraction of inspired oxygen = 0.21); carbon dioxide tension: 44 mm Hg; arterial oxygen saturation: 97%; serum bicarbonates (HCO_3^-): 20 mEq/L; white blood cell count (leukocytes): 9470/ mm^3 (neutrophils 45%, lymphocytes 42%, monocytes 8%); platelets: 234,000/ mm^3 ; hemoglobin: 12.6 gm/dL; serum glucose: 5.94 mmol/L; blood urea nitrogen: 5.61 mmol/L; serum creatinine: 26.5 $\mu\text{mol/L}$; serum sodium (Na^+): 136 mEq/L; serum potassium (K^+): 3.5 mEq/L; serum chloride (Cl^-): 107 mEq/L (anion gap: 9 mEq/L); erythrocyte sedimentation rate: 3 mm/h; aspartate aminotransferase: 23

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Received August 20, 2003; accepted December 29, 2003.

Table 1. Carbamazepine concentrations in patient's blood during hospitalization

Time (h)	Admission (0)	24 h	48 h	72 h	96 h	120 h	144 h
Blood levels ($\mu\text{mol/L}$)	276.2	192.0	136.3	83.8	66.0	39.3	17.8
Blood levels ($\mu\text{g/mL}$)	65.3	45.4	32.2	19.8	15.6	9.3	4.2

U/L; and alanine aminotransferase: 14 U/L. Blood and gastric content samples were sent for toxicologic analysis, including serum acetaminophen, aspirin levels, and a qualitative tricyclic antidepressant screen. Head computed tomographic scan revealed signs of an old ischemic cerebral infarct. Electroencephalogram revealed diffuse increase of slow waves, mostly on the left side.

The differential diagnosis included epileptic episode and acute drug poisoning. Upon awaiting for the blood results, phenytoin (250 mg bolus), mannitol (5 mL/kg/24 h), dexamethasone (1 mg/day), and intravenous fluids were administered. A gastric lavage with activated charcoal was performed. Blood carbamazepine level was toxic (276.2 $\mu\text{mol/L}$ [65.3 $\mu\text{g/mL}$]). Carbamazepine concentration in stomach fluids was low (3.38 mmol/L [0.8 mg/mL]). Serial blood carbamazepine levels revealed prolonged carbamazepine half-life (48 hours) (Table 1). No other toxic substance was detected.

The child gradually recovered from coma, being in good condition on the third day. She was discharged on the seventh day, on phenytoin (100 mg by mouth twice daily) and follow-up appointment. Not having understood the cause of carbamazepine intoxication, 3 months after discharge and carbamazepine discontinuation, we obtained the patient's hair samples to measure carbamazepine levels and construct the long-term carbamazepine profile. Now, 4 years later, the patient is on phenytoin and enjoys an uneventful life.

Hair Sampling

Hair samples from the patient's head were cut as close to the posterior vertex skin as possible, and then cut into consequent, 1-centimeter-long segments along the hair shaft, numbered 1-10 (number 1 being the closest to the hair root). Hairs of healthy individuals, similarly prepared, were used as a blank control. Hair carbamazepine levels were measured as previously described [4] and compared with hair carbamazepine levels of

control epileptic patients with therapeutic carbamazepine blood levels (six patients, 9-16 years of age, receiving carbamazepine 600 mg/day for 18-24 months [4]) (Fig 1).

Discussion

Carbamazepine poisoning in children is usually caused by accidental and rarely by intentional ingestion of large drug dose. Blood levels $>127 \mu\text{mol/L}$ (30 $\mu\text{g/mL}$) have been previously associated with coma and requirement for mechanical ventilation [5]. Our patient was comatose, but despite her high blood carbamazepine level (276.2 $\mu\text{mol/L}$) she did not require mechanical ventilation. Her prolonged carbamazepine half-life indicated decreased drug clearance of unknown etiology.

Chronic carbamazepine use results in a dose-dependent auto-induced metabolism and shorter carbamazepine elimination time [6,7]. Acute carbamazepine poisoning, however, owing to carbamazepine anticholinergic effects, may cause gastrointestinal hypomotility, delayed carbamazepine absorption, and prolonged half-life [7]. Thus acute ingestion of 20 gm of carbamazepine by an adolescent female, on chronic carbamazepine treatment, increased carbamazepine half-life from 13 to 25 hours [8]. Our patient's history and low stomach carbamazepine levels were against acute carbamazepine poisoning. In view of her toxic carbamazepine blood level and carbamazepine

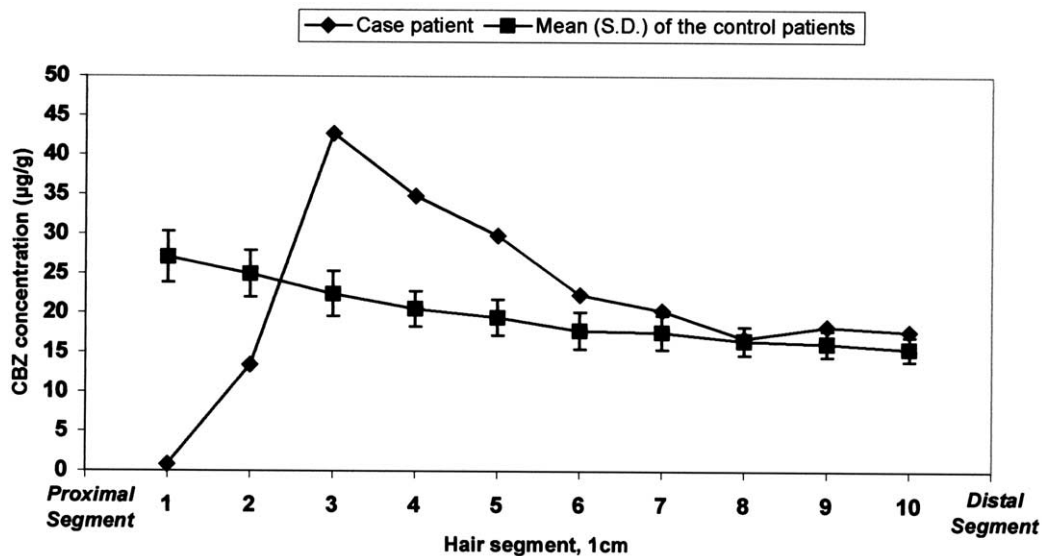


Figure 1. Carbamazepine concentrations in consequent 1-cm hair segments obtained from the study patient and six control patients (mean values \pm S.D.) under carbamazepine treatment (600 mg/day) previously measured [4]. Patients' hair segments 3, 4, 5, 6, 7, 8, 9, 10 correspond to: admission time, 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8 months before admission respectively. Segments 1, 2 correspond to 2-3, 1-2 months after discharge respectively. Control patients: Mean values \pm S.D. of hair carbamazepine levels of six control patients with therapeutic carbamazepine plasma levels, receiving 600 mg/day carbamazepine for 18-24 months, previously measured [4].

half-life of 48 hours, almost double than expected for a chronic carbamazepine user of her age, we considered chronic carbamazepine intoxication.

Carbamazepine is metabolized in the liver by the enzymes CYP3A4 and CYP2C8 to pharmacologically active carbamazepine-10,11-epoxide (carbamazepine E) [1]. Carbamazepine clearance depends on the activity of the above enzymes, affected by multiple causes, including genetic polymorphisms in CYP3A4 or CYP2C8 [9,10]. More than 30 single-nucleotide polymorphisms have been identified for the CYP3A4 gene in different populations, altering the CYP3A4 activity [11], but no “null” allele has been identified yet [12]. Furthermore, coding mutations in the CYP3A4 gene are relatively rare, particularly within Caucasians, and usually exert limited effect on the intrinsic clearance of CYP3A4 substrates [12].

The patient’s prolonged carbamazepine clearance could be the result of CYP3A4 polymorphism, which, however, we cannot prove because we did not measure blood carbamazepine E level, which was not recommended for carbamazepine monotherapy [2]. However, CYP3A4 polymorphism alone could not explain carbamazepine intoxication, because the patient had long carbamazepine treatment and previous therapeutic blood carbamazepine levels. Additional factors must have contributed to the prolonged drug clearance, including variable control of gene transcription by endogenous or exogenous molecules such as circulating hormones or the recent carbamazepine dose increase to 600 mg [9].

If carbamazepine dose increase had played a role in prolonged carbamazepine clearance, then blood carbamazepine levels would have been increasing since the dose increase, for several months before admission. This change would be reflected in the patient’s hair, considering that carbamazepine is incorporated and retained in hair [3]. Indeed, several segments of the patient’s hair had carbamazepine levels higher than those of control epileptic patients receiving 600 mg carbamazepine daily, with therapeutic blood carbamazepine levels [4].

The patient’s hair carbamazepine levels began increasing in segment 8 (Fig 1), becoming higher than that of the control patients in segment 6, finally doubling over time (segment 3). Segments 8, 6, 3 correspond to 5-6, 3-4 months before admission and to the admission time respectively, given that the hair grows approximately 1 centimeter/month [4]. Assuming a correlation between hair and blood carbamazepine levels [4,13], it appears that blood levels began increasing 5-6 months before admission, when carbamazepine dosage was increased, but remained within the control carbamazepine range until 3-4 months before admission (segment 6), correlating with the patient’s last therapeutic carbamazepine blood level. After this time, however, carbamazepine level continued increasing abnormally, reaching the highest level on admission time. We interpret these findings by speculating that with higher carbamazepine dose, the gradually increasing carbamazepine load possibly overcame the patient’s car-

bamazepine detoxification pathways, resulting in toxic carbamazepine blood levels (segments 5, 4, 3) [14]. Figure 1 illustrates excellently how the increase in carbamazepine dose and the long half-life in this child resulted in toxicity.

This patient’s unusual clinical presentation, her excellent outcome, her lack of symptoms despite high carbamazepine blood levels—3 months before the admission—differ from those of patients with acute carbamazepine intoxication of similar severity [5], likely because of the body’s adjustment to the slowly increasing carbamazepine overload or the patient’s young age, or both. This analysis is our best interpretation for this unusual case of chronic carbamazepine intoxication without excluding other unknown contributing factors.

In conclusion, the sectional hair analysis together with the laboratory information unmasked the chronic nature of this patient’s intoxication, suggesting the use of hair analysis in unclear cases of carbamazepine toxicity, or unclear drug dosage history in chronic carbamazepine users.

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