Severe overdosage with the antiepileptic drug oxcarbazepine

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Few published human data are available concerning the acute toxicity of the new antiepileptic drug oxcarbazepine of which the metabolite 10-monohydroxy derivate (MHD) is the pharmacologically effective compound. Two hours after a documented overdosage of more than 100 tablets oxcarbazepine, the serum level of the parent compound was 10-fold higher than the therapeutic dosage (31.6 mg l⁻¹). However, the concentration of MHD, which peaked 7 h after intake, was only twofold higher (59.0 mg l⁻¹). No life-threatening situations occurred and the patient fully recovered. The fact that oxcarbazepine is a prodrug and that the formation of the active MHD metabolite is a rate-limiting process may contribute to the relative low toxicity of the drug in overdose.

Introduction

Oxcarbazepine is a relatively new drug, which is used as an antiepileptic as well as for bipolar effective disorders, and is structurally and chemically similar to the well-established antiepileptic drug carbamazepine [1, 2]. Unlike carbamazepine, it is not metabolized to an epoxide metabolite (which is responsible for many of the toxic effects). The carbonyl group of the parent compound oxcarbazepine is reduced by presystemic 10-keto-reduction to form 10-monohydroxy derivate (MHD), which is the metabolite responsible for the pharmacological effect of oxcarbazepine *in vivo*. Minor amounts are oxidized to the pharmacologically inactive metabolite

10,11-dihydroxy derivative (DHD) [1, 2]. Very low concentrations of the parent drug are found in patients taking therapeutic amounts of oxcarbazepine [3].

One of the presumed mechanisms of action of MHD is thought to be blockade of voltage-sensitive sodium channels, thereby stabilizing hyperexcited neural membranes, inhibiting repetitive neuronal firing and diminishing the propagation of synaptic impulses [4, 5]. The most common side-effects are dizziness, somnolence, headache, ataxia and abdominal complaints, whereas a more serious side-effect is hyponatremia [2, 6].

Few published human data are available concerning the acute toxicity of oxcarbazepine [7, 8].

Case report

A 36-year-old male (weight 78 kg, height 1.80 m) with known epilepsy was admitted to the intensive care unit (ICU) 2 h after an overdose of 102 tablets of 300 mg oxcarbazepine (TrileptalTM, used normal dosage twice daily 300 mg, maximal therapeutic dosage 2400 mg day⁻¹). No other drugs were ingested, which was confirmed by general toxicology screening. On admission the patient was conscious with a blood pressure of 155/105 and a pulse of 98. The ECG was within normal limits (sinus rhythm, QRS 110 ms, QTc 440 ms). Neurologically no abnormalities were found (maximal Glasgow Coma Scale), there were no signs of nystagmus, ataxia or dysarthria and normal tendon and pupillary reflexes were present. As oxcarbazepine can theoretically delay gastric emptying, he was treated with 15 g sodiumsulphate and twice 50 g activated charcoal twice with an interval of 4 h. He became more somnolent from 12 to 24 h after admission, but still had maximal Glasgow Coma Scale as well as normal neurological reflexes and speech. No ECG changes or arrhythmias occurred and he remained haemodynamically and respiratory stable. Also the sodium serum concentration, as well as other electrolytes, arterial blood gases and kidney, and liver functions remained normal.

The serum concentrations of oxcarbazepine, MHD and DHD were assayed by reversed phase high-performance liquid chromatography. After extraction with dichloromethane at pH 9, the organic extract was evaporated to dryness and the redissolved residue was injected on a Symmetry C18 column (150 × 3.9 mm) (Waters, Etten-Leur, the Netherlands), using a mobile phase consisting of 30% acetonitril in 0.045 M phosphate buffer, with a pH of 4.5 and a flow of 1.5 ml min⁻¹, using UV detection at 230 nm (PhotodiodeArray detector Waters model 2996; Waters). Retention times were: oxcarbazepine 3.0 min; MHD 1.7 min; DHD 1.3 min, oxazepam (internal standard) 6.4 min. The within-run coefficient of variation was 1.8% for oxcarbazepine, 1.3% for MHD and 3.9% for DHD.

The serum concentration of oxcarbazepine was 31.6 mg l⁻¹ 2 h after ingestion with a corresponding MHD concentration of 37.2 mg l⁻¹ (see Figure 1). Oxcarbazepine was quickly metabolized (0.67 mg l⁻¹ after 24 h) to MHD, which reached a maximum concentration of 59.0 mg l⁻¹ 7 h after ingestion. These times to peak concentrations and the half-life of the drug are in accordance with previously published reports [3, 9, 10].

Two days after admission the patient was fully recovered and could be discharged after being seen by the psychiatrist.

Figure 1

Serum concentrations in time of oxcarbazepine, its pharmacologically active metabolite 10-monohydroxy derivate (MHD) and inactive metabolite 10, 11-dihydroxy derivate (DHD) after an overdose with 102 tablets 300 mg oxcarbazepine. Oxcarb (◆); MHD (□); DHD (△)

Discussion

This report describes a severe overdose with the anti-epileptic drug oxcarbazepine providing concomitant serum concentrations of both the parent compound and the active metabolite. The maximum serum level of the parent compound was about 10-fold higher than those found during steady state in patients with epilepsy, which are usually below 3 mg l⁻¹ [3]. The concentrations of the MHD metabolite, which peaked 7 h after intake of the overdose of oxcarbazepine, were less than twofold higher than the maximum recommended levels in the treatment of epilepsy (10–35 mg l⁻¹) [3], despite the documented massive overdose. The concentration of the DHD metabolite remained low during the entire observation period, but was still slowly increasing at the last moment of measuring.

The fact that oxcarbazepine is a prodrug and that the formation of the active MHD metabolite is a rate-limiting process may have contributed to the relative low toxicity of the drug in this patient. However, interrupted enterohepatic recirculation/gut dialysis and/or different rates or volumes of distribution should not be excluded.

In contrast, several reports have reported serious side-effects of the drug, including hyponatremia, despite normal dosages [6]. After a comparable overdose, bradycardia, hypotension and coma have been described [7, 8]. This denotes the individual response to the drug and warrants close monitoring of a patient with oxcarbazepine intoxication.

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