Clinical Neurology and Neurosurgery 152 (2017) 1–4

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Case Report

Marked EEG worsening following Levetiracetam overdose: How a pharmacological issue can confound coma prognosis

Baptiste Bouchier[a], Geneviève Demarquay[b,c], Claude Guérin[a,c], Nathalie André-Obadia[c,d], Florent Gobert[a,c,*]

[a] Hospices Civils de Lyon, Hopital de la Croix Rousse, Service de Reanimation Médicale, Lyon, France
[b] Hospices Civils de Lyon, Hopital de la Croix Rousse, Service de Neurologie, Lyon, France, France
[c] Université de Lyon, Université Claude Bernard Lyon 1, Villeurbanne, France
[d] Hospices Civils de Lyon, Hopital Pierre Wertheimer, Service des Explorations Fonctionnelles Neurologique, Bron, France

ARTICLE INFO

Article history:
Received 12 August 2016
Received in revised form 21 October 2016
Accepted 5 November 2016
Available online 9 November 2016

Keywords:
Levetiracetam
Burst suppression
Post anoxic coma
Overdose
Awakening prognosis

ABSTRACT

Levetiracetam is an anti-epileptic drug commonly used in intensive care when seizure is suspected as a possible cause of coma. We propose to question the cofounding effect of Levetiracetam during the prognostication process in a case of anoxic coma. We report the story of a young woman presenting a comatose state following a hypoxic cardiac arrest. After a first EEG presenting an intermediate EEG pattern, a seizure suspicion led to prescribe Levetiracetam. The EEG showed then the appearance of burst suppression, which was compatible with a very severe pattern of post-anoxic coma. This aggravation was in fact related to an overdose of Levetiracetam (the only medication introduced recently) and was reversible after Levetiracetam cessation. The increased plasmatic dosages of Levetiracetam confirming this overdose could have been favoured by a moderate reduction of renal clearance, previously underestimated because of a low body-weight. This EEG dynamic was unexpected under Levetiracetam and could sign a functional instability after anoxia. Burst suppression is classically observed with high doses of anaesthetics, but is not expected after a minor anti-epileptic drug. This report proposes that Levetiracetam tolerance might not be straightforward after brain lesions and engages us to avoid confounding factors during the awakening prognostication, which is mainly based on the severity of the EEG. Hence, prognosis should not be decided on an isolated parameter, especially if the dynamic is atypical after a new prescription, even for well-known drugs. For any suspicion, the drug's dosage and replacement should be managed before any premature care's withdrawal.

1. Introduction

Levetiracetam (LEV) is an anti-epileptic drug with a simple pharmacokinetic profile, a quick efficacy after a rapid intravenous administration and a claimed good tolerance. Side effects such as somnolence, dizziness and psychosis have been reported during chronic LEV treatment for conscious patients with normal dose. Only few cases of LEV overdose are reported and these are usually associated with mild symptoms, suggesting that the safety of this treatment could be extended to the acute phase of brain injury [1]. LEV is largely used in comatose patients with status epilepticus (SE) in the Intensive Care Unit (ICU). In the particular topic of post-anoxic encephalopathy, the systematic treatment of boundary-forms of atypical rhythmic pattern on EEG is not currently recommended *per se*. Indeed, further arguments are required to increase the suspicion for a post-anoxic non-convulsive SE [2]. While an intravenous injection of AED during the EEG recording is commonly used to increase the diagnostic probability [2], long-term therapeutic test with AED is not currently recommended, despite frequently observed, to exclude this reversible cause of coma [3].

Establishing a neurological prognosis after cardiac arrest is a challenging issue. According to international recommendations, it requires a multimodal approach including electrophysiological tests such as electroencephalogram and somatosensory evoked potentials [4]. A burst suppression (BS) pattern on EEG suggests poor neurological outcome but BS' predictive value is not yet

* Corresponding author at: Service de réanimation médicale 103 Grande Rue de la Croix-Rousse, 69004 Lyon France.
E-mail address: gobert.flo@gmail.com (F. Gobert).

http://dx.doi.org/10.1016/j.clineuro.2016.11.004
0303-8467/

recognized as absolute claiming that some possible reversible mechanisms could exist [4].

2. Case description

We report the case of a 31 year-old woman with a past medical history of myofibrillar myopathy complicated by tetraplegia and chronic respiratory failure requiring long term home mechanical ventilation. She was admitted to the ICU after an in-hospital cardiac arrest (two minute no-flow and ten minute low-flow) due to a prolonged hypoxemia after ventilator dysfunction. After ICU admission, she was given continuous intravenous infusion of midazolam and morphine (44 h), and cisatracurium (6 h), a neuromuscular blocking agent to support therapeutic hypothermia (33 °C). The immediate outcome was complicated by cardiogenic shock and acute kidney injury without any significant metabolic disturbance. Over the next 18 days her neurological status evolved to a post-anoxic coma with preserved photomotor, corneal, oculocephalic reflexes but without stimulus-sensitive myoclonic jerks.

An electrophysiological assessment was performed to assess the neurological prognosis (Fig. 1). The first EEG performed after cardiac arrest at Day-2 showed a pattern of diffuse low voltage theta-delta rhythm, which was reactive to auditory stimuli (Fig. 1A). A second EEG was performed at Day-4 to rule out a superimposed reversible cause of coma (Fig. 1B). It showed a different pattern of continuous generalized predominant frontally rhythmic delta without cortical responsiveness to epicritic stimulus. As paroxystic elements were suppressed by injection of benzodiazepine (Clonazepam, 1 mg, Fig. 1C) but without clinical improvement, a possible non-convulsive SE [2] was discussed as a contributing factor to persistent coma. Intravenous LEV was started at 750 mg per 12 h. While the clinical condition was not modified four days after AED introduction, two consecutive EEG tracings showed a clear BS pattern at Day-8 and 9 (Fig. 1D). Blood levels of LEV were significantly overdosed up to 100 mg/L (normal range 10–37) at that time. The EEG performed five days after LEV cessation (LEV blood level 33.7 mg/L) at Day-13 found a low voltage delta rhythm comparable to the first EEG except for the absence of reactivity (Fig. 1E). We have checked that the prescribed LEV regimen was adapted for a moderate renal dysfunction in a normal adult. But an *a posteriori* estimation of glomerular filtration rate based on creatinine clearance measured from a 24 h urine collection found that a dose of 450 mg twice a day would have been the most adapted one, according to a low body weight (45 kg).

After overdose's correction, the level of wakefulness improved from coma to vegetative state (isolated spontaneous eyes opening and absence of both motor and verbal responses to auditory or painful stimulations) but remained then stable for six days.

A complementary analysis of SEPs was conducted during the LEV overdose at Day-10 (Fig. 1F) and after its resolution at Day-15 (Fig. 1G). N20 cortical response was absent in each case. According to this last electrophysiological argument for a poor outcome, we agreed with her family to stop invasive life supports. The patient eventually died nineteen days after the cardiac arrest.

3. Discussion

The first electroencephalographic evaluation is usually performed after hypothermia cessation to precise the prognosis of awakening. The initial background rhythm is regarded as a summation of reversible and irreversible damages. This rule is even more accurate if the first EEG is performed during the days following cardiac arrest itself (reversible anoxic damages) and immediately after sedation withdrawal (reversible pharmacological coma). For the most favourable patterns (Synek-0 to Synek-3), the prognosis of the primary lesion based upon this first EEG remains stable [5]. However, in this case report, the first EEG assessment (performed on day-2), which should have been the most influenced by sedative drug, had a more favourable pattern than later ones (day-8), thus suggesting the responsibility of AEG overdose rather than traces of sedative drugs on the affected EEG background activity.

In fact, additional mechanisms may have altered the natural evolution of the post-anoxic encephalopathy: i) a possible non-convulsive SE as the day-4 EEG fulfilled the criteria recently published [2] (continuous epileptiform discharge, frequency < 2.5 Hz and isolated electrical improvement of EEG after IV BZD injection); ii) a LEV overdose expressed as a BS pattern.

BS is a common periodic and diffuse EEG pattern, defined by alternate high voltage slow/sharp waves and depressed activity. Initially described during anesthesia, spontaneous BS is also observed in post-anoxic coma [5] and classified as the poor-outcome Synek-4 score (post-anoxic encephalopathy, associated with alpha coma and epileptiform discharges). Such pejorative EEG can fluctuate before ending up to an isoelectric pattern (Synek-5).

Clinicians should be alerted by any worsening and look for potential reversible secondary injuries. Our case illustrates two main causes: i) SE is usually suspected after post-anoxic coma in case of pseudo-rhythmic pattern; ii) each treatment including AED must be evaluated as a cause of coma.

As BS is related to various aetiologies and prognosis, unifying BS physiopathology appears difficult. A recent metabolic model proposed a complementary role for suppression (as a functional adaptation to a basal neurometabolic regimen) and burst (as a recovery of basal dynamics at the neuronal circuit level caused by transient increases in energetics) allowing a long-term structural maintenance during a neuronal crisis. The initiation of BS can be related to a cyclic phenomenon possibly triggered by a pharmacological depression, such as BS in anesthesia. But few cases of BS-related coma were reported after overdose of baclofen [6] and carbamazepine, yet never after LEV overdose. According to a recent review [1], a single case of voluntary overdose had previously led to comatose state requiring a short-term intubation. Contrary to the present case, clinical recovery was quick and no EEG was provided to prove BS [7]. Dose/weight ratio was not mentioned, but the serum concentration was 4-fold higher than for the present patient.

LEV overdose might have been here responsible for longer coma duration as patient's eyes opened after drug cessation. It remains unclear whether BS occurrence may indicate that basal brain activity was close to the depression threshold. Transient pharmacological BS [6] has been followed by a rapid awakening should the brain remain undamaged. In our case, depressing so easily EEG activity by an inappropriate dosage of a well-tolerated treatment is rather a proof of brain injury severity.

Anti-epileptic action of LEV [1] is complex and research on BS model is still in progress. Occurrence of BS gives us insights concerning adjunctive GABAergic action of LEV. An *in vitro* study has proposed an indirect inhibitory effect at the pre-synaptic level on Zn-dependant GABA-A receptor. A common electrocortical final pathway could be imagined for antiepileptic drugs with either direct (barbiturate, benzodiazepine, baclofen) or indirect (LEV) effects on GABA neurons.

Concerning the pharmacokinetic issue, it should be noted that in the case of a patient with severe myopathy there is no method that would accurately assess glomerular filtration rate from biomarkers. However, such a limited gap (300 mg/dose) would hardly induce alone such side effects. Besides, in routine the daily doses of LEV in SE are not based on the patients weight or renal clearance (3000 mg is only mentioned as a maximal daily dose for an adult [1]). The dose/weight ratio was low for our patient (only 33.3 mg/kg/day while the limit authorized posology adapted to this decreased renal function would have been 20 mg/kg/day) while Larkin and