Gabapentin-induced coma: A MR-spectrometry analysis

Lamine Abdennour[1]
Paola Sanchez-Peña[2]
Damien Galanaud[3]
Vincent Navarro[4]
Nicolas Weiss[5]
Louis Puybasset[6]

[1]Staff Anesthesiologist, Department of Anesthesiology and Critical Care; [2]Clinical Research Staff, Department of Anesthesiology and Critical Care; [3]Staff Neuroradiologist, Department of Radiology; [4]Staff Neurologist, Department of Neurology and Clinical Neurophysiology; [5]Resident in Neurology, Department of Neurology; [6]Professor in Anesthesiology and Critical Care and Chief of the Unit, Department of Anesthesiology and Critical Care; Centre Hospitalo-Universitaire Pitié-Salpêtrière, Assistance Publique- Hôpitaux de Paris, Université Pierre et Marie Curie, Paris France

Abstract: As for the majority of antiepileptic drugs, encephalopathy, manifested by transient somnolence, mood and motor disorders, is a possible side-effect. To our knowledge, there is little information about gabapentin-induced coma. We report a third case of gabapentin-induced coma where magnetic resonance-spectrometry was performed in diagnosis assessment.

Keywords: MR-spectrometry, gabapentin, encephalopathy, antiepileptic drugs

Introduction

Gabapentin is a widely used antiepileptic drug. As for the majority of these drugs, encephalopathy, manifested by transient somnolence, mood and motor disorders, is a possible side-effect. However, to our knowledge, only two gabapentin-induced coma cases have been reported (Buttler et al 2003; Dogukan et al 2006). We report a third case of gabapentin-induced coma where magnetic resonance (MR)-spectrometry was performed to further assess diagnosis.

Case-report

A 65-year old woman, with a history of nontreated hypertension, was admitted in the neurosurgical intensive care unit after an aneurysmal subarachnoid hemorrhage. After an initial generalized tonic clonic seizure, the Glasgow coma scale was 15/15, without any motor deficit. A diffuse subarachnoid hemorrhage without clot was observed on the initial computed tomography (CT) scan (Fisher scale at 2). The arteriography evidenced an aneurysm of the anterior communicating artery that was treated by coiling within the first 6 hours after admission. A control CT performed after the procedure showed a dilation of the ventricles, thus an external ventricular drainage (EVD) system was inserted. The drainage line was linked to a pressure gauge in order to monitor the intracranial pressure. Because of the initial seizure, a preventive treatment by gabapentin, 600 mg three times/day p.o. was introduced, and as part of our local guidelines: Intravenous nimodipine (2 mg/h), paracetamol (1 g every 6 hours) and oral omeprazole (40 mg per day).

Extubation was carried out at day 1 as the patient was conscious and had no motor deficit. Several hours after extubation, she gradually became comatose. At this time, intracranial pressure, transcranial Doppler and $PaCO_2$ were normal. She was intubated, given ventilatory assistance and sedated by continuous infusion of sufentanil (10 μg/h) and propofol (70 mg/h). A new CT ruled out rebleeding or the occurrence of an ischemic complication and confirmed the correct placement of EVD system. An aspect of moderate diffuse cerebral edema was observed despite a permanent low intracranial pressure.

Sedation was maintained over 72 hours, ie, day 4. During this period, sedatives were daily stopped for neurological evaluation. No improvement in consciousness

Correspondence: Louis Puybasset
Department of Anesthesiology and Critical Care, La Pitié-Salpêtrière Hospital, 47-83 Bd de l'hôpital, 75013 Paris, France
Tel +33 1 4217 3371
Fax +33 1 4216 3370
Email louis.puybasset@psl.aphp.fr

was observed. Despite the normality of plasmatic protein S100B (Weiss et al 2006) and transcranial Doppler, an arteriography was performed at day 8; it ruled out vasospasm. The electroencephalogram (EEG) performed at day 7 without sedation showed evidence of a reactive alternating coma and the presence of diffuse slow waves. At day 9, EEG slowed down, impoverished, with diminished reactivity and rare spike foci located on the anterior area, considered to be potentially epileptic. The diagnosis of seizure was proposed and gabapentin dosage was increased to 900 mg three times/day. A new EEG carried out at day 14 showed triphasic slow waves additionally to the previously described spike foci. Soon after, neurological degradation ensued; she became deeply comatose. A new EEG as well as a most detailed evaluation of the former recordings eventually drew aside the diagnosis of seizure. The constant presence of slow waves with triphasic tendency suggested metabolic encephalopathy. No medical cause was found as the different hepatic, endocrinal and metabolic assessments were normal. A drug-induced encephalopathy was evoked. All treatments (gabapentin, omeprazole, nimodipine and paracetamol) were stopped at day 16. Gabapentin was replaced by oxcarbazepine at a dose of 300 mg twice a day. A progressive improvement of the neurological status was observed, with recovery of consciousness at day 19 allowing weaning of mechanical ventilation. The control EEGs carried out at day 21 and 28 showed the disappearance of the slow triphasic waves.

Magnetic resonance imaging (MRI) was performed at day 18 (48 hours after gabapentin cessation), day 34 and day 58 including an axial fluid attenuation inversion recovery (FLAIR) sequence, diffusion weighted imaging, single-voxel spectroscopy on the pons (TE = 135 ms, TR = 1500 ms) and multivoxel spectroscopy (chemical shift imaging) on the basal ganglia (TE = 135 ms, TR = 1500 ms). Resonances of N-acetyl aspartate (NAA), creatine and choline on the thalami, the lenticular nuclei and the pons were integrated using dedicated software. Morphologic changes were limited to a few ischemic punctiform lesions on the left anterior cerebral artery territory. On spectroscopy, the NAA/choline ratios were markedly reduced on the thalami (normal value = 1.77 ± 0.28, n = 4 controls) and on the lenticular nuclei (normal value = 1.80 ± 0.52, n = 4 control). Subsequent examinations showed a progressive increase of these ratios back to normal levels at day 58 (Figure 1).

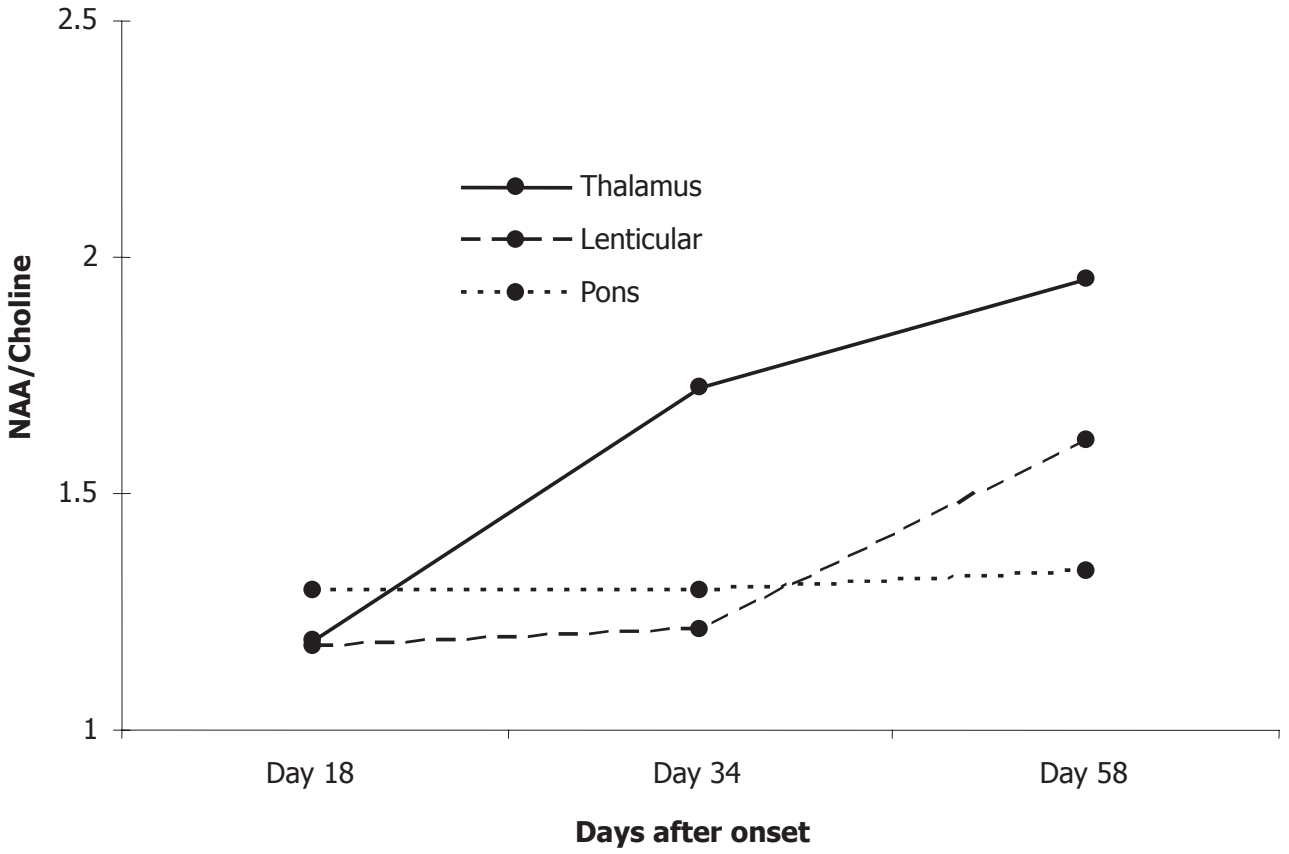

Figure 1 Time changes in NAA/choline ratio in different regions of interest on MRS analysis.

The patient has been included in a ongoing study where a daily blood serum sample was frozen at –80 °C in the first 8-days. These samples were used to measure retrospectively the gabapentin concentration (high performance liquid chromatography, using a fluorimetric method implying molecule derivatisation after extraction of plasma [Lough 1995]) and ammonemia (NH3 Ammoniac kit, Roche Molecular Biochemicals; normal values between 20 and 80 mg/L). The mean value for gabapentin was 5.8 ± 2.4 mg/L with each daily value below the upper threshold of 10 mg/L. As shown on Figure 2, ammonemia raised from day 8.

Discussion

Coma has not been reported in the monograph of gabapentin as a potential side effect (Laboratories 1994). We propose that our patient had gabapentin-induced coma according to 4 levels of evidences: clinical worsening after dose was increased, appearance of triphasic waves suggestive of metabolic encephalopathy on EEG, clinical and EEG improvement after gabapentin was stopped and finally MR-spectroscopy findings that were similar to those described in valproic acid induced-encephalopathy. The time course of clinical events represents the first evidence of this diagnosis. The first neurological deterioration began after the introduction of gabapentin and the second worsening ensued the increase in gabapentin dose. The improvement of consciousness followed gabapentin discontinuation. The second evidence was EEG showing triphasic waves suggestive of metabolic encephalopathy. Triphasic waves were first observed by Bickford and Butt in 1955 (Bickford and Butt 1955). These waves have been described in metabolic encephalopathy and drug-induced toxicity cases such as the one secondary to sodium valproate (Rehman and Zafar 2005). They have also been described in several other brain damage such as accidental anoxia, hepatotoxicity, renal failure, hyperosmotic states and acute intoxications (Bahamon-Dussan et al 1989; Karnaze and Bickford 1984). In our case, the absence of lesion on CT and diffusion or FLAIR MRI sequences ruled out the features other than metabolic or drug-induced encephalopathy. EEG expert reviewing drew aside the diagnosis of seizure. Other potential metabolic encephalopathies were excluded since different hepatic, endocrinal and metabolic assessments were normal. Furthermore, the slow triphasic waves increased contemporary to increasing gabapentin dose and disappeared after gabapentin was stopped. The CT showed a diffuse cerebral edema but

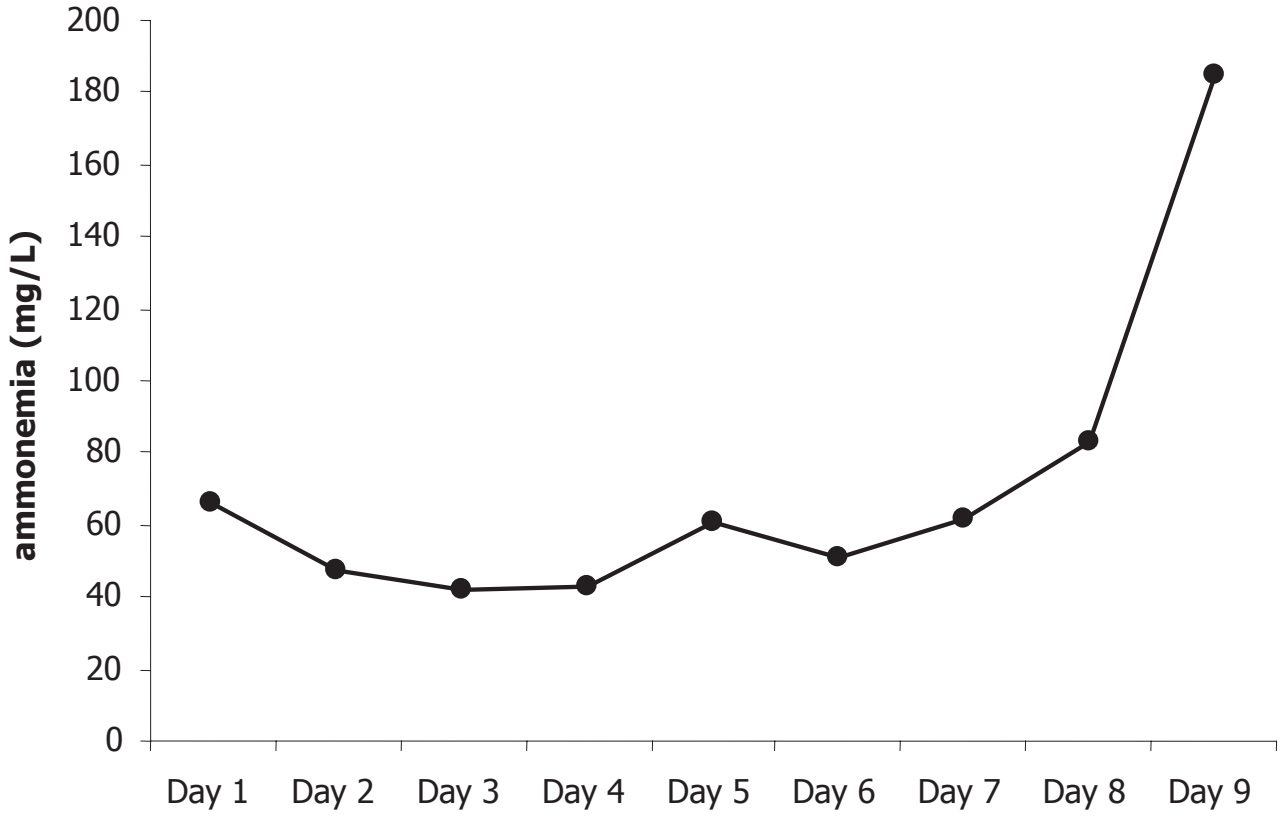

Figure 2 Ammonemia from day 1 to day 9.

intracranial pressure was not increased. This morphological aspect, consistently observed in our patient, has also been already observed in patients with hepatic or toxic encephalopathies (Bernthal et al 1987; Silver et al 1996; Messiwala and Loeser 2001). On MR-spectroscopy, a decrease in the NAA/choline ratio, assumed to assess neuronal tissue, was observed while the patient was in a deep comatose state. The NAA/choline ratio is classically normal in subarachnoid hemorrhage normal appearing white and grey matter. These anomalies, contrasting with normal morphological sequences, have already been described in the valproic acid induced-encephalopathy, which brain toxicity is mediated by hyperammonemia (Ziyeh et al 2002; Hamer et al 2000). It seems unlikely that metabolic encephalopathy was due to ammonemia since clinical symptoms occurred at day 2, ie, five days before the onset of ammonemia increase. This indicates that hyperammonemia could be the consequence of gabapentin toxicity rather than the cause of the coma itself. The normalization of the NAA/choline ratio after gabapentin discontinuation followed the course of clinical and EEG improvement and further argues for a direct relationship between the modifications observed on MR-spectrometry and the drug effect on consciousness as in the case of valproic acid induced-encephalopathy. Some limitations exist for the implication of gabapentin in our case. The patients had other treatments discontinued at the same time as gabapentin. They did not seem to be a potential causes for coma since they are well-known molecules with no reported cases of drug-induced encephalopathy. Paracetamol can induce coma but through hepatic failure that was not present in our case. Two cases of overdose of gabapetine without serious side effects has been previously reported (Fischer et al 1994; Verma et al 1999). The daily levels of gabapentin were below the upper threshold in our case. This discrepancy might be due to pre-existing brain injury, ie, subarachnoid hemorrhage, which could trigger metabolic encephalopathy with lower levels of gabapentin. Particular susceptibility might exist in some patients as suggested in Buttler's case (Buttler et al 2003).

Our case illustrates the usefulness of MR-spectroscopy in drug-related encephalopathy. A decrease NAA/Cr ratio contrasting with the absence of morphological lesions on MRI could suggest drug-related encephalopathy, especially if this is in accord with time course of drug intake and a suggestive EEG.

References

Bahamon-Dussan JE, Celesia GG, Grigg-Damberger MM. 1989. Prognostic significance of EEG triphasic waves in patients with altered state of consciousness. *J Clin Neurophysiol*, 6:313–19.

Bernthal P, Hays A, Tarter RE, Van Thiel D, et al. 1987. Cerebral CT scan abnormalities in cholestatic and hepatocellular disease and their relationship to neurophysiological test performance. *Hepathology*, 7:107–14.

Bickford RG, Butt AR. 1955. Hepatic coma: the electroencephalographic pattern. *J Clin Invest*, 34:790–9.

Buttler TC, Rosen RM, Wallace AL, et al. 2003. Flumazenil and dialysis for gabapentin-induced coma. *Ann Pharmacother*, 37:74–6.

Dogukan A, Aygen B, Berilgen MS, et al. 2006. Gabapentin-induced coma in a patient with renal failure. *Hemodial Int*, 10:168–9.

Fischer JH, Barr AN, Rogers SL, et al. 1994. Lack of serious toxicity following gabapentin overdose. *Neurology*, 44:982–3.

Hamer HM, Knake S, Schomburg U, et al. 2000. Valproate-induced hyperammonemic encephalopathy in the presence of topiramate. *Neurology*, 54:230–2.

Karnaze D, Bickford RG. 1984. Triphasic waves: a reassessment of their significance. *Electroencephalogr Clin Neurophysiol*, 57:193–8.

Laboratories Pfizer. 1994. Monography for gabapentine. *Vidal.*

Lough WJ, Wainer IW. 1995. High performance liquid chromatography fundamental principles and practice. CRC Press, Boca Raton, USA.

Messiwala AH, Loeser JD. 2001. Bilateral globus pallidus infarction secondary to disulfiram ingestion. *Pediatr Neurosurg*, 34:224.

Rehman A, Zafar S. 2005. Valproate-induced encephalopathy. *J Coll Phys Surg – Pakistan*, 15:571–2.

Silver DA, Cross M, Fox B, et al. 1996. Computed tomography of the brain in acute carbon monoxide poisoning. *Clin Radiol*, 51:480–3.

Verma A, St Clair EW, Radtke RA. 1999. A case of sustained massive gabapentin overdose without serious side effects. *Ther Drug Monit*, 21:615–17.

Weiss N, Sanchez-Pena P, Roche S, et al. 2006. Prognosis value of plasma S100B protein levels after subarachnoid aneurysmal hemorrhage. *Anesthesiology*, 104:658–66.

Ziyeh S, Thiel T, Spreer J, et al. 2002. Valproate-induced encephalpathy: assessment with MR Imaging and 1H MR Spectroscopy. *Epilepsia*, 43:1101–5.