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A range of antiepileptic drugs do not affect the recovery of consciousness in vegetative and minimally conscious states

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ABSTRACT

Since most antiepileptic drugs (AEDs) have cognitive effects, the aim of this study was to evaluate the influence of AED therapy on the recovery of consciousness in 103 consecutive patients in a vegetative or minimally conscious state (VS, MCS). The levels of cognitive functioning (LCF) score was retrospectively compared after a three-month period of rehabilitation between patients who were medicated ($n = 54$) and patients who were not medicated ($n = 49$) with AEDs. Mean LCF scores in AED-medicated and nonmedicated patients were 2.2 ± 0.7 and 2.3 ± 0.8 at admission and 3.8 ± 2.2 and 3.7 ± 2.1 after three months, respectively (p values > 0.05). These results did not change when we compared patients with the same etiology separately, with the same disorder of consciousness only, or patients treated with only one or more than one AED. In conclusion, AEDs did not affect the recovery of consciousness in a large cohort of patients in a VS or MCS following an acute brain injury.

1. Introduction

The vegetative state (VS) and the minimally conscious state (MCS) may occur after surviving a severe brain injury. Following an acute brain injury, patients may remain in a comatose phase until death or a full recovery of consciousness. However, some patients who do not die or recover consciousness develop a condition known as the VS. In this condition, patients appear awake (they spontaneously open their eyes and usually have sleep/wake cycles) but lack any sign of awareness of themselves or of their environment [1–3]. Although the VS can be permanent, in some cases, it evolves into a slightly higher level of consciousness known as the MCS. Transition into a MCS starts when a patient's spontaneous eye movements display focusing, when a patient shows eye tracking with or without head turning in the direction of sudden noises or movements, or when the patient becomes able to follow reproducible simple commands [4]. In other words, during a MCS, patients show poor responses yet exhibit some fluctuating but reproducible signs of awareness. Like a VS, a MCS may be transitory and precede the full recovery of communicative functions, or it may last indefinitely. Although epidemiological data are limited, the prevalence of VS and MCS is continually increasing, as a result of advances in emergency and intensive care treatments. Data regarding the incidence rate of VS in different countries show a range of 14 to 67 individuals per million population at one month after brain injury [5], while the incidence rate of MCS is believed to be greater [4].

Epileptic seizures (ESs) are a common occurrence in patients who have suffered from an acute brain injury, and these may appear after a traumatic brain injury, stroke, or cerebral hypoxia [6–9]. Epileptic seizures can be classified as acute symptomatic seizures (i.e., in close temporal correlation with the brain injury) [10], or they can be due to a structural epilepsy (i.e., induced by structural changes in the brain after the injury) [11]. It has recently been found that ESs caused by structural epilepsy can occur in 24% of patients with disorders of consciousness following an acute brain injury, ranging from 11% of patients in a MCS to 32% of patients in a VS [12].

Data related to antiepileptic drug (AED) use are also remarkable: in a cohort of 96 consecutive patients suffering from severe disorders of consciousness following an acute brain injury (traumatic, hypoxic, or vascular), more than 50% were medicated with AEDs [12]. Antiepileptic drugs markedly affect neuronal excitability properties, mainly by acting on ion channels (typically by blocking sodium channels) or by enhancing inhibitory γ-aminobutyric acid (GABA)-ergic transmission [13]. As a consequence, most of the available AEDs have cognitive effects [14]. In particular, it is well known that first-generation AEDs (i.e., phenobarbital, phenytoin, valproate, and

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carbamazepine) cause attention deficit, memory impairment, and mental slowing [15]. Although new-generation AEDs are believed to have fewer cognitive effects, these effects have been reported for some widely used drugs, such as vigabatrin, tiagabine, topiramate, zonisamide, lamotrigine, and levetiracetam [14].

In patients in a VS and MCS, neuronal functions underlying awareness and cognition are absent or greatly reduced. Therefore, we may hypothesize that drugs with a sedative effect or that impair cognitive functions (even slightly) may strongly affect the recovery of consciousness and the improvement of cognitive functions in these patients. Thus, the aim of the current study was to evaluate the role of AED treatment on the recovery of consciousness and cognitive functions in a large cohort of patients in a VS and MCS following an acute brain injury and after a period of rehabilitative treatment. This work may introduce new information with strong implications for pharmacological ES treatment in patients with severe disorders of consciousness.

2. Methods

2.1. Patients

This study was conducted on 103 consecutive patients (66 males and 37 females; mean age 45.9 ± 19.1 years) suffering from severe disorders of consciousness following acute traumatic, vascular, or hypoxic cerebral injuries. A total of 61 patients in a VS and 42 in a MCS participated in the study. Fifty-four patients (52.4%) were medicated with AEDs; 23 (22.2%) suffered from ESs during the period of the study (21 of whom were medicated with AEDs). The mean time between the acute brain injury and admission to our department was 54.5 ± 25.9 days (see Table 1 and Supplemental Table 1 for more detailed descriptions).

All patients were admitted to our department to undergo an intensive neurorehabilitation program following severe acquired brain injuries; they came from neurosurgery, neurology, and intensive care units. The diagnosis of a VS or a MCS was made at admission by a multidisciplinary team (composed of a neurologist, a neuropsychologist, and a speech therapist) according to the diagnostic criteria for the VS [16] and the MCS [4]. We included in the study all those patients admitted to our department from January 2005 to January 2012 who fulfilled the following criteria: 1) a diagnosis of a VS or a MCS at admission to our department after a traumatic brain injury, stroke, or cerebral hypoxia; 2) a hospitalization in our department of at least three consecutive months; 3) the availability in the patient's clinical file of the levels of cognitive functioning (LCF) scores at admission and after three months; and 4) in medicated patients, the use of the same AED therapy during the evaluation period. Patients with a previous history of epilepsy, traumatic brain injuries, stroke, cerebral hypoxia, neurodegenerative diseases, and tumors or infections of the central nervous system were excluded.

This study was performed according to the Helsinki Declaration and approved by the ethical committee of the Fondazione Istituto San Raffaele G. Giglio (Cefalù, Italy).

2.2. Clinical evaluation

We used the LCF scale [17] to evaluate the recovery of consciousness and cognitive functions. This scale is based on eight levels: levels I and II define patients in a VS, while the other levels denote a progressive improvement of cognitive functions; level VIII describes patients with cognitive functions close to their premorbid abilities. This feature of the LCF scale is important for the aim of this study, because, unlike the Coma Recovery Scale—Revised, a total score higher for VS patients than for MCS patients cannot be assigned. Then, we retrospectively compared the LCF score variation after a three-month period of rehabilitation between patients who were medicated and patients who were not medicated with AEDs.

2.3. Statistical analysis

Differences in demographic and clinical data were assessed by a Student's *t*-test. The main statistical analysis was chosen to evaluate whether AEDs influence the LCF score (i.e., consciousness and cognitive function levels) three months after admission to our rehabilitation department. Thus, we used a two-way repeated measures analysis of variance (ANOVA) with the factor group (patients medicated with AEDs vs. patients not medicated with AEDs) as the between-subjects factor and the factor time (LCF score at admission vs. LCF score at three months) as the within-subjects factor.

As the outcome of patients medicated with AEDs may differ depending on ES occurrence, we also performed a subset of analyses distinguishing, among medicated patients, those who suffered from ESs from those who did not. Accordingly, we used an ANOVA with three levels in the factor group (patients with ESs medicated with AEDs vs. patients without ESs medicated with AEDs vs. patients not medicated with AEDs) as the between-subjects factor and the same two levels in the factor time (LCF score at admission vs. LCF score at three months) as the within-subjects factor.

To show the presence of differences related to the brain injury etiology, the main statistical analysis (patients medicated with AEDs vs. patients not medicated with AEDs as the between-subjects factor and the LCF score at admission vs. LCF score at three months as the within-subjects factor) was also performed separately for the different etiologies (i.e., traumatic brain injuries, cerebrovascular diseases, or cerebral hypoxia). Moreover, to see if patients in a VS or MCS were affected differently by medication with AEDs, the same ANOVA model was used, but we only included patients in either a VS or a MCS.

Finally, in the group of medicated patients, we compared the outcome of patients medicated with only one AED with that of patients medicated with more than one AED. In this case, we used a two-way

Table 1
Demographic and clinical data of patients with and without AED medication.

Number of patients	Gender	Mean age (years)[a]	Days between brain injury and admission[a]	Disorder of consciousness at admission[a]	Mean LCF score at admission[a]	Etiology of the brain injury
Patients medicated with AEDs						
54	39 males and 15 females	42.6 ± 20.2	57.9 ± 28.6	34 VS (63%) and 20 MCS (37%)	2.2 ± 0.7	23 traumatic brain injuries, 22 cerebrovascular diseases, and 9 cerebral hypoxias
Patients not medicated with AEDs						
49	27 males and 22 females	49.5 ± 17.5	50.7 ± 22.1	27 VS (51.1%) and 22 MCS (44.9%)	2.3 ± 0.8	22 traumatic brain injuries, 13 cerebrovascular diseases, and 14 cerebral hypoxias

AEDs, antiepileptic drugs; LCF, levels of cognitive functioning; MCS, minimally conscious state; VS, vegetative state.
[a] Data related to the admission to the rehabilitation department.