İstanbul Journal of Pharmacy,
IJP 2025, 55 (2): 173–182

https://doi.org/10.26650/IstanbulJPharm.2025.1579713
Submitted: 05.11.2024
Revision Requested: 29.12.2024
Last Revision Received: 16.01.2025
Accepted: 16.02.2025

İstanbul University Press

İstanbul Journal of Pharmacy

Original Article

Open Access

Clinical Course of Amantadine in Patients with Prolonged Consciousness Disorder in the Intensive Care Unit

Yunus Emre Ayhan [1], Betül Özgan [2], Enes Emir İlerler [2] & Sait Karakurt [3]

[1] Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Clinical Pharmacy, İstanbul, Türkiye
[2] Marmara University, Faculty of Pharmacy, Department of Clinical Pharmacy, İstanbul, Türkiye
[3] Marmara University, Faculty of Medicine, Department of Pulmonary and Intensive Care Unit, İstanbul, Türkiye

Abstract

Background and Aims: This study aimed to evaluate the clinical course of amantadine treatment on consciousness recovery in patients with prolonged impairment admitted to the intensive care unit (ICU) for various reasons.

Methods: This was a retrospective descriptive study. The study included patients hospitalised in the ICU within 2 years (01.01.2022-01.09.2023) and who were administered intravenous amantadine to treat the prolonged consciousness disorder. Improvement in consciousness was defined as at least a two-point increase in the Glasgow Coma Scale (GCS) score.

Results: This study encompassed 21 participants, with an average age of 68.3±17.6 years. The median (Inter Quantile Range [IQR]) starting dose of amantadine was 400 mg/day (150-600), initiated 16.6±9.5 days post-ICU admission. Notably, 76.2% experienced consciousness recovery within a median (IQR) time of 3.5 days (2-5.75) after amantadine initiation. A significant positive correlation between consciousness recovery and sex (r: 0.533, p:0.013) was observed, with all men and 45.4% of women achieving recovery. Chi-square analysis indicated a sex-related significant difference in consciousness recovery status (p:0.015). However, the logistic regression analysis failed to establish a meaningful model.

Conclusion: Amantadine treatment shows promise in improving cognitive status in ICU patients with prolonged consciousness disorders. Further confirmatory studies with larger sample sizes, randomised designs, and standardised outcome measures are warranted to validate these findings.

Keywords Amantadine · Recovery of Consciousness · Prolonged Consciousness Disorder · Intensive Care Unit

Citation: Ayhan, Y. E., Özgan, B., İlerler, E. E. & Karakurt, S. (2025). Clinical course of amantadine in patients with prolonged consciousness disorder in the ıntensive care unit. *İstanbul Journal of Pharmacy*, *55*(2), 173-182. https://doi.org/10.26650/IstanbulJPharm.2025.1579713

This work is licensed under Creative Commons Attribution-NonCommercial 4.0 International License.

© 2025. Ayhan, Y. E., Özgan, B., İlerler, E. E. & Karakurt, S.

Corresponding author: Betül Özgan ozganbetul@gmail.com

INTRODUCTION

Amantadine is a drug used to treat Parkinson's disease and influenza, and it acts as an N-methyl-D-aspartate (NMDA) antagonist and, indirectly, a dopamine agonist. However, its mechanism of action still needs to be fully explained (Peeters et al., 2002). At the same time, amantadine is thought to improve alertness and arousal by decreasing dopamine reuptake and altering the configuration of postsynaptic dopaminergic receptors (Giacino et al., 2012; Sawyer et al., 2008). Therefore, it is among the neurostimulant agents frequently used for patients with long-term impaired consciousness (Oommen et al., 2019). It has a favourable safety profile and is generally recognised by patients. It is well tolerated (Stelmaschuk et al., 2015).

The neurostimulator efficacy of amantadine in patients with prolonged impairment of consciousness due to traumatic brain injury (TBI) has been demonstrated in various studies. In the study of Giacino et al., in which they examined 184 patients with TBI, a faster improvement in Disability Rating Scale (DRS) scores was observed in the amantadine group compared to placebo (Giacino et al., 2012). In the single-centre retrospective cohort study of Hadgu et al., significant increases were observed in the Glasgow Coma Scale (GCS) scores within 72 h in patients who were started on amantadine treatment (Hadgu et al., 2021). A recent study by Oommen et al. showed that amantadine as a neurostimulator agent has a high positive response in TBI. However, its effect on the length of stay in the intensive care unit (ICU) and hospital, duration of mechanical ventilation (MV), and general medical costs could not be evaluated (Oommen et al., 2019). The initiation of amantadine therapy in patients ranges from 3 days to 16 weeks from injury. Administration has been done orally in many studies, with the dose of amantadine ranging from 100 mg twice daily to 200 mg twice daily. The mean duration of treatment is 4-6 weeks, and treatment was continued until the target outcome was determined in some studies (e.g., extubation, GCS>8) (Abbasivash et al., 2019; Loggini et al., 2020; Stelmaschuk et al., 2015). Studies have evaluated cognitive outcomes using variable measures. DRS and GCS scores were the most commonly used cognitive measures. (Stelmaschuk et al., 2015). Limited data are available on the efficacy of amantadine in patients with prolonged unconsciousness due to causes other than TBI.

Extensive research and evidence support the widespread use of amantadine in managing prolonged disorders of consciousness associated with TBI. However, there is limited research on its use in prolonged disorders of consciousness resulting from other causes in ICU patients. This study aimed to evaluate the clinical course of amantadine treatment on consciousness recovery in patients with prolonged impairment admitted to the ICU for various reasons, the starting time of amantadine, its dose, method of administration, possible side effects, and the time it takes for the patient to regain consciousness after treatment.

MATERIALS AND METHODS

Design of the Study

This retrospective study was conducted between January 2022 and September 2023 on patients who were hospitalised for more than 24 h in the 8-bed ICU of Marmara University Hospital and received amantadine for the treatment of prolonged loss of consciousness. Patients with missing information and data were not included in the study.

Ethical Approval

Ethical approval of the study was approved by the Marmara University Non-Interventional Clinical Research Ethics Committee. (No: 09.2023.504). Because the study was retrospective, written informed consent was not obtained from the patients. All procedures adhered to the ethical standards of the University of Siena and the principles of the 1964 Helsinki Declaration and its later amendments.

Inclusion and Exclusion Criteria

Patients aged 18 years and older, hospitalised in the ICU, and using amantadine were included in the study. Patients who used amantadine but whose data could not be reached were excluded from the study.

Sample Size

Because this was a retrospective study, all patients who met the inclusion criteria were included, resulting in 21 patients. Assuming an estimated amantadine usage rate of 1% in the ICU, the required sample size was calculated as 15 patients, with a significance level (α) of 0.05 and a statistical power ($1-\beta$) of 95%. Notably, no missing data were observed among the included patients, ensuring the completeness of the dataset.

Data Collection and Evaluation

Demographic information such as age, sex, comorbidities, clinical conditions that cause prolonged unconsciousness and potential to affect brain functions, kidney function, length of stay in the hospital and ICU, MV duration, mortality status, and disease history of the patients were reviewed retrospectively. When the amantadine treatment was started, drug information such as the drugs used by the patient, the dosage regimen of the amantadine treatment, the route of administration, the duration of treatment, drug interaction information, and amantadine-related adverse events, and various score information were obtained from the hospital information management system in order to evaluate the effect of amantadine treatment on cognitive functions. The GCS score was used for cognitive assessment, and the Sequential Organ Failure Assessment (SOFA) score was used to assess organ damage. Brief product information/instructions for use and UpToDate® (Wolters Kluwer Health Inc.) resources were used to evaluate the dose, route of administration, side effects, and drug-drug interactions of the drugs. In the study, the Naranjo Drug Side Effect Probability Scale was used to evaluate the side effects in patients receiving amantadine. The scale was applied after excluding other clinical conditions and haves that could have side effects in the examination of drug side effects. The Naranjo scale consists of 10 questions answered with ''Yes'', ''No'' or ''I don't know''. Different point values are assigned to each answer (-1, 0, +1 or +2). Total points range from −4 to +13: If the score is 9, the reaction is considered definite; if it is 5 to 8, it is considered probable; if it is 1 to 4, it is considered possible; and if it is 0 or less, it is considered doubtful (Naranjo et al., 1981).

Baseline Predictors of Consciousness Recovery and Amantadine Response

Prolonged consciousness disorder is defined as a condition characterised by a significant impairment of consciousness that persists beyond the acute phase of illness or injury. In the context of this study, it involves patients in the ICU who experience prolonged unconsciousness or limited responsiveness due to various underlying causes, including TBI, stroke, or hypoxic-ischaemic encephalopathy (Abbasivash et al., 2019; Giacino et al., 2012; Oommen et al., 2019).
Some clinical conditions and parameters were examined to check that other possible causes of prolonged conscious disorders in patients were excluded. These include patients' sepsis, thyroid function tests, carbon dioxide levels (blood gas), hypoxaemia, glucose, encephalopathies (uraemic, hepatic), concurrent drug use that may cause sedation, acidosis, vitamin B12 levels, folic acid levels, electrolyte status, and brain imaging. The presence of any new findings was also examined. We defined improvement in consciousness as at least a two-point increase in the GCS score. In the literature, significant changes in the GCS have been defined with varying increments. While some studies consider a 1-point increase to be significant, at the centre where this study was conducted, a 2-point increase was deemed to represent a more meaningful change in the patient's clinical condition (Leclerc et al., 2021; Oommen et al., 2019).

Statistical Analysis

Statistical evaluation was analysed with IBM SPSS Statistics for Windows, Version 29.0 (Armonk, New York: IBM Corp.). Continuous variables are expressed as mean, median, standard deviation (SD), interquartile range (IQR), or counts and percentages, while categorical variables are expressed as frequency and percentage. The normality of the variables was found using the Shapiro-Wilk test analysis. When the two groups were compared on continuous variables, the t-test was used when the distribution was normal, and the Mann–Whitney U test was used when the distribution was not normal. Chi-square tests were used to compare categorical variables. The Pearson correlation coefficient was calculated in the correlation analysis. According to the correlation coefficient r value, 0.01-0.29 was defined as low, 0.30-0.70 as medium and 0.71-0.99 as high (Chan, 2003).

The significance of the variable(s) was determined by univariate logistic regression analysis ($p<0.02$). Binary logistic regression analysis was performed on the significant variables. The Nagelkerke R-square value and Hosmer and Lemeshow tests were used to evaluate the explanatory power and fit of the model, respectively. $p<0.05$ was considered statistically significant.

RESULTS

Twenty-one patients with prolonged consciousness disorder in the ICU and treated with amantadine were included in the study. The patients' mean ± SD age was 68.3±17.6 years, and most were female (52.4%). The main reason for ICU admission of the patients was respiratory failure (52.3%), the most common comorbidity was hypertension (14.5%), and the reason for prolonged consciousness disorder was ischaemic cerebrovascular accident (28.6%). Other demographic characteristics of the patients are shown in Table 1.

The clinical conditions and laboratory values of patients under amantadine treatment were also examined to evaluate prolonged consciousness disorders due to other reasons. At the centre where the study was conducted, it was determined that amantadine treatment was started after normalising other conditions that may cause consciousness disorders. At the beginning of amantadine treatment, 66.7% of the patients had normal renal status, all carbon dioxide (blood gas) values were at normal levels, and 4.8% were hypothyroid. Other clinical conditions and laboratory values that may affect the patient's state of consciousness at the beginning of treatment are presented in Table 2.

The median (IQR) starting dose of amantadine treatment was 400 (150-600) mg (200 mg every 12 hours), and treatment

Table 1. Demographic characteristics of the patients

Variable	Total (n:21)	Consciousness recovery		*p* value
		Yes (n:16)	No (n:5)	
Age (years), Mean±SD	68.3±17.6	68.6±11.8	67.2±32.1	0.874
Sex, n (%)				
Male	10 (47.6)	10 (62.5)	0 (0)	0.015
Female	11 (52.4)	6 (37.5)	5 (100)	
Cause of prolonged unconsciousness, n (%)				
Ischaemic cerebrovascular accident	6 (28.6)	4 (25)	2 (40)	0.762
Status epilepticus	5 (23.8)	3 (18.75)	2 (40)	
Hypoxic ischaemic encephalopathy	3 (14.3)	2 (12.5)	1 (20)	
Dementia	1 (4.8)	1 (6.25)	0 (0)	
Subarachnoid haemorrhage	2 (9.5)	2 (12.5)	0 (0)	
Unknown	4 (19)	4 (25)	0 (0)	
Comorbidities, n (%)				
Hypertension	9 (14.5)			
Diabetes mellitus	5 (8.06)			
Atrial fibrillation	5 (8.06)			
Benign prostatic hyperplasia	5 (8.06)			
Dementia	4 (6.4)			
Pulmonary embolism	4 (6.4)			
Other	30 (48.3)			
Number of comorbidities, Median (IQR)	3 (2-4)	3 (2-4)	2 (1.5-3.5)	0.354
ICU application GCS, Mean±SD	7.1±3.3	7.3±3.6	6.6±2.1	0.661
ICU discharged GCS, Median (IQR)	4 (3-10.5)	9 (3-11)	3 (3-7)	0.283
Total length of stay in the ICU (day), Median (IQR)	39 (26.5-66)	38.5 (26.25-56.75)	41 (24-95.5)	0.603
Mortality, n (%)				0.525
Yes	10 (47.6)	7 (43.75)	3 (60)	
No	11 (52.4)	9 (56.25)	2 (40)	

GCS: Glasgow coma scale, ICU: Intensive care unit, IQR: Interquartile Range, SD: Standard deviation

was started on average ± SD 16.6±9.5 days after admission to the ICU. All doses were administered intravenously. When we observed other drug groups that were used together with amantadine treatment and had the potential to affect the central nervous system, anti-seizure medication use was found in 13 (61.9%) of the patients. The anti-seizure medications used were levetiracetam, lamotrigine, and valproic acid, which do not have a significant sedative effect. Recovery of consciousness occurred in 16 (76.2%) patients. The median (IQR) time to recovery of consciousness after the initiation of amantadine treatment was 3.5 (2-5.75) days. Hypernatremia, a side effect associated with amantadine, was noted in 3 patients in this study. The amantadine-metoclopramide drug-drug interaction was observed in two of the patients. Detailed information about Amantadine treatment is shown in Table 3.

In the correlation analysis between the recovery of consciousness and categorical data (sex, cause of prolonged consciousness disorder, renal status, sepsis, epilepsy, mortality, and laboratory values), a statistically significant positive correlation was observed only with sex (r: 0.533, p: 0.013). Recovery of consciousness was achieved with amantadine treatment in all men and 6 (45.4%) women. Other numerical data (age,

Table 2. Clinical condition of the patient at the beginning of Amantadine treatment

Variable	Total (n:21)	Consciousness recovery		*p* value
		Yes (n:16)	No (n:5)	
Renal status, n (%)				
Normal (>60 ml/min/1.73 m2)	14 (66.7)	12 (75)	2 (40)	
Decreased GFR (<60 ml/min/1.73 m2)	1 (4.8)	1 (6.25)	0 (0)	0.194
Continuous venovenous haemodialysis	6 (28.6)	3 (18.75)	3 (60)	
Carbon dioxide status, n (%)				
Normal	21 (100)	16 (100)	5 (100)	-
Sodium levels, n (%)				
Normal	20 (95.2)	16 (100)	5 (100)	0.567
Glucose level, n (%)				
Normal	19 (90.5)	15 (93.75)	4 (80)	0.579
High level	2 (9.5)	1 (6.25)	1 (20)	
Lactate level (blood gas), n (%)				
Normal	16 (76.2)	13 (81.25	3 (60)	0.330
High level	5 (23.8)	3 (18.75)	2 (40)	
Folic acid level (serum) n (%)				
Normal	16 (76.2)	12 (75)	4 (80)	0.819
High level	5 (23.8)	4 (25)	1 (20)	
Low level	0 (0)	0 (0)	0 (0)	
Vitamin B12 level, n (%)				
Normal	19 (90.5)	15 (93.75)	4 (80)	0.361
High level	2 (9.5)	1 (6.25)	1 (20)	
Hypothyroidism, n (%)				
Yes	1 (4.8)	1 (46.25)	0 (0)	0.567
No	20 (95.2)	15 (93.75)	5 (100)	
Alcohol use, n (%)				
Yes	0 (0)	0 (0)	0 (0)	-
Sepsis condition, n (%)				
Yes	0 (0)	0 (0)	0 (0)	-
Epilepsy condition, n (%)				
Yes	8 (38.1)	6 (37.5)	2 (40)	0.920
No	13 (61.9)	10 (62.5)	3 (60)	

GFR: Glomerular filtration rate

number of ICU hospitalisation days, comorbidities, time to recovery of consciousness, time in MV, average amantadine dose, and treatment duration and scores) were categorised according to their median and mean values. The relationships between these data, categorised by consciousness recovery states, were analysed. Accordingly, no significant correlation was found between the variables and consciousness recovery. The chi-square analysis found only a statistically significant difference between sex and consciousness recovery status (p:0.015). The statistical analysis results of the relationship between all patient parameters and their recovery status are presented in Tables 1, 2, and 3.

To investigate the reason for the statistically significant relationship between sex and consciousness recovery, no significant difference was observed in any parameters in the analysis made between characteristics according to sex. According to the independent t and Mann–Whitney U tests performed among the continuous variables of patients with recovery of consciousness, no parameter with a statistically significant difference was found ($p>0.05$). Because of the

Table 3. Clinical condition of the patient at the beginning of Amantadine treatment

Variable	Total (n:21)	Consciousness recovery		*p* value
		Yes (n:16)	No (n:5)	
Dose (daily total), Mean±SD	353.8±200.5	356.1±185.3	346.4±268.6	0.927
Starting dose (mg). Median (IQR)	400 (150-600)	400 (200-600)	400 (66-600)	0.796
Dosing start day from ICU admission, Mean±SD	16.6±9.5	15.3±9.5	21±9	0.255
Drug administration route, n (%)				
Intravenous	21 (100)	16 (100)	5 (100)	-
Total treatment time, Median (IQR)	10 (7-16.5)	10 (7-26.25)	8 (6-11)	0.404
GCS at drug start, Mean±SD	7.2±2.8	7.1±3.0	7.6±2.3	0.752
GCS at the end of the drug, Median (IQR)	7 (3-10)	9 (3-10.75)	3 (3-7)	0.173
SOFA at drug start, Mean±SD	7.4±2.9	6.9±2.9	9.0±2.6	0.175
Consciousness recovery, n (%)				
Yes	16 (76.2)	16 (100)	5 (100)	-
Time to consciousness recovery (day), Median (IQR)	3.5 (2-5.75)	3.5 (2-5.75)	-	-
Amantadine side effects, n (%)				
Yes	3 (14.3)	3 (18.75)	0 (0)	0.296
No	18 (85.7)	13 (81.25)	5 (100)	
Drug-drug interaction with Amantadine, n (%)				0.351
Yes	2 (9.5)	1 (6.25)	1 (20)	
No	19 (90.5)	15 (93.75)	4 (80)	
MV duration during treatment (day), Median (IQR)	11 (3.5-34.5)	11.5 (0.75-36.75)	10 (5.5-49)	0.772
Drug group used together with Amantadine, n (%)				0.920
Anti-seizure	13 (61.9)	10 (62.5	3 (60)	
None	8 (38.1)	6 (37.5)	2 (40)	

GCS: Glasgow coma scale, IQR: Interquartile range, MV: Mechanical ventilation, SOFA: Sequential Organ Failure Assessment

operations performed in the logistic regression analysis, no meaningful model could be established.

DISCUSSION

In this retrospective study, we attempted to examine the effect of amantadine treatment in patients with prolonged impaired consciousness. Most of the patients included in the study had ischaemic cerebrovascular events. When the patients were examined, it was seen that other possible causes for the disorder of consciousness were excluded. In the treatment, 200 mg intravenous amantadine sulphate was generally used twice a day. Recovery of consciousness has been observed in most patients with prolonged consciousness disorder using amantadine treatment.

Dosage and Consciousness Recovery Effectiveness of Amantadine Treatment

Amantadine, recognised for its mechanism of action, demonstrates heightened efficacy in enhancing consciousness recovery rates and GCS scores, particularly in patients with TBI (Giacino et al., 2012; Meythaler et al., 2002; Saniova et al., 2004; Sawyer et al., 2008). Hughes et al., in a cohort study involving 123 patients with severe TBI in a coma, administered amantadine (100 or 200 mg BID) in 28 cases, noting clinical improvements within 1 week. The odds ratio (OR) for coma resolution in the treatment group compared with the control group was 1.42 (95% CI: 0.607 to 3.325) (Hughes et al., 2005). In another study, Saniova et al. retrospectively analysed 74 severe TBI patients (GCS score<8), observing a significant increase in GCS scores in the amantadine-treated group (mean GCS score: 10 vs. 6 in the placebo group; p<0.0001) (Saniova et al., 2004). Meythaler et al.'s double-masked trial with 35 patients with TBI revealed a consistent trend towards faster functional recovery with 200 mg amantadine compared with placebo over six weeks (Meythaler et al., 2002). Salihoğlu et al. reported that 74.1% of patients with TBI achieved complete clinical improvement with amantadine sulphate infusion therapy (Salihoğlu & Şahin, 2019).

In the literature, studies on the use of amantadine for treating consciousness disorder have been carried out on very heterogeneous patient groups. Most of these studies were conducted on patients with TBI, and it was emphasised that amantadine treatment has a positive place in the treatment, but randomised controlled and better-designed studies are needed (Akçıl et al., 2018; Khasanova et al., 2009; Krivonos et al., 2010). Among the patients in this study, there were no patients with impaired consciousness or ICU admission due to TBI. On the other hand, studies conducted on the dose and effect of amantadine treatment in patients with consciousness disorder help guide patients with consciousness disorder for other different reasons.

There are many heterogeneous reports regarding the potential effectiveness of amantadine in patients with different types of stroke (Akçıl et al., 2018; Gagnon et al., 2020; Khasanova et al., 2009; Krivonos et al., 2010; Leclerc et al., 2021). Khasanova et al. compared the clinical effectiveness of amantadine (n:20) and magnesium sulphate (n:20) infusions in the acute phase of ischaemic stroke. A more significant improvement in consciousness and regression in neurological deficits were observed in patients treated with amantadine, especially in the first phase of treatment. (Khasanova et al., 2009). Krivonus et al. showed that using 200 mg/day intravenous amantadine sulphate treatment for ten days in addition to conventional treatment in acute stroke patients reduced the frequency of neurological deficits (Krivonos et al., 2010). Akçıl et al. administered a total of 200 mg intravenous amantadine per day for five days after admission to patients with aneurysmal subarachnoid haemorrhage (SAH) and then 100 mg amantadine perorally/enterally twice a day for 25 days. Significant neurocognitive improvement was achieved in the amantadine treatment group compared with the standard treatment group (Akçıl et al., 2018). In a comprehensive retrospective study, Leclerc et al. reviewed hospital records to evaluate the safety and effectiveness of amantadine and/or modafinil (both usually at a dose of 100 mg twice daily), neurostimulant used for acute stroke care in the ICU. Patients receiving only amantadine monotherapy and/or the combination of amantadine and modafinil met the responder's definition. The average response time was three days (Leclerc et al., 2021). Gagnon et al. systematically reviewed 10 amantadine studies (n: 121 patients) in post-stroke cases. The common starting doses ranged from 100 mg once or twice daily (100-200 mg/day) to a final daily dose of 200 mg. Disorders of consciousness were the primary indication in 30% of the cases. Positive responses on clinical efficacy measures were observed in 70% of amantadine publications. Notably, only one publication, examining 10% of cases (n:5 patients), focused on acutely hospitalised or ICU patients. Both publications are thus cited as randomised trials demonstrating amantadine's positive impact on neurocognitive function (Gagnon et al., 2020).

Recovery of consciousness occurred in two SAH patients (2/2 patients) included in this study. However, recovery of consciousness could not be achieved in all patients with prolonged consciousness disorder due to stroke (recovery of consciousness in 4/6 patients). It is stated that 200 mg/day amantadine treatment is generally used for treating consciousness disorder in stroke patients, and recovery of consciousness is achieved. In the patients included in our study, amantadine treatment was generally started at a dose of 400 mg/day. From other studies, the use of high-dose amantadine treatment did not create a significant difference in the rates of patients experiencing recovery of consciousness (Akçıl et al., 2018; Gagnon et al., 2020; Leclerc et al., 2021).

In this study, no statistically significant difference was observed in mortality between patients with and without recovery of consciousness. ICU admission GCS values of the patients included in this study are also at a level similar to the literature. Such studies, especially in TBI patients, need to be proven by better-designed studies specific to stroke and its subtypes. In this study, no studies were found in the literature on patients with status epilepticus, hypoxic-ischaemic encephalopathy, and dementia, which are causes of prolonged consciousness disorder. The effectiveness of amantadine in patients with consciousness disorder has been demonstrated in the studies examined. However, there is no standard practice regarding the dosage and duration of treatment. Differences in the definition of recovery of consciousness may also explain the differences in amantadine effectiveness rates in the literature.

Time to Start Amantadine Treatment and Achieve Recovery of Consciousness

In the study by Hughes et al., amantadine treatment was prescribed 2-5 weeks (mean 20-25 days) after transfer from the ICU to the ward (Hughes et al., 2005). Saniova et al. started treatment for severe head injury patients on the third day of admission to the hospital. Recovery (emergence from coma) has been noted as tending to occur within a week of starting amantadine treatment (Saniova et al., 2004). Meythaler et al. started amantadine treatment within a wide range of time, such as 4 days to 6 weeks after the trauma (Meythaler et al., 2002). Salihoğlu et al. also started amantadine treatment in patients with TBI before the 10th day of hospitalisation. The mean time until consciousness regained was 13.48 (±10.4) days (Salihoğlu & Şahin, 2019). Khsanova et al. stated that patients treated with amantadine showed a more pronounced recovery of consciousness with the most intensive restoration of the neurological deficit on the first day. Therefore, it has been stated that the use of amantadine sulphate in the first hours of ischaemic stroke and the recanalization treatment of ischaemic stroke will allow the prevention of reperfusion injury (Khasanova et al., 2009). Based on the data obtained by Akçıl et al., they believed that adding amantadine to standard treatment in the early stages of SAH would improve neurocognitive functions. (Akçıl et al., 2018). Leclerc et al. stated that amantadine used for acute stroke care in the ICU is usually started 1-27 (mean 7) days after the stroke (Leclerc et al., 2021). Gagnon et al. In the 10 amantadine studies included in the systematic review, amantadine treatment was started an average of 39 days after stroke. Recovery times after acute or later post-stroke amantadine interventions vary between studies (Gagnon et al., 2020). While Akçıl et al. stated the time taken to recover consciousness as five days, Avecillas-Chasín et al. stated it as three days, the time taken was not reported in other studies of the systematic review (Akçıl et al., 2018; Avecillas-Chasín & Barcia, 2014; Gagnon et al., 2020). Meythaler et al. stated that in the clinical study conducted on TBI patients within the first 24 h after admission, they saw perfect clinical improvement in most patients (Meythaler et al., 2002).

In this study, amantadine treatment was started 2-3 weeks after admission to the ICU. In the mentioned studies, it is stated that starting amantadine treatment as soon as possible after the patient's application gives better results in the state of consciousness. Another noteworthy point is that, as in this study, recovery of consciousness occurs in a very short time (3-5 days) after amantadine treatment (Akçıl et al., 2018; Avecillas-Chasín & Barcia, 2014). Although there was no significant difference between them, we found that treatment was started earlier in patients with recovery of consciousness. Based on these data, we propose that initiating amantadine treatment earlier in patients with, or at risk of, prolonged disorders of consciousness may be beneficial. Additionally, the effectiveness of amantadine appears to be more evident in the first days of treatment.

Side Effects Due to Amantadine Treatment

In their study, Barra et al. examined the side effects of stimulating treatments. Accordingly, TBI patients frequently (85.4%) observed the adverse effects of agitation and urinary retention due to amantadine (Barra et al., 2020). Salihoğlu et al. also reported the side effect of arrhythmia, which causes ECG changes due to amantadine (Salihoğlu & Şahin, 2019). Considering the ICU environment and the predisposition of TBI patients to agitation, they concluded that amantadine treatment was tolerated with modifications such as dose reduction and drug discontinuation in TBI patients with impaired consciousness (Barra et al., 2020; Gramish et al., 2017). Visual hallucinations (2% of patients), dizziness (5% of patients), and dry eyes or mouth (5% of patients) were reported as amantadine-related side effects in approximately 50% of the publications included in Gagnon et al.'s systematic review (Gagnon et al., 2020). In this study, hypernatremia, a side effect associated with amantadine, was recorded in 3 patients. Side effects due to amantadine-metoclopramide (contraindicated level drug interaction) drug-drug interaction observed in two of the patients did not occur.

Considering the effectiveness of amantadine in patients with consciousness disorder, it can be used safely in such patients, provided that the adverse effects are monitored. No serious adverse effects related to amantadine were mentioned in the studies. Amantadine side effects were observed in this study at rates consistent with the literature. We can explain that intravenous amantadine treatment causes hypernatremia due to its high sodium content (Kalın et al., 2022).

Factors Affecting the Consciousness Recovery Status of Amantadine Treatment

When similar studies with amantadine were examined, the parameters that affect and explain the state of consciousness recovery were not detailed. This study revealed a statistically significant difference between sexes, with mainly male patients being more prone to recovery of consciousness. However, when all parameters were examined between male and female sexes to explain this situation, no statistical difference could be found that could explain this situation.

The effectiveness of amantadine in promoting neurological recovery in these cases has not yet been determined. However, its effectiveness in promoting neurological recovery in these cases has yet to be determined. Previous studies have reported several limitations. (Akçıl et al., 2018; Gagnon et al., 2020; Krivonos et al., 2010; Leclerc et al., 2021). The results of existing studies are often not comparable for reasons such as drug regimens, timing of administration, and different outcome measures. These also affect the clarity of the benefit of the treatment.

Limitations

This study has some limitations due to its retrospective nature. Some parameters that should be evaluated during the hospitalisation of the patients (discharged SOFA, long-term consciousness monitoring) could not be reached. Some statistical evaluations could not be performed because some patients received amantadine treatment. Another area for improvement is that the study is single-centred. The results of this study do not generalise to other ICU and prolonged consciousness disorder patients.

CONCLUSION

According to the results of this study, although statistically significant results were not obtained with amantadine treatment, consciousness was improved in most of the patients. The data obtained from this study indicate that adding amantadine to treatment in the early period will be more effective in the recovery of consciousness. In addition, the effectiveness of amantadine was even more evident in the first days of treatment. Future controlled studies using an appropriate sample size, randomised design, and standardised objective outcome measures are needed to confirm the outcome of the recovery of consciousness.

Ethics Committee Approval	The study received ethical approval from the Non-Interventional Clinical Research Ethics Committee of Marmara University in Istanbul, Turkey (No: 09.2023.504).
Informed Consent	Informed consent was obtained from the participants.
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of Study: Y.E.A., S.K.; Data Acquisition: B.Ö., E.E.İ.; Data Analysis/Interpretation: Y.E.A.; Drafting Manuscript: Y.E.A.; Critical Revision of Manuscript: S.K.; Final Approval and Accountability: Y.E.A., B.Ö., E.E.İ., S.K.
Conflict of Interest	The authors have no conflict of interest to declare.
Financial Disclosure	The authors declared no financial support.

Author Details

Yunus Emre Ayhan

[1] Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Clinical Pharmacy, İstanbul, Türkiye

0000-0001-6093-0849

Betül Özgan

[2] Marmara University, Faculty of Pharmacy, Department of Clinical Pharmacy, İstanbul, Türkiye

0000-0002-3268-8028 ozganbetul@gmail.com

Enes Emir İlerler

[2] Marmara University, Faculty of Pharmacy, Department of Clinical Pharmacy, İstanbul, Türkiye

0000-0003-4651-5790

Sait Karakurt

[3] Marmara University, Faculty of Medicine, Department of Pulmonary and Intensive Care Unit, İstanbul, Türkiye

0000-0002-6699-5798

REFERENCES

Abbasivash, R., Valizade Hasanloei, M. A., Kazempour, A., Mahdkhah, A., Shaaf Ghoreishi, M. M., & Akhavan Masoumi, G. (2019). The effect of oral administration of amantadine on neurological outcome of patients with diffuse axonal injury in ICU. *Journal of Experimental Neuroscience, 13*, 1179069518824851. https://doi.org/10.1177/1179069518824851

Akçıl, E. F., Dilmen, K. Ö., Vehid, H., & Tunalı, Y. (2018). Can amantadine ameliorate neurocognitive functions after subarachnoid haemorrhage? A preliminary study. *Turkish Journal of Anaesthesiology and Reanimation, 46*(2), 100–107. https://doi.org/10.5152/TJAR.2018.20280

Avecillas-Chasín, J. M., & Barcia, J. A. (2014). Effect of amantadine in minimally conscious state of non-traumatic etiology. *Acta Neurochirurgica, 156*(7), 1375–1377. https://doi.org/10.1007/s00701-014-2077-x

Barra, M. E., Izzy, S., Sarro-Schwartz, A., Hirschberg, R. E., Mazwi, N., & Edlow, B. L. (2020). Stimulant therapy in acute traumatic brain injury: Prescribing patterns and adverse event rates at 2 level 1 trauma centers. *Journal of Intensive Care Medicine, 35*(11), 1196–1202. https://doi.org/10.1177/0885066619841603

Chan, Y. H. (2003). Biostatistics 104: Correlational analysis. *Singapore Medical Journal, 44*(12), 614–619.

Gagnon, D. J., Leclerc, A. M., Riker, R. R., Brown, C. S., May, T., Nocella, K., Cote, J., Eldridge, A., & Seder, D. B. (2020). Amantadine and modafinil as neurostimulants during post-stroke care: A systematic review. *Neurocritical Care, 33*(1), 283–297. https://doi.org/10.1007/s12028-020-00977-5

Giacino, J. T., Whyte, J., Bagiella, E., Kalmar, K., Childs, N., Khademi, A., Eifert, B., Long, D., Katz, D. I., Cho, S., Yablon, S. A., Luther, M., Hammond, F. M., Nordenbo, A., Novak, P., Mercer, W., Maurer-Karattup, P., & Sherer, M. (2012). Placebo-controlled trial of amantadine for severe traumatic brain injury. *The New England Journal of Medicine, 366*(9), 819–826. https://doi.org/10.1056/NEJMoa1102609

Gramish, J. A., Kopp, B. J., & Patanwala, A. E. (2017). Effect of amantadine on agitation in critically ill patients with traumatic brain injury. *Clinical Neuropharmacology, 40*(5), 212–216. https://doi.org/10.1097/WNF.0000000000000242

Hadgu, R. M., Borghol, A., Gillard, C., Wilson, C., Elqess Mossa, S., McKay, M., Jastram Jr., C., & Onor, I. O. (2021). Evaluation of outcomes in patients receiving amantadine to improve alertness after traumatic brain injury. *Hospital Pharmacy, 56*(5), 486–494. https://doi.org/10.1177/0018578720920803

Hughes, S., Colantonio, A., Santaguida, P. L., & Paton, T. (2005). Amantadine to enhance readiness for rehabilitation following severe traumatic brain injury. *Brain Injury, 19*(14), 1197–1206. https://doi.org/10.1080/02699050500309296

Kalın, B. S., Sert, A. İ., Altun, K., & Öztürk, Ü. (2022). Can amantadine cause resistant hypernatremia in the treatment of hypoxic brain injury due to cardiac arrest? *Turkish Journal of Nephrology, 31*(4), 385–388. https://doi.org/10.5152/turkjnephrol.2022.211295

Khasanova, D. R., Saĭkhunov, M. V., Kitaeva, E. A., Khafiz'ianova, R., Islaamov, R. R., & Demin, T. V. (2009). Amantadine sulfate (PK-Merz) in the treatment of ischemic stroke: A clinical-experimental study. *The Journal of Neurology and Psychiatry named after S.S. Korsakov, 109*(5 Suppl 2), 37–43.

Krivonos, O. V., Amosova, N. A., & Smolentseva, I. G. (2010). Use of the glutamate NMDA receptor antagonist PK-Merz in acute stroke. *Neuroscience and Behavioral Physiology, 40*(5), 529–532. https://doi.org/10.1007/s11055-010-9292-6

Leclerc, A. M., Riker, R. R., Brown, C. S., May, T., Nocella, K., Cote, J., Eldridge, A., Seder, D. B., & Gagnon, D. J. (2021). Amantadine and modafinil as neurostimulants following acute stroke: A retrospective study of intensive care unit patients. *Neurocritical Care, 34*(1), 102–111. https://doi.org/10.1007/s12028-020-00986-4

Loggini, A., Tangonan, R., El Ammar, F., Mansour, A., Goldenberg, F. D., Kramer, C. L., & Lazaridis, C. (2020). The role of amantadine in cognitive recovery early after traumatic brain injury: A systematic review. *Clinical Neurology and Neurosurgery, 194*, Article 105815. https://doi.org/10.1016/j.clineuro.2020.105815

Meythaler, J. M., Brunner, R. C., Johnson, A., & Novack, T. A. (2002). Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: A pilot double-blind randomized trial. *The Journal of Head Trauma Rehabilitation, 17*(4), 300–313. https://doi.org/10.1097/00001199-200208000-00004

Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., Janecek, E., Domecq, C., & Greenblatt, D. J. (1981). A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology & Therapeutics, 30*(2), 239–245. https://doi.org/10.1038/clpt.1981.154

Oommen, J. K., Wang, S., Axelrad, A., Hanna, A., Muralidharan, R., & Osias, J. (2019). Efficacy of modafinil, methylphenidate, amantadine, and zolpidem in consciousness recovery in intensive care unit patients with traumatic brain injury. *PT: The Journal for Physical Therapy, 44*(11), 676–681.

Peeters, M., Page, G., Maloteaux, J. M., & Hermans, E. (2002). Hypersensitivity of dopamine transmission in the rat striatum after treatment with the NMDA receptor antagonist amantadine. *Brain Research, 949*(1–2), 32–41. https://doi.org/10.1016/s0006-8993(02)02961-x

Salihoğlu, E., & Şahin, A. S. (2019). Can amantadine sulfate infusion be a life saver in intensive care unit? *Turkiye Klinikleri Journal of Medical Sciences, 39*(2), 129–134. https://doi.org/10.5336/medsci.2018-62457

Saniova, B., Drobny, M., Kneslova, L., & Minarik, M. (2004). The outcome of patients with severe head injuries treated with amantadine sulphate. *Journal of Neural Transmission, 111*(4), 511–514. https://doi.org/10.1007/s00702-004-0112-4

Sawyer, E., Mauro, L. S., & Ohlinger, M. J. (2008). Amantadine enhancement of arousal and cognition after traumatic brain injury. *The Annals of Pharmacotherapy, 42*(2), 247–252. https://doi.org/10.1345/aph.1K284

Stelmaschuk, S., Will, M. C., & Meyers, T. (2015). Amantadine to treat cognitive dysfunction in moderate to severe traumatic brain injury. *Journal of Trauma Nursing, 22*(4), 194–203. https://doi.org/10.1097/jtn.0000000000000138