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Amantadine minimally improves arousal in patients with severe traumatic brain injury

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ABSTRACT A critical appraisal and clinical application of Giacino JT, Whyte J, Bagiella E, et al. Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury. *New England Journal of Medicine*. 2012;366(9):819-826. doi: 10.1056/nejmoa1102609.

Keywords: *amantadine, anoxic brain injury, severe traumatic brain injury, arousal, cognition, rehabilitation*

Clinical Context

John Stryker (pseudonym) is a 20-year old man who was involved in a motor vehicle accident (MVA). He suffered anoxic encephalopathy as well as intraventricular and subarachnoid hemorrhages, cerebral edema, multiple skull and mandibular fractures, bilateral pneumothorax, aspiration pneumonia, respiratory failure, traumatic shock and acute kidney injury. He was transferred for inpatient rehabilitation (IPR) which requires 3 hours per day, 5 days per week of physical, occupational and speech therapy. On arrival to IPR, Mr. Stryker was in a minimally conscious state secondary to anoxic brain injury. Amantadine was added to his medication regimen to promote arousal and to better tolerate his therapies. This medication is commonly used at this IPR where active participation in therapy is critical to recovery. Arousal and cognition were monitored weekly via the JFK Coma Recovery Scale (CRS)-Revised, which assessed auditory, visual, motor, oro-motor, communication, and arousal processes.[1] The patient's CRS score was five out of 23 on admission. It increased to six a few days after starting amantadine. His family was joyfully tearful witnessing his minor progress. He had been in a stable yet non-improving condition for months following his injury, and these first few days at our IPR provided them with their first glimpse of hope. The patient is currently taking amantadine and continually being assessed for improvement.

Clinical Question

Does amantadine improve arousal in traumatic brain injury patients?

Research Article

Giacino JT, Whyte J, Bagiella E, et al. Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury. *New England Journal of Medicine.* 2012;366(9):819-826. doi: 10.1056/nejmoa1102609.

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Related Literature

PubMed database was searched with the following search terms: head injury OR brain injury AND amantidine OR gocovri. Meta analyses and systematic reviews were assessed for additional references that might be relevant. Animal studies as well as human studies with a mean patient age <16 or >65 years were excluded due to their degree of difference from the clinical context.

Several medications are used clinically to promote arousal through modulation of dopaminergic or noradrenergic pathways. These neuronal pathways may be damaged during injury or secondarily, long after initial insult.[3] The literature behind mechanism and efficacy of these medications is currently lacking. A Cochrane review from 2006 evaluated the utility of monoaminergic agents, such as amantadine, in acute TBI. It concluded that there was insufficient evidence to support the use of monoamines in these patients.[4] However, a number of randomized control trials (RCT) have reported significant benefit of amantadine in TBI recovery.[5-10] Hammond et al. found that amantadine reduced aggression and irritability.[5,6] Although in a separate study, only the clinicians and patients subjectively perceived this finding, all of whom were blinded to the medication. The research observer, and thus the results, did not note any changes in patient behavior.[7]

Meythaler et al. found that 200mg of amantadine increased recovery speed in a variety of measures including Glasgow Outcome Scale, Mini Mental Status Exam, Disability Rating Scale (DRS) and Functional Independence Measure Cognitive Score.[9] Another study presented a positive amantadine response via increased Glasgow Coma Scale (GCS) scores and decreased fatality rates.[11] However, this study had half the sample size of the article chosen for the current appraisal. Interestingly, two studies found that amantadine even improved motor recovery.[12,13] Whyte et al. concluded that there was no increase in adverse events in patients on amantadine vs. controls.[10] Although these results are promising, they do not address the question of improved arousal with amantadine therapy.

A number of case reports have shown improved arousal with amantadine.[14-20] Remarkably, these cases demonstrate that amantadine may benefit patients of all ages, ranging from 18 to 82. A few interesting responses to amantadine should be noted. Sood et al. found that dosing amantadine every other day drastically increased arousal, compared to everyday.[21] A separate patient showed greater improvement with a combination of amantadine and Levodopa/Carbidopa than amantadine alone.[22] From a side effect profile, a predisposed individual suffered from hallucinations with standard dose amantadine.[23]

Despite promising case reports, a clinical trial of 40 TBI patients taking amantadine for six weeks did not find any positive effect on consciousness, memory, disability, cognition, mortality or performance 6 months into therapy. Of note, the research showed a statistically significant improvement in cognition during the first six days.[24] Whyte et al. also reported improvement one week into amantadine use, measured via the DRS.[25] A separate RCT of ten patients reported no difference in cognitive improvement between amantadine and control groups, however this may be attributed to small sample size and high drop out rate.[26] One study reported improved executive function with amantadine via increased left pre-frontal cortex activity on positron emission tomography (PET). Unfortunately, this study used high dose amantadine therapy that is not often administered clinically.[8] An RCT using standard amantadine dosing found decreased cognitive processing within the first 28 days of therapy. However, the effect size was small and mean scores on neuropsychological tests for both treatment and control groups were within normal limits for severe TBI patients.[27]

Articles that have synthesized the limited available research have proposed conflicting results. One literature review concluded that amantadine improved behavioral symptoms[28] while another noted improvement in a variety of cognitive functions, including arousal.[29] However, a more recent study suggested that the evidence is still too weak to make systematic clinical recommendations.[30]

The study conducted by Giacino and colleagues was chosen to appraise because it best suited the clinical picture of the patient presented. It was a randomized, double-blinded, placebo-controlled trial of TBI patients at an IPR facility within 4-16 weeks of injury. It had the largest sample size (n = 184) of the previously referenced articles, and included eleven sites across three countries. Subjects were given two weeks of amantadine (100mg twice daily), which was increased to 150mg during week three and 200mg during week four, if DRS scores had not improved by at least two points. The medication was tapered off over 2-3 days and patients were assessed for an additional two weeks. The authors concluded that amantadine accelerated the pace of recovery due to quicker emergence of cognition and functionally meaningful behaviors, such as response to commands, intelligible speech and object use. They also showed that recovery rate slowed during the wash out period, and thus the response was drug-dependent. Importantly, there was no difference in adverse events between treatment and control groups.[3]

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Critical Appraisal

This study is most applicable to the case presented due to the young mean age of subjects, as well as the patient's baseline CRS-revised score falling within the range of this trial. The patient met inclusion criteria of the study being assessed. Additionally, he took the same initial dose of amantadine and it was increased in a similar fashion. Other strengths of this research include its randomization method, which yielded similar demographics in treatment and control groups. The authors utilized multiple assessment tools, such as CRS-revised and DRS. All subjects enrolled were included in the final analysis, thus loss to follow up was minimized.

A weakness was that one third of subjects used potentially confounding medications, and that the two groups differed in types of medications used. The treatment group used antiepileptics more frequently ($p = 0.04$) while the placebo group used narcotics more frequently ($p = 0.07$). Other limitations include its short duration and bias towards IPR patients. This is particularly important because the process of admitting patients to IPR is selective towards those that show signs of potential for improvement. Another point of concern is lead-time bias. It is difficult to ascertain whether amantadine improved arousal and cognition, or simply accelerated cognition to the same level of function that would eventually be achieved without it. The level of evidence given to the appraised research is Level 1b, according to the Oxford Centre for Evidence-Based Medicine.

Clinical Application

The results of this study suggest that amantadine has a beneficial effect on arousal in TBI patients. Although Mr. Stryker is still early in recovery, his clinical trajectory is aiming towards a similar response. His initial prognosis was poor due to his minimally conscious state and delay in rehabilitation until months following the inciting trauma. Even small changes in his arousal could allow for greater intensity of therapy and thus a better chance of neurorecovery and shortened length of stay. The study suggests that patients who are minimally conscious, rather than vegetative, and start amantadine early after injury (within 28-72 days) vs late (> 72 days) have the best outcomes. However, all subject groups showed improvement in arousal. Thus, it is reasonable to trial amantadine therapy in all TBI patients, barring no contraindications, to improve arousal, therapy tolerance and overall recovery. Lack of treatment could potentially cause prolonged recovery, greater length of stay in hospital and thus increased susceptibility to infections. Even if final functional status is equivalent with or without amantadine, accelerating the time to reach this final state will improve outcomes in TBI patients.

Learning points:

1. All TBI patients should be assessed for potential amantadine therapy during their rehabilitation.
2. Speed of recovery from TBI is an important factor in overall quantity of functional recovery.
3. More research is needed to study the long-term effects of amantadine and other neuromodulators on TBI recovery.

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