

Modafinil for treatment of coma and unresponsiveness associated with edema of the reticular activating system (RAS) in a pediatric patient

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Abstract

Modafinil is a dopamine re-uptake blocker and increases wakefulness through actions in the central nervous system. Approved by the United States Food and Drug Administration (FDA) for the treatment of narcolepsy, modafinil has been used post-operatively to treat disorders of wakefulness causing lethargy or obtundation. Although modafinil is not approved by the FDA or the manufacturer for use in children under the age of 18, modafinil has been used clinically and reported in many pediatric studies. Modafinil has been used in clinical studies for children with Attention Deficit Hyperactivity Disorder (ADHD) and narcolepsy. This report illustrates the case of an 11-year-old child that underwent a brain stem tumor resection. Post-operatively, the patient did not wake up despite normal intra-operative physiological studies. Post-operative somato-sensory evoked potentials (SSEP's), motor evoked potentials, cranial nerve testing and brain stem auditory evoked responses (BAER's) were repeated and were found to be normal. Electroencephalography (EEG) showed increased slowing with delta and theta waves. Magnetic resonance imaging did not show any definite hemorrhage or ischemia. There was edema noted in the posterior mesencephalon and caudal hypothalamus. Modafinil was started in an attempt to stimulate the reticular activating system. Within 48 hours, the patient started opening his eyes and following commands. Modafinil was eventually discontinued while patient was an inpatient at a pediatric rehabilitation hospital. The patient continues to be awake and alert now, several months after surgery.

Introduction

Modafinil is recommended as a possible treatment for ADHD, narcolepsy, obstructive sleep apnea, and shift work disorder in adults but is not recommended by the FDA or manufacturer for use on pediatric patients due to some of the observed side effects in clinical studies [6]. Some of the observed side effects in adults include, but are not limited to, serious rash, depression, hallucinations, mania, irregular heartbeat, and troubled breathing [1]. In children, side effects seen in clinical studies include but are not limited to hostile behavior, low white blood cell count, increase in sudden loss of muscle tone, Tourette's syndrome, and increases in suicidal thoughts [1]. There have not been many clinical studies that test the efficacy and safety of prescribing modafinil to children, especially as a treatment for narcolepsy and ADHD. While not recommended by the FDA, modafinil has on occasion been used off-label after brain surgery to treat disorders of wakefulness.

Although the mechanism of modafinil is currently unknown it is presumed to be similar to that of amphetamine-based stimulants albeit the differing pharmacologic profile [1]. In hypocretin receptive neurons of the tuberomammillary nucleus, an area of the brain associated with arousal and wakefulness, modafinil was found to excite neuronal activity [2]. The half-life of modafinil is reported to be 15 hours and a peak absorption time of between 2 and 4 hours with food not having an overall impact on its bioavailability [1]. Despite the lack of effect on bioavailability, food may delay the time it takes to reach peak consumption [1].

We report an unusual case of a child with post-operative coma and RAS edema who responded well to Modafinil. It is also interesting that when the Modafinil was temporarily stopped, his unresponsiveness returned. After Modafinil was re-started, the child woke up again.

Case Report

An 11-year-old male presented to the emergency department with severe headaches for a week and vertical nystagmus for approximately two years. The patient had a history of ADHD. Vital signs were stable. Upon neurological examination, patient was alert and cooperative. He did have nystagmus, mild dysmetria and dysidiadochokinesia. The patient had been seen by an ophthalmologist a day before presenting to the ER and an MRI of the brain was taken with and without contrast.

Pre-Operative MRI Imaging

The MRI showed obstructive hydrocephalus due to a mass lesion in the fourth ventricle, obstructing the aqueduct of Sylvius. The dimensions of the mass were found to be approximately 3 cm x 2.5 cm by 2 cm. The lesion was felt to be an ependymoma by the neuro-radiologists because of cystic changes within the tumor and its location. The mass caused some fullness of the temporal horns of the lateral ventricles. Options were discussed including the surgical resection of the mass along with the risks and benefits of the procedure.

The patient underwent an elective resection of the fourth ventricular tumor. A left frontal external ventricular drain (EVD) was placed prior to surgery, to manage the obstructive hydrocephalus during surgery.

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Informed consent from the patient's mother was received after all the risks and benefits of the procedures were explained. The tumor resection was completed via a combination of microscopic resection using bipolar and suction and cavitating ultrasonic aspiration (CUSA). Multiple specimen was obtained to determine pathology. Surgical pathology was consistent with a glial tumor, but was ultimately classified as a pilocytic astrocytoma Grade I. The tumor actually originated from the tectum of the midbrain and there was a rim of unresectable, residual tumor left along the dorsal aspect of the midbrain.

During surgery, intraoperative physiological monitoring was performed. Baseline readings all showed good, reliable responses and readings throughout the procedure accounted for influences from anesthesia as well as temperature of the operating room. The somatosensory evoked potentials (SSEP) readings displayed no significant changes in any of the measured potentials throughout the duration of the procedure. The brainstem auditory evoked potentials (BAEP) readings also displayed no significant changes throughout the duration of the surgery. There was no significant electromyography (EMG) reading except for some bursts and trains of activity. Although the bursts and trains suggest mild irritation of the nerves, they do not necessarily indicate neurological deficits. There was no sustained EMG activity documented at any time, or after completion of surgery.

Immediately after surgery, patient was unarousable. His pupils were fixed and dilated. He had no corneal blink response. He had no gag reflex. He did not breathe spontaneously or trigger the ventilator. He had no motor response to pain. There was no autonomic response to pain. An emergent post-op CT scan showed the presence of intracranial air but was negative for intracranial hemorrhage. A follow-up MRI showed that there was approximately 2-3% of residual tumor and extensive edema along the upper brainstem around the reticular activating system (RAS). There was no ischemia or infarct seen. Comprehensive post-operative neuro-physiological examinations were conducted in order to determine the etiology of coma and to see if studies were similar to those performed during surgery. SSEP reading were equal bilaterally and normal. Transcranial motor evoked potentials (tcMEP) were measured and determined to be normal and consistent. Auditory brainstem responses (ABR) were present in both ears after stimulation of the auditory nerve. The response on the right was decreased in comparison with the left but was not determined to be significantly decreased. Electroencephalography (EEG) data was recorded and displayed theta and delta waves. In summation, the physiological data was consistent with baselines and was normal, except for deep coma documented on EEG.

After a few days of having difficulty with arousing the patient or establish wakefulness, the doctors decided to put the patient on 75 mg of modafinil once daily, 200 mg of caffeine once daily, and 100 mg of amantadine twice daily. The patient began opening his eyes. One week later, the patient had elevated BUN and creatinine levels of 26 and 1.3 respectively. Due to the increased levels, the vancomycin and amantadine were both discontinued. The patient's BUN creatinine levels remained elevated for the next 2 days and hovered around 25 and 1.5 respectively. As a result, the doctors decided to discontinue the modafinil and caffeine until the patient's BUN and creatinine levels normalized.

Approximately 10 days later, the modafinil was restarted to aid in the wakefulness of the patient. Caffeine was restarted approximately 10 days after that as a means to further promote wakefulness. The modafinil was gradually increased from 25 mg once daily to 75 mg once daily

whereas the caffeine remained at 200 mg once daily. These medications were then discontinued upon being discharged from the hospital a week later and were not restarted because the patient was very awake and alert. While on the modafinil, the patient had improved neurological function appreciated by the patient's ability to remain awake, to remain alert, and to be able to follow commands. While the patient improved to the point where he could open his eyes spontaneously and follow commands, he still had significant hypotonia and dysphasia. He also began to start mouthing words. The patient did develop some mild skin rashes, most likely as a side effect of the modafinil.

Discussion

Despite its off-label uses on patients after brain surgery with disorders of wakefulness, on patients with narcolepsy, or on patients with ADHD, the FDA and Cephalon, Inc recommend not using Provigil on children as it is not currently approved for use in children [1]. It has been shown in clinical studies in adults to have a lower risk of abuse in comparison to amphetamine-based stimulants [3]. Medications that modafinil has used in combination with include but are not limited to antidepressants [4,5]. The elimination half-life for the medication is 15 hours in adults, but it believed to be much shorter in children, with the major route of elimination via the liver [1].

The mechanism of modafinil's ability to cause wakefulness is currently unknown but it has been suggested to be similar to stimulants like amphetamine despite its rather different pharmacologic profile [1]. Peak levels of absorption of modafinil in the body lies between two and four hours with food having no overall effect its bioavailability [1]. However, it appears as though modafinil affects and/or modulates areas of the brain associated with normal wakefulness including but not limited to the hypothalamus and associated cortical pathways [2].

Clinical studies involving modafinil in the treatment of ADHD or narcolepsy make up the vast majority of clinical studies in which modafinil was used on children. Multiple level one studies have tested the efficacy and safety of modafinil on children with ADHD [6-12]. Each of these studies recommended that modafinil could serve as a well-tolerated and effective treatment route for pediatric patients affected by ADHD. A level two study also supported this claim but was classified as a level two study because the study was non-randomized and was retrospective [13]. A level one study found that modafinil was an effective treatment but as an alternative to patients that did not respond well to other stimulants [14]. Modafinil was also recommended as an alternative treatment for ADHD in children when patients suffered from anorexia that limited the safe use of stimulants [15].

In multiple studies, modafinil appears to serve as an effective treatment for narcolepsy and somnolence [16-26]. Specifically in adults, modafinil has been proven to be effective in treating somnolence, narcolepsy, and other related disorders and is recommended as a form of treatment by the FDA and the manufacturer [1,21,22,25]. However, modafinil was found to be as effective as caffeine, which is a much more readily available and cheaper stimulant [26]. Despite not being recommended for use in pediatric cases, modafinil has shown to improve wakefulness with level three evidence and data based on clinical experience [16,19]. Data from nine doctors who have given their patients, between the ages of 4 and 18, modafinil in dosages ranging from 50-600mg per day suggests improvements in the patient condition enough to recommend further investigation as to confirm the correct dosage amount and use for pediatric patients [19]. In another retrospective study, doctors examined the effectiveness of modafinil on 51 of their pediatric patients and found it effective and would

recommend it for children of all ages [16]. Other evidence for the use of modafinil in children to treat narcolepsy came from case reports in which doctors saw rapid improvement [23,24]. A non-randomized study looking at the treatment of excessive daytime sleepiness (EDS) in children found that modafinil was effective especially when prescribed with certain other medication including an antidepressant and called for further clinical trials to look more closely at the mechanism of modafinil in children as well as the role that modafinil plays in young patients with disorders of wakefulness, especially EDS [18].

On occasion, Modafinil has been used after brain surgery if a patient develops or presents with a disorder of wakefulness. There are very few reports of using modafinil in these circumstances in pediatric patients [20]. Using modafinil in treating or managing disorders of wakefulness has been more studied in adults in which modafinil has been found to improve patient condition and promote wakefulness after brain surgery [27-29]. The recovery times were noted to be hastened and found that patients were more alert post-operatively. While modafinil has been found to promote wakefulness, it has not been found to improve psychomotor skills [27]. In one of the case reports, an 11-year-old boy underwent surgery for resection of an astrocytoma and came out of surgery in a persistent vegetative state [20]. The patient's condition did not improve for two months until being placed on 200 mg of modafinil, after which the patient's condition improved dramatically [20].

Conclusion

Although modafinil is not recommended for use on children due to adverse side-effects, studies have shown that modafinil is an effective and well-tolerated treatment for ADHD and narcolepsy. Based on clinical experience, modafinil has been seen to be effective in arousing kids from a vegetative state post-operatively after brain tumor resection. Further studies should be conducted to better understand the mechanism of modafinil in children as well as the potential uses that modafinil may have in arousing pediatric patients with disorders of wakefulness post-operatively.

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