Use of Cannabinoid Agonists in Brain Injury with Aggression: Case Series

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Background

Behavioral disturbances are common sequelae of brain injury. Treatment of this condition often requires a combination of modalities including environmental management, behavioural methods, and pharmacotherapy[1]. In the case of aggressive patients, medications are often needed to diminish affective, psychotic, or disinhibited impulses which may manifest as behavioral disturbances.

As a group, patients with brain injury are heterogenous in composition depending on the nature and extent of injury, neuropathological disturbance, effect of the traumatic experience, and premorbid patient factors. As a result, pharmacological treatment will need to be individualized and this may consist of combinations of medications[2]. Since no specific class of medications can be considered universally effective for aggression, it is important to expand the options available, including consideration of novel agents.

Objective

The BC Neuropsychiatry Program is a tertiary provincial program in British Columbia, Canada. One of the clinical goals of our program is that of assessment and treatment of brain injury patients throughout the province.

This poster consists of a sample of patients collected during clinical practice over the last 5 years within the Program with diagnosis of brain injury and aggression. Despite the varied forms of brain injury in each case, management became complex and each showed resistance to the usual pharmacotherapeutic trials. Each case demonstrated success in treatment with a cannabinoid agonist medication; sometimes the patient became quite remarkably improved. These cases describe the treatment doses used, and summarize response achieved.

Cases

I. A previously healthy 31 year old male construction worker with a 20-foot fall onto concrete resulting in traumatic brain injury with posttraumatic amnesia of 7 weeks. Neuroimagery demonstrated frontal lobe contusions, subdural hematoma requiring right frontal craniotomy. He developed posttraumatic epilepsy. The primary neuropsychiatric syndrome was that of disinhibited personality change and cognitive disturbances. He was sexually inappropriate and had frequent anger outbursts with little provocation towards his wife. Numerous medication trials were insufficiently effective including antipsychotics and mood stabilizers. Finally he was treated with nabilone (Cesamet) 2 mg daily with significant improvement in his irritability and almost complete resolution of anger outbursts as reported by collateral sources. The patient denied side effects and had excellent tolerance to the medication. At the time of stabilization, other medications included: gabapentin 300mg daily, carbamazepine 400 mg BID.

II. Previously healthy 25 year old woman with a closed head injury from a snowboarding accident. The initial documented Glasgow Coma Scale (GCS) was 5. Anoxic encephalopathy was also diagnosed resulting in dementia secondary to brain injury and mixed frontal apathetic and disinhibited syndromes. Motor impairment included spasticity, dystonia and gait disturbance. Her behaviour was characterized by outbursts of anger and verbal threats to kill caregivers, inappropriate sexual comments, and shoplifting. She showed depressed mood at times. With ongoing management issues, numerous medications including antidepressants, antipsychotics, lithium, mood stabilizers, and donepezil were tried with minimal effect. Eventually, dronabinol (Marinol) was added and gradually increased to 5mg TID. Shortly after this addition, behavior stabilized. The irritability and anger decreased. Major verbal outbursts stopped as noted by caregivers. The patient subjectively reported improved well-being and there were no complaints of significant side effects.

III. A 26 year old man sustained severe head injury resulting from a motor vehicle accident (MVA). He had an extensive history of polysubstance abuse and was probably under the influence of cocaine and alcohol during the MVA. Initial GCS was 7; CT head revealed multiple small hemorrhages. He was comatose for 1 month in the ICU. After discharge from ICU, he demonstrated nonpsychotic unpredictable aggressive behavior, agitation and disinhibition. Physical restraints and constant observation were required. He remained in this condition for 6 months despite multiple medication trials. Sensitivity to antipsychotics (extrapyramidal effects, oversedation) was noted. Sertraline was useful to decrease sexual disinhibition. While awaiting a locked unit for placement, dronabinol 2.5 mg TID was added. Within three days of the initiation of treatment, the patient improved. His aggressive behavior resolved almost completely to the point of cooperativeness and even friendliness. He was able to be placed in the community rather than a locked facility. Medications on discharge included: sertraline, dronabinol 2.5 mg daily only, rabeprazole, valproic acid and baclofen.

IV. An 18 year old female with a long history of borderline personality disorder. She attempted suicide with acetaminophen overdose resulting in hepatic necrosis (requiring liver transplant), along with toxic and anoxic encephalopathy. Over the next 6 months, cognition declined and personality changed with disinhibited emotional lability, neglect of personal hygiene, negativism and physical and verbal aggression with any form of limit-setting by caregivers. Despite pharmacotherapy with antipsychotics (loxapine, risperidone, olanzapine), mood stabilizers/ anticonvulsants (valproate, topiramate), and SSRI antidepressants, the patient failed community placement and required rehospitalization primarily due to severe aggression. Nabilone 2mg BID was started and well tolerated. Within 2 weeks, the patient settled significantly. She was discharged shortly afterwards back to a community setting with supervision. Final discharge medications included nabilone 1mg BID, olanzapine 2.5mg AM & 5mg HS, valproate 500mg BID, and citalopram 40mg AM.

Summary

These four cases collected over a 5 year period demonstrate instances where the cannabinoid agonist class of medications (both nabilone and dronabinol are CB1 agonists[3]) showed promise in treatment of the aggressive brain injured patient.

As a class, the cannabinoids have shown benefits in dyskinesia, pain management[4], as antinauseants, and appetite stimulants[5]. A small study has suggested the potential for cannabinoids to improve behavior in severely demented Alzheimer's disease patients[6]. Despite the potential benefits, cannabinoids have been associated with adverse neuropsychiatric effects including the potential for frontocerebellar network dysfunction[7], potential for further substance abuse, dyphoric and psychotic symptoms, sedation, confusion and short-term memory loss[8].

These cases suggest that cannabinoid agonists have therapeutic potential for some neuropsychiatric patients with agitation after brain injury. In each case, there appeared to be a "serenic" effect decreasing irritability and promoting emotional stability. Further research into this class of medications could add significantly to the pharmacological management of brain injury.

References

1. Corrigan PW, Yudofsky SC, Silver JM. Pharmacological and behavioral treatments for aggressive psychiatric inpatients. Hosp Comm Psychiatry 1993; 44:125-133
2. Silver JM, Yudofsky SC, Anderson K. Aggressive Disorders, in Textbook of Traumatic Brain Injury. American Psychiatric Publishing, Inc., 2005
3. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinetics 2003; 42(4):327-360
4. Hosking RD, Zajicek JP. Therapeutic potential of cannabis in pain medicine. Br J Anesthesia 2008; 101(1): 59-68
5. Croxford JL. Therapeutic potential of cannabinoids in CNS disease. CNS Drugs 2003; 17(3): 179-202
6. Volicer L, Stelly MJ, Morris J, et al. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's Disease. Int J Geriatric Psych 1997; 12(9):913-919
7. Lundqvist T, Jonsson S, Warkentin S. Frontal lobe dysfunction in long-term cannibis users. Neurotoxicology and Teratology 2001; 23:437-443
8. Tramer MR, Carroll D, Campbell FA, et al. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ 2001; 323(7303):16-21