Characterizing the Use of Nabiximols (Δ9-Tetrahydrocannabinol–Cannabidiol) Buccal Spray in Pediatric Patients

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ABSTRACT

Background: Nabiximols is a commercially available cannabinoid buccal spray containing 2.7 mg Δ9-tetrahydrocannabinol (THC) and 2.5 mg cannabidiol (CBD) per spray. It is approved by Health Canada for adults with cancer pain or spasticity/neuropathic pain related to multiple sclerosis. Despite a lack of published studies regarding the use of nabiximols in children, it is being used in clinical practice for indications of pain, nausea/vomiting, and spasticity.

Objective: To describe the use of nabiximols in children.

Methods: This retrospective single-cohort study involved hospitalized pediatric patients who received at least 1 dose of nabiximols between January 2005 and August 2018. Descriptive statistical analyses were performed.

Results: A total of 34 patients were included. The median age was 14 (range 0.6–18) years, and 11 patients (32%) were admitted under the oncology service. The median dose of nabiximols was 1.9 (range 0.3–10.8) sprays per day, and the median duration was 3.8 (range 1–213) days. Nabiximols was most commonly used to treat pain and nausea/vomiting and was most frequently prescribed by pain specialists. Perceived effectiveness was documented in 17 (50%) of the cases, with variable results being reported. The most commonly reported adverse effects were drowsiness and tachycardia (3/34, 9%, for each).

Conclusion: In this study, nabiximols was prescribed for children in all age groups, for a variety of conditions, but most commonly for pain and nausea/vomiting. Further study, in the form of a large, prospective randomized controlled trial with clearly defined efficacy and safety end points for nausea/vomiting and/or pain, is needed to determine whether nabiximols is effective and safe in children.

Keywords: nabiximols, Sativex, pediatric

RÉSUMÉ

Contexte : Le nabiximols est un vaporisateur buccal cannabinoïde disponible dans le commerce qui contient 2,7 mg de Δ9-tetrahydrocannabinol [THC] et 2,5 mg de cannabidiol [CBD] par vaporisation. Il est approuvé par Santé Canada pour les adultes souffrant de douleur cancéreuse ou de spasticité/douleur neuropathique liée à la sclérose en plaques. Malgré le manque d'études publiées concernant l'utilisation du nabiximols chez les enfants, il est utilisé en pratique clinique pour des indications de douleur, de nausées/vomissements et de spasticité.

Objectif : Décrire l'utilisation du nabiximols chez les enfants.

Méthodes : Cette étude rétrospective à cohorte unique comprenait des patients pédiatriques hospitalisés ayant reçu au moins 1 dose de nabiximols entre janvier 2005 et août 2018. Des analyses statistiques descriptives ont été réalisées.

Résultats : Au total, 34 patients ont été inclus. L'âge médian était de 14 ans [intervalle de 0,6 à 18 ans] et 11 enfants (32 %) étaient des patients en oncologie. La dose médiane de nabiximols était de 1,9 [intervalle de 0,3 à 10,8] vaporisation par jour et la durée médiane était de 3,8 [intervalle de 1 à 213] jours. Le nabiximols était le plus couramment utilisé pour traiter la douleur et les nausées/vomissements et était le plus souvent prescrit par des spécialistes de la douleur. L'efficacité perçue a été documentée dans 17 (50 %) des cas, avec des résultats variables rapportés. Les effets indésirables le plus fréquemment rapportés étaient la somnolence et la tachycardie (3/34, 9 % chacun).

Conclusion : Dans cette étude, le nabiximols a été prescrit à des enfants de toutes les tranches d'âge, pour diverses pathologies, mais le plus souvent pour des douleurs et des nausées/vomissements. Une étude plus approfondie, sous la forme d'un vaste essai contrôlé randomisé prospectif avec des paramètres d'efficacité et d'innocuité clairement définis pour les nausées/vomissements et/ou la douleur, est nécessaire pour déterminer si le nabiximols est efficace et sûr chez les enfants.

Mots-clés : nabiximols, Sativex, pédiatrique

INTRODUCTION

Over the past several years, anecdotal reports at our institution have indicated an increase in the use of cannabinoids for medicinal purposes in children, particularly those with neurological disorders or cancer and those receiving palliative care.

Medicinal cannabinoids exist in many forms, including products for inhalation, oral ingestion, and topical administration. The 2 cannabinoids with known pharmacologic effects are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[1] THC is believed to have euphoric, analgesic, and antiemetic properties, whereas CBD is believed to

possess anticonvulsant and anxiolytic properties.[2,3] The concentration of THC and the ratio of THC to CBD (in combination products) determine the therapeutic effects of a cannabinoid product.

One challenge in clinical use is the lack of standardization in terms of THC and CBD content, because of variable manufacturing practices, which typically lack both quality control and standardized testing for product content.[4] Both the lack of evidence and the lack of standardized products may make clinicians uncomfortable with prescribing medicinal cannabinoids for their patients. However, products from pharmaceutical companies that use Good Manufacturing Practices are available.[5]

Currently, 2 standardized, commercially available cannabinoid products are approved by Health Canada: nabilone (Cesamet) and nabiximols (Sativex). Nabilone is a synthetic cannabinoid that is chemically similar to THC and is administered orally.[6] It is approved for adults with chemotherapy-induced nausea and vomiting. Adverse effects include drowsiness, vertigo, dry mouth, and euphoria.[6] Nabiximols is a plant-derived cannabinoid buccal spray containing 2.7 mg THC and 2.5 mg CBD per spray. Nabiximols is approved for adults with spasticity, neuropathic pain related to multiple sclerosis, and cancer pain.[7,8] Adverse effects include tachycardia, vertigo, fatigue, blurred vision, dry mouth, and nausea.[8] Compared with THC-predominant products, the approximately equal ratio of THC and CBD in nabiximols may theoretically reduce the risk of psychotropic effects, because of the antagonistic effect of CBD on THC.[9] Nabilone contains no CBD, and therefore is expected to have different clinical effects and potential applications from those of nabiximols.

Case reports and small studies have described the use of cannabinoids in children for refractory seizure disorders, dystonia, pain, and chemotherapy-associated nausea and vomiting.[10,11] A 2017 systematic review of medicinal cannabinoids in children concluded that further research is needed.[12] Despite evidence of benefit for chemotherapy-induced nausea and vomiting and seizure disorders, the review's conclusions were limited by small sample sizes, a lack of randomized controlled trials, and heterogeneous products.[12] Furthermore, there is concern about potential adverse effects in children, including the risk of mental illness, psychosis, and impaired neurodevelopment.[13-15] In a recent randomized controlled trial of pediatric patients, nabiximols was used for spasticity related to cerebral palsy or traumatic brain injury.[16] No significant reduction in spasticity was observed in the group that received nabiximols, but the medication was well tolerated.[16]

Nabiximols is a regulated product, and many clinicians are therefore comfortable prescribing and administering it in a health care setting, because they can trust that the product contains the labelled ingredients. Despite the limited literature regarding the efficacy and safety of nabiximols in children, it is being prescribed in clinical practice at our institution for a variety of indications, which reportedly include seizures, dystonia and dystonic crises, pain, nausea and vomiting, and possibly others.

The primary objective of this study was to describe the use of nabiximols in children admitted to hospital. The secondary objectives were to describe the effectiveness of nabiximols as perceived by the health care team and by patients/caregivers and to describe the adverse effects of nabiximols.

METHODS

This retrospective single-cohort study involved patients admitted to BC Children's Hospital, a tertiary care teaching pediatric hospital, who received nabiximols on an inpatient basis, as supplied by the hospital pharmacy. Patients were identified using the Pharmacy Department's database. One of the study team members (L.H.) used a standardized data collection tool to retrieve data from patients' health records; the data were then entered into REDCap (Research Electronic Data Capture), a secure, web-based application designed for managing online databases. Of the data collected, 10% were chosen randomly for audit by a second study investigator (S.L.) to ensure the integrity of data collection. The study was approved by the institutional research ethics board.

Pediatric inpatients (up to 19 years of age) who received at least 1 dose of nabiximols during their hospital stay between January 1, 2005, and August 31, 2018, were included. Patients who received nabiximols before admission without receiving a dose in hospital were excluded.

For any given patient, if 10 or more days elapsed between nabiximols doses during the same hospital admission, the courses of nabiximols therapy were analyzed as separate incidents. Given the irregular frequency of administration, the average dose per day of nabiximols was calculated by dividing the total number of sprays received by the number of days between the first and last doses. Therefore, the final dose is presented in terms of number of sprays per day.

Effectiveness was assessed on the basis of documentation in the health record that a health care provider or patient/caregiver reported nabiximols to be effective or ineffective. Any documentation indicating a response to nabiximols was recorded, including notes by the patient's physician or any other health care providers. The indication for use was inferred by reviewing inpatient documentation and the prescriber's practice area (e.g., pain service team).

Adverse effects were reported if they occurred within 48 hours after a nabiximols dose, based on documentation in the health record. The Naranjo Adverse Drug Reaction Probability Scale was used to determine the likelihood that the adverse effect was associated with nabiximols.[17] The Naranjo score was calculated independently by 2 of the investigators (L.H., S.L.). Discrepancies were resolved by the third

investigator (R.C.), who was blinded to the assessments of the first 2 investigators. Adverse effects with Naranjo scores of 3 or greater (possible adverse effect) were reported.

Statistical Analysis

Descriptive statistics were used. A sample size of convenience was used.

RESULTS

Fifty-five patients were screened for inclusion in the study, of whom 34 were included. Of the 21 excluded patients, 14 had a prescription for nabiximols but did not receive a dose in hospital, 4 had health records that were unavailable for data extraction, and 3 were older than 19 years of age when they received nabiximols.

The characteristics of patients and their use of nabiximols are described in Table 1. The majority of patients (n = 23) were adolescents, 12 to 19 years of age; in addition, 1 patient was an infant (7 months of age), and 10 patients were 9 to 12 years of age. The indications for nabiximols use are described in Figure 1. Five patients received nabiximols for both pain and nausea/vomiting, and one of these patients also received nabiximols for a third indication, anxiety. Nabiximols was used on an as-needed basis by 10 (29%) of the patients. Nabiximols was prescribed by pain specialty services for 18 patients (53%), by palliative care for 7 patients (20%), by oncology for 5 patients (15%), by general pediatrics for 1 patient (3%), by psychiatry for 2 patients (6%), and by hematology for 1 patient (3%). Eleven patients (32%) had been admitted under the oncology service.

For 2 patients, the dose received was unclear because a dosage range had been prescribed (e.g., 1–2 sprays), and the amount received was not documented in the health record. In these cases, we assumed that the number of sprays received was the highest possible number based on the physician's order. This assumption did not affect the value for median number of sprays received per day.

TABLE 1. Characteristics of Patients and Their Use of Nabiximols

Characteristic	Result *n* = 34
Patients	
Age (median and range)	14 (0.6–18) years
Weight (median and range)	50 (7.4–81.9) kg
Sex, male (no. and %)	16 (47)
Nabiximols use	
Dose (median and range)	1.9 (0.3–10.8) sprays/day
Duration of therapy (median and range)	3.8 (1–213) days
No. of admissions per patient during which nabiximols was received (mean and range)	1 (1–4)
Changes in prescribed dosage (no. and %)	18 (53)
Nabiximols discontinued in hospital (no. and %)	11 (32)[a]
Nabiximols prescribed on discharge (no. and %)	13 (38)[b]

[a]Three of these patients had subsequent admissions during which nabiximols was not discontinued.
[b]For 2 of these patients, nabiximols was prescribed on discharge multiple times.

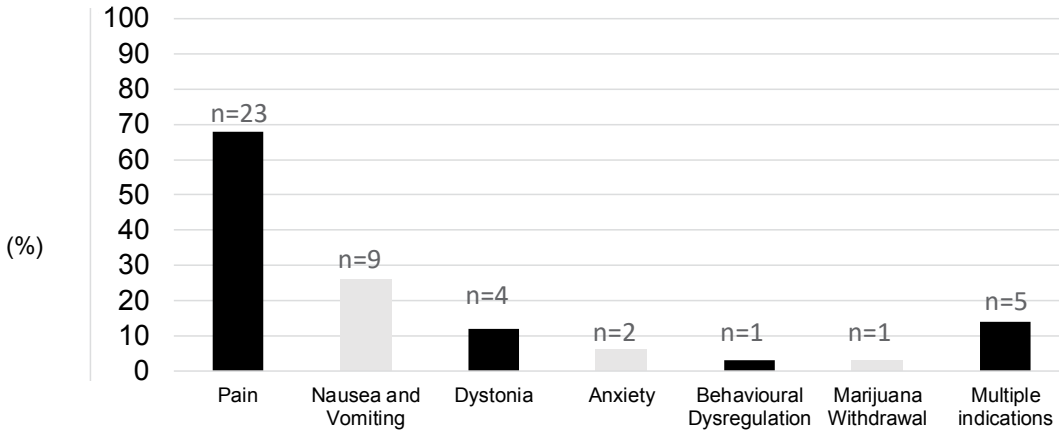

FIGURE 1. Indications for use of nabiximols.

The perception of effectiveness (or lack thereof) by the health care team and by the patient/caregiver was documented for approximately 50% of patients (Figure 2). Two patients had conflicting documentation in the health record indicating that nabiximols was both effective and ineffective. Five patients (15%) agreed with their health care provider that nabiximols was effective, 3 patients (9%) agreed with their health care provider that nabiximols was ineffective, and 3 patients (9%) disagreed with their health care provider as to whether nabiximols was effective.

The most commonly reported adverse effects were drowsiness and tachycardia (9% each) (Table 2). A burning sensation in the mouth upon application of nabiximols spray was reported for 2 patients, who had pre-existing mucositis. Two patients experienced more than 1 adverse event: one of these patients experienced drowsiness, euphoria, mouth burning, and tachycardia, whereas the other patient experienced agitation and bradycardia. Among the 11 patients for whom nabiximols was discontinued in hospital, none of the discontinuations were due to adverse events.

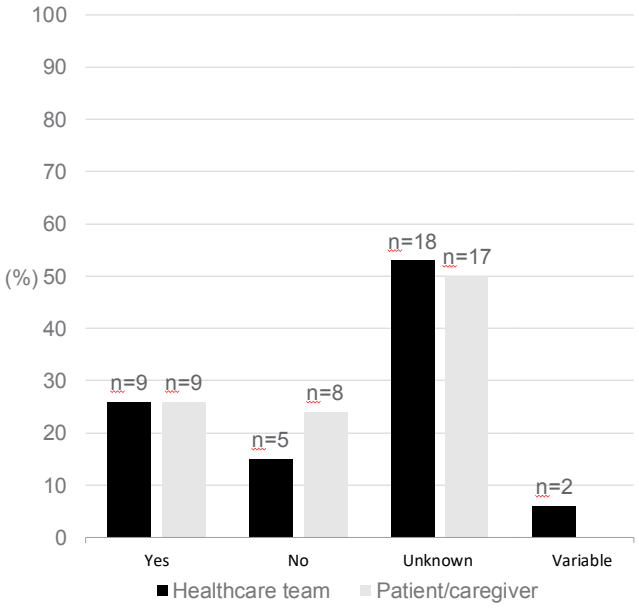

FIGURE 2. Perceived effectiveness of nabiximols.

TABLE 2. Adverse Effects

Adverse Effect	No. (%) of Participants (*n* = 34)
Drowsiness	3 (9)
Tachycardia	3 (9)
Mouth burning	2 (6)
Euphoria or "feeling high"	1 (3)
Agitation	1 (3)
Vision changes	1 (3)
Bradycardia	1 (3)
Hypertension	1 (3)
Vomiting	1 (3)
Patients with > 1 adverse effect	2 (6)

DISCUSSION

Despite the limited evidence supporting use of cannabinoid products for pain and nausea/vomiting in children and despite the fact that nabiximols is not approved by Health Canada for use in children, this product is being prescribed in this age group and fills a gap in terms of a cannabinoid product that is produced by a manufacturer compliant with Health Canada Good Manufacturing Practices.[5]

The low use of nabiximols for dystonia and seizures observed in this study may relate to the use of alternative medicinal cannabinoid products. Cannabidiol (Epidiolex) is an oral CBD solution that is commercially available in the United States, which has demonstrated benefit in reducing seizure frequency for patients at least 2 years of age who have Dravet syndrome or Lennox–Gastaut syndrome.[18] This product is not currently available in Canada, and anecdotal reports indicate that other forms of cannabidiol are commonly used at our institution; however, it was not possible to quantify such use in our study. Concerns remain about prescribing and administering products that may not meet quality assurance standards for content and manufacturing practices. In accordance with institutional policies during the period of the study, such products could not be administered by nurses or entered onto a patient's medication administration record. In addition, because Epidiolex does not contain THC, its clinical effects and use in practice may differ from products such as nabiximols or nabilone.

The doses of nabiximols observed in this study were generally lower than doses used in adult studies. The median dose in our study was approximately 2 (range 0.3 to 10.8) sprays per day (representing 5.4 mg THC and 5 mg CBD), whereas the dose in adult studies has ranged from 7 to 9 sprays per day.[19-22] The product monograph recommends between 4 and 8 sprays per day for adults as the usual dose range.[8] In a recent pediatric study of nabiximols administered for spasticity, the mean number of sprays per day ranged from 5 to 7.[16] There have been few studies of medicinal cannabinoid use in children, and these have used heterogeneous products with differing concentrations and dosages; as such, it is challenging to make comparisons with these studies and determine appropriate doses for children.[13]

It was difficult to assess the perceived effectiveness of nabiximols because of a lack of documentation in the health records and subjective monitoring of the indications for which nabiximols was prescribed. Further measures of

effectiveness, such as frequency of vomiting for patients with nausea/vomiting or pain scores for patients with pain, were considered but were found to have many confounding variables. For example, a patient's pain score before and after receipt of nabiximols was often confounded by concurrent changes in other analgesics and/or changes in disease states that would affect pain. Therefore, it was not possible to draw meaningful conclusions from these outcome measures. Given the retrospective nature of this study, there were no standardized monitoring procedures or documentation in place for assessment.

Similarly, assessment of the safety of nabiximols was challenging, because most patients could have experienced effects such as drowsiness, tachycardia, and vomiting from concurrent medications or medical conditions. However, the rates of documented adverse effects were generally low and similar to rates reported in adults.[19-22]

Our study was limited by reliance on health record documentation to determine effectiveness and safety and by the small sample size. Collecting information about medications used concurrently by the patients might have been useful for better assessment of the effectiveness and safety of nabiximols. To mitigate these limitations, the Naranjo Adverse Drug Reaction Probability Scale was used to help determine the likelihood that adverse effects were associated with nabiximols.

CONCLUSION

To the authors' knowledge, this study is the first to characterize the use of nabiximols in children. Further study, in the form of large, prospective randomized controlled trials for treatment of nausea/vomiting and/or pain with well-defined doses of THC and CBD and clearly defined efficacy end points, is needed to determine whether nabiximols is effective and safe for children with these indications.

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