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AN EFFICIENT NEW CANNABINOID ANTIEMETIC IN PEDIATRIC ONCOLOGY

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Summary

Delta-8-tetrahydrocannabinol (delta-8-THC), a cannabinoid with lower psychotropic potency than the main Cannabis constituent, delta-9-tetrahydrocannabinol (delta-9-THC), was administerd (18 mg/m2 in edible oil, p.o.) to eight children, aged 3-13 years with various hematologic cancers, treated with different antineoplastic drugs for up to 8 months. The total number of treatments with delta-8-THC so far is 480. The THC treatment started two hours before each antineoplastic treatment and was continued every 6 hrs for 24 hours. Vomiting was completely prevented. The side effects observed were negligible.

Key Words: **tetrahydrocannabinol, vomiting, Dronabinol**

Cannabis preparations have been used for millenia as antiemetic drugs [1]. With the identification of delta-9-tetra-hydrocannabinol (delta-9-THC) (Fig 1) as the psychoactive Cannabis constituent [2] its evaluation as an antivomiting agent was also made possible. It was indeed found that delta-9-THC prevents or reduces vomiting induced by anticancer chemotherapy [3-5]. Delta-9-THC is marketed under the generic name Dronabinol [5]. Depending on the clinical protocol used, delta-9-THC (5-10 mg/m2 p.o.) prevents vomiting and nausea in some patients and reduces these symptoms in others. The side effects are those noted in marijuana users, in particular elderly ones: drowsiness, dizziness and in rare cases anxiety. Mood changes usually predominate in younger patients.

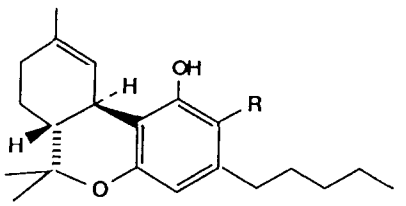
Delta-8-THC (Fig 1) is a double bond isomer of delta-9-THC. It is less psychotropic than delta-9-THC [6], but its antiemetic potential has not been investigated so far. In preclinical antiemetic studies in pigeons (to be reported separately), using the methodology previously described by us for delta-9-THC [7], we found that delta-8-THC is at least as potent as delta-9-THC. It is much more stable than delta-9-THC to various chemical treatments, including oxidation, and is considerably less expensive to produce than delta-9-THC. Hence, it seemed of potential therapeutic interest to investigate the antiemetic effect of delta-8-THC in patients. We chose to administer delta-8-THC to children, who were expected to vomit on anticancer chemotherapy. The reason for the age limitation was the general (but not documented) belief that most side effects of delta-9-THC, in particular anxiety, are more prevalant in an adult population than in a younger one. Hence delta-8-THC could possibly be administered to children in higher doses than those given to adult patients.

We report now that delta-8-THC in an open label evaluation was found to be an excellent pediatric antiemetic with nonsignificant side effects. We chose an open label trial for ethical reasons. A clinical trial based on placebo versus delta-8-THC as an antiemetic agent during anticancer treatment is unacceptable. Our original protocol envisaged a comparison between metoclopramide (0.3 mg/kg) and delta-8-THC (18 mg/m2). However preliminary results indicated complete block of emesis with delta-8-THC, while metoclopramide showed variable results. Most of the children (5 out of 8) vomited with this dose of metoclopramide. In higher doses (0.5 mg/kg dose or above) metoclopramide caused extrapyramidal effects. Hence for ethical reasons the protocol was modified to an open trial design. However, we would like to point out that over a period of about 10 years, when most of the antineoplastic protocols followed in the present study were used in our clinic, emesis was observed in about 60% of all pediatric cases even though metoclopramide (0.3 mg/kg) was used as antiemetic agent.

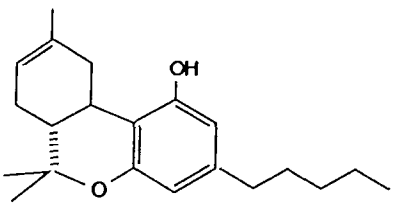
Ondansetrone and other HT3-receptor blockers are today the drugs of choice for chemotherapy-induced vomiting and nausea [8]. While such therapy is superior to previously used treatments (dopamine antagonists, corticosteroids) adverse effects such as headache are troublesome [8] and its efficiency in delayed vomiting is questionable. Ondansetrone is also a very expensive drug and less expensive alternatives should be made available. Hence additional therapeutic protocols are required.

Materials, patients and clinical protocol

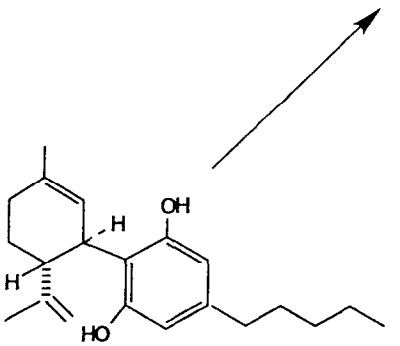
Delta-8-THC was prepared from natural cannabidiol by cyclization (Fig 1) and purified by chromatography as previously described [9]. It was analyzed by gas chromatography and was found to be at least 98% pure.



Δ^9-tetrahydrocannabinol (Δ^9-THC)



Δ^8-tetrahydrocannabinol (Δ^8-THC)



cannabidiol (CBD)

Fig. 1

Eight children with various blood cancers (see Table) were administered delta-8-THC (18 mg/m2 p.o.) two hours before the start of the anticancer treatment. The drug was dissolved in corn or olive oil (6 mg/ml), and was administered directly as oil drops on the tongue, or on a bite of bread. The same dose was repeated every 6 hrs for 24 hrs. The treatment for each child is presented in the Table. Whenever additional cycles of antineoplastic therapy were required, delta-8-THC was administered following the same time procedure described above. Children received delta-8-THC only during days when emetogenic drugs were administered. Established anticancer drug protocols were followed with all patients. These are indicated below and in Table 1:

High-dose Cytarabine and Asparaginase. [10] (Patient 1). MOPP - ABV protocol. [11] (Patient 2); This protocol is a standard combination of Mechlorethamine hydrochloride, Vincristine, Procarbazine, Prednisone, Doxorubicin, Bleomycin and Vinblastine. BFM protocol. [12] (patients 3 and 8). This protocol is a complicated standard protocol consisting of numerous antineoplastic drugs (Vincristine, Daunorubicine, L-Asparaginase, Cyclophosphamide, Cytarabine, Mercaptopurine, Etoposide, Methotrexate, Thioguanine) and 3 types of corticosteroids (Prednisone, Hydrocortisone, Dexamethasone) in p.o., i.v. and intratecal administrations. National Wilms tumor study protocol (NWTS-4). [13] (Patient 4). This protocol is a standard combination of Vincristine, Doxorubicin, Dactinomycin. Amsacrine-high dose Cytarabine protocol. [14] (Patient 5). This is a standard protocol consisting of Cytarabine and Amsacrine. Burkitt's lymphoma protocol. [15] (Patient 6). This is a standard protocol consisting of Vincristine, Doxorubicin Cyclophosphamide, Methotrexate, and Prednisone. Rezidive study, A.L.L. - Rez BFM 87 protocol. [16] (Patient 7). This is a standard complicated protocol consisting of numerous antineoplastic drugs. In addition to drugs mentioned above it includes Ifosfamide and Vindesine.

Results

The present study on prevention of vomiting due to antineoplastic therapy took place over a 2 year period with 8 patients. Details of their antineoplastic treatment and side effects of the antiemetic therapy are presented in Table 1. The mild side effects observed were reported by the physician and nurse in charge. Chemotherapy protocols of the types indicated almost invariably cause intense vomiting, which starts about 2 hrs after the initiation of chemotherapy and gradually ends over a 24 hr period. In prelimary trials we tried to end the antiemetic therapy after the first or second dose of the cannabinoid, i.e. after 6 or 12 hrs. Vomiting started in most cases. Hence, in the recorded trial, all children were given 4 doses (every 6 hours) for 24 hrs. When the antiemetic protocol described in the "Methods, patients and clinical protocol" section was strictly followed, no emesis was noted during the 24 hrs of treatment or over the next two days. In one case (patient D.E.), delta-8-THC therapy initially was refused. The patient experienced debilitating vomiting for 24 hrs after the antineoplastic treatment. During the second treatment cycle (which took place after 8 days), at the patient's family request, delta-8-THC treatment was initiated. No vomiting occurred. In a second case (A.M.), the patient refused antiemetic treatment during a relapse of his disease as it was based on an "illicit drug" (Cannabis). Repeated vomiting took place. Renewal of the THC treatment, before the next administration of antineoplastic drugs, prevented additional vomiting. As indicated in Table 1 the side effects were observed in only 2 of the the 8 patients: some irritability and slight euphoria which in children is difficult to quantify. No anxiety or hallucinogenic effects were noted in spite of the high doses administered.

Table 1.
Delta-8-THC Administered to Children Treated for Various Hematologic Cancers.[a]

No.	Name sex	Age (years)	Diagnosis treatment[c]	Antineoplastic	Number and effect of antiemetic treatments
1.	A.M.	10 m	A.L.L.[b] pre B, in relapse	Cytarabine-L-Asparaginase	(32), no side effects
2.	C.O.	3.5 m	Hodgkin's disease	MOPP-ABV protocol	(64), slight irritability during first 2 cycles
3.	L.H.	4 f	A.L.L., T type	BFM protocol	(76), slight irritability and euphoria[1]
4.	M.H.	3 f	Wilm's tumor, stage III	NWTS-4 protocol	(30), no side effects
5.	R.M.	13 f	A.L.L. T type in second relapse	Cytarabine, Amsacrine protocol	(24), no side effects
6.	D.E.	7 m	Burkitt's lymphoma	Burkitt's lymphoma protocol	(114), no side effects[2]
7.	K.K.	6 f	A.L.L.	Rez BFM 87 protocol	(64), no side effects[3]
8.	A.A.	5 m	A.L.L.	BFM protocol	(76), no side effects

[a] Delta-8-THC, 18 mg/m2. For details see text. In all cases complete prevention of vomiting was noted. [b] Acute Lymphoblastic Leukemia (A.L.L.). [c] see Methods, patients and clinical protocol.

[1] Metoclopromide (0.3 mg/kg) p.o. or i.v. in previous treatment failed to prevent vomiting.
[2] During first cycle, refusal to take THC caused profuse vomiting.
[3] Treatment during remission after 2nd relapse and during 3rd relapse.

Discussion

Delta-8-THC is an isomer of delta-9-THC, the major natural constituent of Cannabis from which it differs only in the position of the double bond. The stereochemistry of the two isomers is identical; their chemical behavior is in most cases very similar [17]; their metabolism in vivo and in vitro follow the same pathways [18]. The major chemical difference between them is that delta-9-

THC is easily oxidized to the biologically inactive cannabinol; delta-8-THC is stable, does not oxidize to cannabinol and has a very long shelf life. Due to their close structural similarity, delta-9-THC and delta-8-THC present essentially identical pharmacological profiles [19-21]. Quantitatively, however, delta-8-THC differs from delta-9-THC in being about twice less potent in most, but not all pharmacological tests.

In monkeys delta-8-THC causes a general behavior depression in doses reported to be higher than the doses of delta-9-THC required to produce similar effects [22, 23].

A direct comparison of the effects of delta-8-THC (20 and 40 mg total dose) and of delta-9-THC (20 mg total dose) orally administered to human volunteers has been published [24]. The spectrum of clinical effects was similar with both isomers, but delta-8-THC was considered to be only 3/4 as psychotropically potent as delta-9-THC. The same ratio of activity was observed on i.v. administration.

Delta-9-THC (4 mg/kg i.m.) blocked the emetic response in cats caused by cisplatin (7.5 mg/kg i.v.) [25]. The metabolite 11-hydroxy-delta-9-THC, which is considerably more psychotropic than delta-9-THC, was less antiemetic than delta-9-THC showing that, in cats at least, there is no parallelism between the psychotropic effects and the antiemetic ones. Indeed, we have recently shown that a non-psychotropic cannabinoid (HU-211) is more potent than delta-9-THC as an antiemetic [7].

The LD50 values for Fischer rats treated orally with single doses of delta-9-THC and delta-8-THC, and observed for 7 days, are 1910 mg/kg and 1980 mg/kg (for males) respectively and 860 mg/kg (for females) [26]. The histopathological changes caused by these extremely high doses were essentially the same for both delta-8-and delta-9-THC. LD50 could not be determined in either rhesus monkeys or dogs as single oral doses of up to 9000 mg/kg of either delta-8-or delta-9-THC in dogs or monkeys were non lethal. Histopathological alterations did not occur in either dogs or monkeys. A chronic oral toxicity study in rats with both isomers has been reported. Delta-8-THC was found to be slightly less toxic than the delta-9 isomer [27]. With delta-8-THC, after 119 days of consecutive administration, no deaths were observed in males with daily doses of up to 400 mg/kg; 1/10 deaths occurred at 500 mg/kg. With females, no deaths were caused by doses of up to 250 mg/kg; 5/13 deaths were recorded at 400 mg/kg and 12/67 were recorded at 500 mg/kg. The above described animal and human data indicated that delta-8-THC can be safely administered to human patients.

We found, as expected, that young children with different hematologic cancers, who were treated with a variety of anticancer drug protocols, could be administerd doses of delta-8-THC considerably higher than the doses of delta-9-THC generally administered to adult cancer patients without the occurence of major side effects, (5-10 mg/m2 of delta-9-THC generally recommended for adult patients [28] versus 18 mg/m2 of delta-8-THC used by us in children). As mentioned above, the prevention of vomiting was complete, regardless of the antineoplastic protocol followed. We observed no delayed nausea or vomiting. Although the number of pediatric cancer patients treated so far is small, the total number of treatments is considerable (480 times) as most patients underwent several treatment cycles. Without the cannabinoid therapy we would have expected the patients to vomit in most treatments.

In summary, the complete success in preventing vomiting due to antineoplastic treatment in children, and the essential lack of side effects, leads us to believe that delta-8-THC at a dose

considerably higher than the doses of delta-9-THC usually administered to adults, can serve as a new, inexpensive antiemetic agent in pediatric cancer chemotherapy.

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