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ORIGINAL ARTICLE

On the application of cannabis in paediatrics and epileptology

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Abstract An initial report on the therapeutic application of delta 9-THC (THC) (Dronabinol, Marinol) in 8 children resp. adolescents suffering from the following conditions, is given: neurodegenerative disease, mitochondriopathy, posthypoxic state, epilepsy, posttraumatic reaction. THC effected reduced spasticity, improved dystonia, increased initiative (with low dose), increased interest in the surroundings, and anticonvulsive action. The doses ranged from 0.04 to 0.12 mg/kg body weight a day. The medication was given as an oily solution orally in 7 patients, via percutaneous gastroenterostomy tube in one patient.
At higher doses disinhibition and increased restlessness were observed. In several cases treatment was discontinued and in none of them discontinuing resulted in any problems.
The possibility that THC-induced effects on ion channels and transmitters may explain its therapeutic activity seen in epileptic patients is discussed.

Casuistics

1. In the case of the boy P. G., treatment was begun with delta 9-THC (THC) at the age of 8 years and 9 months and continued until shortly before his death at the age of 9 years and 4 months. Approximately 0.07 mg THC/kg body weight a day was administered in two doses via percutaneous gastroenterostomy tube. The aim was to lessen the severity of spasticity brought on by neuronal ceroid lipofuscinosis, Jansky-Bielschowsky variant, which was causing the boy to suffer and to make it difficult to care for him. The treatment brought about a noticeable reduction in spasticity. Prior treatment with a combination of baclofen and tetrazepam had been unsatisfactory owing to the degree of spasticity. There was no noticeable worsening of the myoclonia symptomatic of the disease. Moreover, the patient's mother observed that the boy seemed more awake. This increased alertness may be ascribed to the discontinuation (without adverse reaction) of meperidine. Following the initiation of treatment, it was observed that the boy turned his head with greater precision towards his mother and laughed when she spoke to him. He seemed happier, although mood swings were also observed. "He would still have a smile on his face when suddenly he would seem to weep". These changes however did not fail to leave their mark on the interaction between mother and son: Sometimes the boy's mother was sadder than previously owing to her awareness that the loss of her increasingly alert son nevertheless was in-

evitable. It is impossible to evaluate the effect of THC treatment on the boy's epileptic seizures owing to the progression of the disease and modifications made to his antiepileptic treatment [1].

2. In the case of L. S., a 12 year-old girl with spasticity arising from mitochondriopathy, to whom approximately 0.09 mg THC/kg body weight a day orally was administered in two doses, the parents reported the following: their child became "more relaxed, more interested, more alert, more interested in her surroundings". L. spent "half an hour investigating her ear, as if it was the first time she had ever noticed it". Nodding spasms and tonic seizures improved considerably. Despite this, a temporary increase in seizure severity was observed.

3. The mother of the 12 year-old girl K. D., who suffers from severe spasticity and seizures as a result of severe hypoxia (foetomaternal transfusion) and who 0.07 mg THC/kg body weight a day orally in two doses was given, reported that she became "relaxed, less stiff, completely happy, open to everything". Whereas before initiation of the treatment she did not show any reaction when exposed to bad smells (her parents are farmers), after that her mimic behaviour demonstrated, that she would smell. In the case of this child, there was also a noticeable reduction in the number of epileptic seizures, heretofore unsatisfactorily treated with valproic acid. Versive seizures with nystagmus became less frequent, but when they occurred any tonic-clonic seizures were "extreme".

4. A 14 year-old girl, A. K., with neuronal ceroid lipofuscinosis, Spielmeyer-Vogt variant, was given 0.04 mg THC/kg body weight a day orally in two doses. In the case of this patient, the aim is to lessen her gait disturbance, manifested by problems of initiation of movements and a stiffening over longer distances ("no ground-covering steps"). L-dopa and amantadine had proved only partially successful: they only improved the initiation. During THC therapy, her gait improved considerably. The stiffness in the left leg lessened and the patient was able to cross the street again. The problem of starting off was not affected by THC. There was another improvement to observe: The girl suddenly developed initiative (setting the breakfast table of her own accord and changing her clothes when she wet herself). Her concentration when playing also improved slightly. Despite the progression of the disease, the number of focal seizures that progressed to grand mal seizures was slightly lower.

5. The case of the 13 year-old boy C. D. is characterised by spasticity, athetosis, myoclonia, and epileptic seizures of uncertain aetiology. He was given 0.14 mg THC/kg body weight a day orally in two doses. His parents reported that: the boy "has become more awake, he speaks more, makes more eye contact, takes part in things more, is more alert. It's great, he's more conscious of everything. For instance, in the past when touching him, he would continue to bite. He is happier, he laughs more, is more relaxed". A definite influence on the epileptic seizures (both focal and primary generalised) was not observed. There was a reduction in the severity but not in the frequency of myoclonia.

6. A 11 year-old girl, S. P., suffered a spinal contusion (Th11-Th12) with total paraplegia following a traffic accident. She also had a frontal skull fracture and suspected haemorrhaging near the clivus. Owing to the severity of injuries to the abdomen, a subtotal ileum resection was carried out. Despite psychotherapy, the patient developed an eating disorder – without, however, losing weight. This seemed to indicate post-traumatic reaction, although the influence of organic factors remained difficult to assess. She was given 0.09–0.12 mg THC/kg body weight a day, orally administered in two doses. During treatment vomiting decreased. She said, that she was hungry, ate more and started to drink again. Her weight remained constant. The girl became "more accessible, for the first time open to therapy", was no longer on a " ,No- trip", and "emerged from her previously destructive attitude". She could look others in the eye and was happier. On increasing the dosage, the patient demonstrated a high degree of associative thinking and verbal disinhibition concerning sexual contents. After three months treatment was stopped and there were no symptoms of withdrawal. Even after discontinuing the medication, the patient's body weight remained stable and her mood improved.

7. The youngest patient, a boy J. H., aged 3 years and 10 months became paraplegic as the result of a traffic accident. During his stay in hospital he became considerably withdrawn and ate little. He was given a brief course of treatment using 1 mg THC a day orally – to good effect. The improvement did not seem attributable solely to adjusting to the new environment.

8. A 14 year-old boy, M. Ö., suffers from severe idiopathic early infantile grand mal epilepsy with tonic-clonic seizures and falling. Owing to the modification of antiepileptic treatment, the influence of THC (0.12 mg/kg body weight a day orally given) on the epileptic seizures is impossible to assess. Appetite, playfulness, and mood improved. An epilepsy clinic claimed the boy's restlessness was attributable to the THC medication. However, restlessness was already present before this treatment was established. Therefore, ending the THC medication effected only a slight reduction in the degree of restlessness. Discontinuation of the medication caused no apparent difficulties.

Discussion

The following insights may be derived from the case reports:

1. THC also is a valuable means of treating children and adolescents.

2. Effects, side – effects and averaged daily doses of THC can be summarized as follows: reduced spasticity (0.09mg/kg body weight a day), improved dystonia within the context of a neurodegenerative disease affecting the basal ganglia (0.04mg/kg body weight a day), increased initiative (0.04 mg/kg body weight a day), improved posttraumatic reaction (0.09 mg/kg body weight a day), increased interest in surroundings (0.1mg/kg body weight a day), anticonvulsive action (0.07 mg/kg body weight a day), aided discontinuation of meperidine (approximately 0.07 mg/kg body weight a day), disinhibition concerning thinking and speaking (0.12mg/kg body weight a day), slight increase in preexisting restlessness (0.12mg/kg body weight a day).
3. In several of the cases treatment was discontinued and in none of them this caused any signs of withdrawal..

Looking for most suitable dosages of THC in paediatrics requires further investigation. Optimal doses seem to be varying greatly according to indication. Thus, when compared to doses recommended for treatment of cytostatica-induced emesis (more than 4mg/kg body weight a day [2]), THC doses applied in the described patients were much lower. Side effects of THC in children (mood changes) differ from those in adults (drowsiness, dizziness and in rare cases anxiety) [3]. CB1-receptors increase gradually during postnatal development, so psychotropic side effects in young children may be minor [4]. The effects of cannabinoids on the CNS are often biphasic. When administered to rodents, lower doses increased activity, while higher doses induced sedation and cataleptic behaviour [5]. This observation may explain the increased initiative of A.K., when lower doses (0.04mg/kg body weight a day) are given. It may be interesting to note, that augmented initiative may be explained by findings from positron-emission-tomography revealing improvement in blood circulation to the anterior insula and orbitofrontal and temporopolar cortices [6 and 7]). On the other hand, since autistic behaviour was diminished by higher doses (0.1mg/kg body weight a day), it may be speculated, that THC counteracted inhibitory mechanisms underlying autism.

The following observations are interesting to note: In the patients S.P. and J.H. THC improved posttraumatic reaction consistent with findings, that endocannabinoids extinct aversive memories (demonstrating actions on the basolateral amygdala) [8]. There is an ethical discussion, if it is justified, to extinct memories by drugs [9]. Apart from the ethical question, remembering traumatic experiences may result in suffering and obsession and may inhibit autonomy. In the patient K.D. reaction upon bad smells increased. A similar observation only, as far as I know, has been described by the astronomer Carl Sagan, who experienced with cannabis: "The enjoyment of food is amplified; tastes and aromas emerge that for some reason we ordinarily seem to be too busy to notice. I am able to give my full attention to the sensation." [10]. It may be speculated, that this amplification is not only due to changed attention, but is due to changes in olfactory system, too. The positron-emission-tomography study cited above [6] gives hints that regions of the brain processing olfactory stimuli participate in improved blood circulation, such as amygdala (again), which is involved in aversive olfactory sensations. An other indication is, that in the bulbus olfactorius of the rat the expression of CB1-receptor protein has been demonstrated [11]. In contrast to this hypothesis there has been found no difference in olfactory identification tasks between groups of cannabis users, former cannabis users and drug free controls [12]. Systematic evaluation seems to be much promising. There could be applied the sniffin' sticks – method [13]. Interestingly, preliminary evidence suggests, that cannabinoids are able to improve night vision, another form of sensory function [14].

Concerning the antiepileptic effects of cannabinoids to this point of time there is no systematic knowledge. But there are anecdotal reports even from medieval times: Al Badri (1443–1489) reports, that Ali ben Makki had helped the epileptic Zahir ad din Mohammed ben Ismail ben al Wakil with music and folia of the cannabis plant: the patient had forgot (!) his illness [15].

In addition to these clinical observations future insights as well into ion channel and transmitter mechanisms of epilepsy as into cannabinoid actions will benefit clinical advances in this area.

THC can have a proconvulsive and an anticonvulsive effect. Which one is generated depends on the dose and the type of seizure. It is effective in treating some forms of partial and generalised convulsive epilepsies, but it has no effect on other types of partial epilepsies and petit mal absences [16]. In terms of its antiepileptic effect, cannabidiol, the other major cannabinoid in the cannabis plant, is by far the more interesting substance. It has anticonvulsive properties without demonstrating any proconvulsive effect. In animal petit mal absence models, however, it has been found to block the effectiveness of antiepileptic drugs [17].

Six of the eight patients treated with THC in the present report suffered from epilepsy. In two of the six (L.S. and K.D.), the frequency of seizures decreased considerably upon THC administration. In one patient (A.K.), the frequency of seizures did not increase and severity of seizures remained constant (except for the last seizure), despite the progression of the principal

disease. In one patient (C.D.), a definite influence of THC on seizure activity could not be assessed. Evaluation of two patients proved impossible: in the case of the first because of marked progression of the principal disease (P.G.), in the second (M.Ö.) because of an extensive change in the antiepileptic medication. The effect of THC treatment on the epilepsies of L. S. and K. D. was most impressive. Suffering fundamental pyruvate dehydrogenase deficiency, L. S. demonstrated clinical nodding spasms and tonic seizures. EEG records revealed a left parietotemporal spike-wave and sharp-slow wave focus with generalisation. K. D. suffered from residual symptomatology following severe postnatal hypoxia. Seizures were to classify as versive ones accompanied by nystagmus. EEG records revealed a right temporal sharp-wave and sharp-slow wave focus. In the case of both patients, there was a temporary increase in apparent seizure severity. A.K. demonstrated focal initiated grand mal seizures, her EEG records revealed generalised and multifocal spike waves.

A number of animal experiments may explain the anticonvulsive effect of cannabinoids:

In rat hippocampal neurons, WIN 55.212-2 (WIN are non classical synthetic analogues of cannabinoids) inhibits N and P/Q-type calcium channels [18] regulated by G proteins. In cats L-type calcium channels of cerebral arterial muscle cells are inhibited by CB 1 – receptor [19]. Calcium channels play a role in the initiation and spread of epileptic activity. According to new findings L-type calcium channels play an important role in epileptogenesis [20]. In the case of generalised convulsive seizures non-T – type channels come into play [21]. On the other hand, T –type channels are not inhibited by low cannabinoid concentrations [22]. These channels play an active role in petit mal absences [21].

Inward leading sodium channels, which initiate depolarisation, are inhibited by THC in mouse neuroblastoma cells [23]. Increased sodium conductance is a contributing factor of epileptogenesis.

In addition, CB1 receptors mediate an increase of the outward current of potassium via A channels in hippocampal neuron cultures [24], thereby stabilising the membrane potential of excited cells.

Glutamate release in rat hippocampal cells is reduced [25] by CP54.939, CP55.940 and WIN55.212-2.

GABA, which produces an outward current of chloride that changes direction at –60 mV, thus preventing the depolarisation threshold from being reached [26], is an important transmitter effecting inhibition of epileptogenesis. In rat globus pallidus, GABA reabsorption is blocked by nabilon [27]. Globus pallidus neurons are able to generate epileptic activity [28].

Cannabinoids reduce the potassium efflux via M channels in rat hippocampal slices. This fact could play a role in convulsant action of cannabinoids.

There are no hints, that cannabinoids influence AMPA-receptors [30], which play an important role in epileptogenesis [20].

It has been demonstrated by electric shock model in mice, that the endogenous cannabinoid system inhibits the epileptic excitability of the CNS [31]. In this model NMDA-receptors are involved [21]. Anandamide reduces glutamate release in rat hippocampal cells. Arachidonic acid and its metabolites, the eicosanoids, though produced upon degradation of anandamide and 2-arachidonylglycerol [32], exert different action from that of cannabinoids (e.g. decreasing of potassium outward currents via A-channels) [29]. So the arachidonic acid must be rapidly removed to prevent convulsant effects (and it seems to be reincorporated into membrane phospholipids) [32].

The potential benefit of HU 211, a synthetic non psychactive, non CB1-receptor binding cannabinoid in catastrophic epilepsies and in status epilepticus should be examined. In brain injury a neurotoxicity reducing effect has been observed [33]. It should be considered, however, that apoptosis of cells belonging to an epileptic focus is advantageous for the surviving of the surrounding cells [34].

Further effects of THC which can exert influence on seizure activity must be taken into account:

the influences of THC on vigilance and sleep structure (reducing REM-sleep) [35], the endocrine system (increasing melatonin secretion [35], reducing production of gestagenic hormones [36]), and the immune system.

Under cannabinoid influence, the EEG revealed a "desynchronisation" [39]. On examining 8 healthy volunteers other researchers could not establish any change under CBD influence [38].

Conclusion

THC should be considered in the treatment of neurodegenerative disease or posthypoxic state or posttraumatic reaction not only in adults but also in children or adolescents. Hopefully, future studies of the anticonvulsive effects of cannabinoids will support the current assessment and lead to new antiepileptic drugs.

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