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On the application of cannabis in paediatrics and epileptology

*Key words: Cannabinoids - children - epilepsy - ion channels - neurodegenerative disease - posthypoxic state - posttraumatic reaction*

Abstract: An initial report on the therapeutic application of THC 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 (when low dose is given ) , increased interest in surroundings , anticonvulsive action . The doses ranged from 0.04 to 0.12 mg/kg body weight a day.

At higher doses disinhibition and increased restlessness were observed. In several of the cases treatment was discontinued and in none of them coming off revealed any problems

The action of THC on ion channels perhaps explaining the effects seen in epileptic patients are discussed.

Casuistics:

1. In the case of the boy P. G., treatment was begun with THC at the age of 8 years and 9 months and continued until shortly before his death at the age of 9 years 4 months. Every day approximately 0.07 mg THC/kg body weight was administered in two doses via PEG 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 making nursing him difficult. 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 he seemed more awake. Whether this was due to the discontinuation (totally unproblematic by the way) of meperidine treatment prior to beginning cannabis treatment remains to be seen. 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 about 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 inevitable. 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 was administered approximately 0.09 mg THC/kg body weight in

two separate 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 was treated with 0.07 mg THC/kg body weight every day in two separate doses, reported that she became "relaxed, less stiff, completely happy, open to everything". 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. The 14 year-old girl, A. K. with neuronal ceroid lipofuscinosis, Spielmeyer-Vogt variant, is given 0.04 mg THC/kg body weight every day in two doses. In the case of this patient, the aim is to lessen her gait disturbance, manifested by problems starting off and a stiffening over longer distances ("no ground-covering steps"). L-dopa and amantadine had proved only partially successful: they only improved her starting off. 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 problems of starting off remained uninfluenced by THC. Moreover 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. Every day he is treated with 0.14 mg THC/kg body weight 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". It was impossible to establish whether the THC medication had a definite influence on the epileptic seizures (both focal and primary generalised). There was a reduction in the severity but not in the frequency of myoclonia.

6. The 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 posttraumatic reaction, although the influence of organic factors remained difficult to assess. She was treated every day with 0.09-0.12 mg THC/kg body weight, administered in two doses. During treatment vomiting decreased. Of a morning the patient would say, "I'm 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 attitu-

de". She could look others in the eye and was happier. On increasing the dosage, the patient did demonstrate very associative thinking and verbal disinhibition concerning sexual contents. After three months treatment was stopped and there were no symptoms of withdrawal. Even after coming off the medication, the patient's body weight remained stable and her mood improved.

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

8. The 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) on the epileptic seizures is impossible to assess. Appetite, playfulness, and mood improved. An epileptological clinic claimed the boy's restlessness was attributable to the THC medication, though it already had been existing before this treatment was established. So ending the THC medication effected only a slight reduction in the degree of restlessness. Coming off 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 in mg/kg body weight a day can be summarized as follows: reduced spasticity (0.09), improved dystonia within the context of a neurodegenerative disease affecting the basal ganglia (0.04), increased initiative (0.04), improved posttraumatic reaction (0.09), increased interest in surroundings (0.1), anticonvulsive action (0.07), aided coming off meperidine (approximately 0.07), disinhibition concerning thinking and speaking (0.12), slight increase in preexisting restlessness (0.12).
3. In several of the cases treatment was discontinued and in none of them coming off revealed any problems.

Looking for most suitable dosages of THC in paediatrics requires further efforts. They may be child- and indication-dependent. There seems to be an extreme therapeutic range of THC, if doses given to the described patients and those recommended for treatment of cytostatica-induced emesis, which amount to more than 4 mg/kg body weight a day (2), are compared. Side-effects of THC in children (mood changes) differ from those in adults (drowsiness, dizziness and in rare cases anxiety) (3). Cannabinoid effects often are dose dependent. So cannabinoids have both a depressing and a stimulating effect on the CNS - higher doses are predominately depressing. When administered to rodents, lower doses provoke increased activity, higher ones on the contrary bring on sedation and cataleptic behaviour (4). This fact

may explain the increased initiative of A.K. , when lower doses (0.04) are given.( By the way , augmented initiative may be explained by PET - findings revealing an improvement in blood circulation to the anterior insula and orbitofrontal and temporo-polar cortices (5 and 6) ). On the other hand , autistic behaviour was diminished by higher doses (0.1) -an indication , that inhibitory mechanisms requiring inhibition are relevant ?

In the following will be focussed on the anticonvulsive effects of THC observed in the described patients . To this point of time there is no systematic knowledge in that topic , and there will be no progress if not by evaluating casuistics and researching the pathophysiological basics of epilepsy and pharmacological effects of cannabinoids. It may be advantageous , that in this period epileptic research focuses on molecular genetics of epilepsy, and this condition will give insights into relevance of the different ion channels in the different epilepsies , too.

THC can have both a proconvulsive and an anticonvulsive effect. Which is generated depends on the dose and the type of seizure. It is effective in treating some forms of partial and generalised convulsive seizure, but it has no effect on other types of partial seizure and petit mal absences. In terms of its antiepileptic effect, CBD 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 AED (7).

Six of the eight patients treated with THC were epileptics. In two of the six, the frequency of seizures decreased considerably under THC. In the case of a further patient, the frequency of seizures did not increase and severity of seizures remained constant (except for the last seizure), despite progression of the principal disease. The seizures of another remained completely unaffected. Evaluation of the last two patients proved impossible: in the case of the first because of marked progression of the principal disease , in the second, because of a total change in the antiepileptic medication . The effect treatment had on L. S. and K. D. was most impressive. Suffering fundamental pyruvate dehydrogenase deficiency, L. S. demonstrated clinical nodding spasms and tonic seizures. The EEG revealed a left parietotemporal spike-wave and sharp-slow wave focus with generalisation. K. D. demonstrated residual symptomatology following severe postnatal hypoxia. Seizures were to describe as versive ones accompanied by nystagmus. The EEG 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. In the case of A. K. presenting no significant progress in seizure activity despite disease progression, focal seizures progressing to grand mal seizures were to assess. The EEG revealed generalised and multifocal spike waves.

The following findings may explain the anticonvulsive effect of cannabinoids:

In rat hippocampal neurons, WIN 55.212-2 inhibits (high-voltage activated, presynaptic) N and P/Q-type calcium channels (8), which are regulated by G proteins. In cats L-type calcium channels of cerebral arterial muscle cells are inhibited mediated by CB 1 - receptor (9).Calcium channels play a role in the initiation and spread of epileptic activity. In the case of generalised convulsive seizures, non-T - type channels come

into play (10). On the other hand, (low voltage-activated) T -type channels that are not inhibited by low cannabinoid concentrations (11) play an active role in petit mal absences (10).

Inward leading sodium channels, which initiate depolarisation, are inhibited by Delta-9 THC in mouse neuroblastoma cells (12) ( which are derived from embryonic sympathetic nerve tissue and are able to develop into various different nerve cells). Increased sodium conductance is a contributing factor of epileptogenesis.

In addition, mediated by CB1 receptors, the outward current of potassium via A channels in hippocampal neuron cultures increases (13), thereby stabilising the membrane potential of excited cells.

CP 54.939 > CP 55.940 > WIN 55.212-2 > anandamide reduce glutamate release in rat hippocampal cells (14).

An important transmitter effecting inhibition of epileptogenesis is GABA, which produces an outward current of chloride that changes direction at - 60 mV, thus preventing the depolarisation threshold from being reached (15). In rat globus pallidus, GABA - reabsorption is blocked by nabilon (16). Globus pallidus neurons are able to generate epileptic activity (17).

That WIN 2 inhibits the outward chloride current via M channels in sections of rat CA1 hippocampal neurons may explain the proconvulsive effect of cannabinoids (18). This chloride current is responsible for maintaining membrane potential close to resting level.

To what extent these findings can be applied to the epileptic neuron remains to be seen. According to recent findings revealed by sections of neocortical temporal lobes of epileptic patients obtained by surgery L- type calcium channels play an important role in the epileptic neuron. Unexpectedly AMPA - type glutamate receptors , which, so far as it is known , are not influenced by THC (19) , are very important concerning epileptogenesis (20).

The endogenous cannabinoid system inhibits the epileptic excitability of the CNS (21). Proof was ascertained using the electric shock model in mice. This is a model for tonic and tonic-clonic seizures (22) involving NMDA - type glutamate receptors and non-T - type calcium channel currents (10).

Under cannabinoid influence, the EEG revealed a "desynchronisation" ( 23); on examining eight healthy volunteers, other researchers could not establish any change under CBD influence (24).

It is a question open to discussion , if it could be convenient in the case of patients with catastrophic epilepsy to administer a cannabinoid such as dexamabinol, with the intention of reducing neurotoxicity caused by the increased release of excitatory transmitters ( in analogy to :25). But that is a very complicated topic and it should be considered , that apoptosis of cells belonging to an epileptic focus is not only a disadvantageous event because surrounding cells may be protected by it (26).

In examining the contradictory effect of cannabinoids on epileptic seizures, other influences (not addressed in this report) need to be taken into account - such as vigilance and sleep structure (reducing REM sleep (27) ), the endocrine system (increasing melatonin secretion (27), reducing production of gestagenic hormones (28) ), and the immune system. The density of CB1 receptors in the epileptogenous area and the fact that the effectiveness of cannabinoid receptors is known to vary between different parts of the CNS may also be significant (13).

#### Conclusion :

Not only in adults but in children and adolescents , too , suffering from neurodegenerative disease or posthypoxic state or posttraumatic reaction , THC should be considered as a medication effecting a decrease of spasticity and dystonia and an increase of initiative (when low doses are given) and of interest in surroundings . Perhaps the expectation will fulfill , that further investigations of the anticonvulsive effects of cannabinoids will lead to new antiepileptic drugs.

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