Cannabis as an anticonvulsant

There are records of the cannabis plant being used for medicinal purposes in ancient times, and in the 19th century it was used as an effective anti-epileptic drug (AED) in children. However, because of its abuse potential, most countries imposed laws restricting its cultivation and use, and this has greatly inhibited research into possible therapeutic uses. Things are now changing, and cannabis derivatives are now used legally to treat, for example, pain, nausea and spasticity.

The plant contains over 100 biologically active compounds, and recently it has been possible to isolate these and identify the neurochemical mechanisms by which some of them operate: one in particular, cannabidiol (CBD), has almost none of the well-known psychoactive properties, but can act as an anticonvulsant, probably through actions on neuronal transmembrane receptors and ion channels.

‘Recreational’ cannabis, although mostly illegal, is widely available, and patients with epilepsy and their carers have for years reported benefits in seizure reduction with its uncontrolled use. This has now been backed up with two rigorous double-blind placebo-controlled trials of CBD, each involving patients with the most intractable forms of epilepsy. Both were multinational, and recruited from specialist clinics.

The first recruited 120 children with Dravet syndrome, proven by genetic analysis (Devinsky O et al. NEJM 2017. doi: 10.1056/NEJMoa1611618). All were already on multiple AEDs with poor control. They ranged in age from 2 to 18 years (mean 9.8). The intervention group received 20 mg/kg/day of oral CBD for 14 weeks. Compared with placebo, their seizure frequency decreased significantly, by 23% (95% CI 41% to 5%; p=0.01), and 43% of cases achieved a 50% or more reduction in seizure frequency, compared with 27% in the placebo group (OR 2.0, P=0.08). Carers in the intervention group were happier, as judged by a significant improvement in the Caregiver Global Impression of Change (CGIC) scale compared with placebo (p=0.03).

The second trial recruited 171 children and adults with an equally difficult refractory condition, Lennox-Gastaut syndrome (Thiele E et al. Lancet 2018. doi.org/10.1016/S0140-6736(18)30136-3). The age range was 2-45 years (mean 15.5); two-thirds were under 18. Again, all were on multiple AEDs and the cases received the same intervention as for the Dravet’s trial. CBD was again effective in reducing seizure frequency, specifically drop attacks, which fell by 44% in the CBD group compared to 22% in controls (difference 17%, 95% CI 30%-4%; p=0.014). CGIC scores were similarly better in the intervention group (p=0.02).

Adverse effects were common in the intervention groups in both trials, including diarrhoea, vomiting, fatigue and somnolence, but none of them reported impressions of being ‘stoned’, which seems to confirm the lack of psychoactivity of pure CBD. Transient liver enzyme abnormalities were common, but only in those also taking valproate.

A review article describes the pharmacology in detail, and also points out that some of the benefits in both studies might have been related to drug interactions: CBD can increase blood levels of other AEDs considerably, particularly clobazam, which many were taking (Perruca E. J Epilepsy Res 2017. doi: 10.14581/jer.17012).

Further trials are underway in other epilepsy syndromes, and eventually we may see it used as a first-line: for a drug that has been around for millennia, it seems a pity that it has taken so long.