

The legalisation of Cannabis for medical use

AC Moffat

Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London SE1 7JN, United Kingdom
A paper presented at the Forensic Science Society AGM and Autumn Conference 'Agony and Ecstasy', November 2001

Introduction

Cannabis comes from the plant *Cannabis sativa* and appears illicitly as the plant, as resin or as an extract of the resin (hash oil). It contains about 60 different cannabinoids including tetrahydrocannabinol (THC, dronabinol), cannabinal, cannabidiol, cannabigerol and cannabichromene. It is the THC that is the psychoactive constituent and gives the "high" normally associated with the use of Cannabis. The relative and absolute amounts of the various cannabinoids in any sample of Cannabis will be dependent not only on the variety of Cannabis grown, but also on the part of the World where it is grown and its growing conditions. Varieties grown for hemp fibre are very low in THC content, whilst plants grown for their medicinal value can be rich in THC or cannabidiol or other cannabinoids depending on their intended use. Many synthetic analogues of THC have been prepared in laboratories, but only Nabilone has made it to the market as a medicine.

Chemistry

Analysis of an extract of Cannabis by high performance liquid chromatography separates all the cannabinoids and also shows that many of them naturally occur as their acid precursors. For example, some samples of Cannabis do not contain any THC, but do contain THC-acid that is converted to THC by heating at 120°C for one hour. Thus, samples of Cannabis that are to be used for medicinal purposes must first be heat treated to obtain the free cannabinoids. Cannabinoids are liable to oxidation by atmospheric oxidation and THC is readily converted to cannabinal if stored under poor conditions. The relative amounts of cannabinoids present in a sample of Cannabis is therefore not just a function of the variety and growing conditions, but also on the storage and treatment of the plant material.

Uses

Historically, Cannabis has been used for thousands of years and appears in Assyrian tablets around 700 BC. The Herbal of Dioscorides mentions it in 60 AD and so does Nicolas Culpeper's Herbal of 1653. The first pharmacopoeial mention of Cannabis was in the New Edinburgh Dispensatory of 1788. It was subsequently added to the British Pharmacopoeia in 1914 and was last mentioned in the British Pharmaceutical Codex of 1949 as an extract and tincture. Its medicinal use included the treatment of muscle spasms, menstrual cramps, rheumatism, tetanus convulsions, rabies and epilepsy. Its modern day therapeutic potential is still in the area of muscle relaxation and cannabinoids are currently advocated for the treatment of anorexia, bronchial asthma, epilepsy, glaucoma, hypertension, muscle spasticity, nausea, vomiting and pain. The cannabinoids

work through receptors in the central nervous system (CB1 receptors) as well as peripherally (CB2 receptors).

There are two cannabinoids currently licensed for medicinal use. The first is THC (Marinol) which is made synthetically and licensed in the USA for the treatment of nausea following cancer chemotherapy and appetite enhancement in patients with AIDS. The second is Nabilone, which is a completely synthetically derived cannabinoid. It is licensed in the UK for the treatment of nausea caused by chemotherapy. Both may be used in the UK on a named patient basis for any of the therapeutic indications listed above. A third synthetic cannabinoid, Dexanabinol, is in Phase III clinical trials in a number of European countries.

There has been a lot of discussion as to whether THC alone or an extract of Cannabis (containing a mixture of cannabinoids) has a greater therapeutic effect. Some recent unpublished research by David Baker's group at University College, London and Elizabeth Williamson from The School of Pharmacy, University of London showed that an extract of Cannabis has a far greater muscle relaxant effect in mice than the same dose of THC on its own. It will be for the clinical trials to prove or disprove this in humans.

Cannabis does have some toxicity, but it is very low in comparison with many other drugs. The acute toxic effects include increased heart rate, lowering of blood pressure, euphoric intoxication and toxic psychosis. The main chronic toxicity involves loss of cognitive performance. There is little problem with tolerance in long term therapy and there are no severe dependence problems.

Clinical Trials

In spite of its history of use, the many small clinical trials that have been published and anecdotal evidence that Cannabis can be used as a medicine, there is no good scientific evidence that Cannabis, Cannabis resin or the cannabinoids and their derivatives have therapeutic benefit. Thus, the World Health Organisation lists them under their Schedule I drugs, so that medical practitioners may not prescribe them. All countries who are signatories to the United Nation's Single Convention on Narcotic Drugs (1961) follow this lead, so that there is a

© The Forensic Science Society 2002

Key words Forensic science, *Cannabis sativa*, clinical trials, THC.

AG Moffat:

The legalisation of Cannabis for medical use

world-wide ban on the medicinal use of Cannabis and cannabinoids (except in Canada, see later). The only exception to this is THC, which was rescheduled to Schedule 2 in 1995 to allow it to be prescribed. It has subsequently been further reduced to Schedule 3 in the USA due to its proven medicinal value.

Against this background, the Royal Pharmaceutical Society of Great Britain produced a statement in April 1995 asking for clinical trials for cannabinoids. It said:

"More clinical research is needed to investigate the potential therapeutic uses of cannabinoids in specific medical conditions. Scientifically designed trials will help to establish which of the cannabinoids produces the various beneficial effects described, or whether they result from a combination of cannabinoids. Research would also help to characterise the unwanted effects of individual cannabinoids more fully."

The Society subsequently produced protocols for two clinical trials. The first is a double blind, placebo controlled, multicentre clinical trial for the treatment of multiple sclerosis which is now being run by Dr John Zajicek from Derriford Hospital in Plymouth. It will involve a total of 660 patients – 220 on an extract of Cannabis (Cannador, standardised to contain 2.5mg THC), 220 on THC alone (Marinol, 2.5mg THC) and 220 on a placebo. This will show whether Cannabis has any therapeutic benefit and, if it has, whether it is due solely to the THC. The patients take capsules orally and are tested for spasticity, pain, tremor, micturition disturbances and overall quality of life. It started in January 2001 and is due to continue for about two years. The trial is funded by the Medical Research Council (£950,000).

The second trial is again a double blind, placebo controlled, multicentre clinical trial for the relief of post-surgical pain. It too is funded by the Medical Research Council (£400,000). There will be 400 patients participating – 100 using Cannador, 100 using THC, 100 using a placebo and 100 using a conventional analgesic. This trial is expected to start early in 2002.

These trials are a very good example of international co-operation. The trials will be run in England, with the THC (Marinol) coming from Unimed in the USA, the Cannabis being grown in Switzerland and the capsules of the extract (Cannador) being provided by the European Institute for Oncology and Immunological Research in Germany.

There are other trials being conducted by GW Pharmaceuticals in the UK using Cannabis extracts. These trials are for the treatment of multiple sclerosis and other neurological disorders and use a sub-lingual spray as the method of drug delivery. They assure that the source of Cannabis is the same from batch to batch by propagating the plants from cuttings and growing them in greenhouses under standardised conditions. Different varieties are grown to give plants with known contents of cannabinoids. For example, one variety may contain virtually all THC whilst another may contain only cannabidiol.

GMP

For Cannabis products, it is obviously important to maintain a source of plant material that is consistent in character and also to process it using Good Manufacturing Practice (GMP). Similar principles are applied in the elaboration of pharmacopoeial monographs for plant extracts that define: 1. The plant material used as the starting material – cultivation, harvesting, primary processing, packaging, storage and transportation. 2. The solvent used for extraction. 3. The manufacturing process.

The contents of the extracts still have to be defined and a proposal being considered by the European Pharmacopoeia is for extracts to be: Standardised – where known constituents are solely responsible for clinical efficacy. The material is assayed for a single/group of constituents with limits of $\pm 10\%$ declared value, eg Belladonna Leaf. Quantified – where the active components have not been identified. The material is assayed for a minimum of two constituents with limits of $\pm 25\%$ declared value, e.g., St John's wort and Valerian.

Any medicinal product prepared from Cannabis will have to comply with one or other of these requirements.

Legal position

Provided that the evidence can be produced that Cannabis does have therapeutic benefit, the way is open for the World Health Organisation and governments around the world to change the legal position of Cannabis in medicine. The English Home Office Minister Charles Clarke has stated that: "If the clinical trials into cannabis are successful, the government is clear that we are willing to amend the Misuse of Drugs Act to allow prescribing."

Although the laws in a particular country may not have been changed, there are many examples of the decriminalisation of Cannabis. In the UK twenty years ago, the possession of Cannabis may have attracted a term of imprisonment on conviction. But over the years, suspended sentences were used and later police cautions instead of bringing the case to trial. Now, police in some areas simply confiscate the Cannabis without any further action. The Home Secretary (David Blunkett) has now proposed that Cannabis should be classified from Class B to Class C so that the possession of Cannabis would no longer be an arrestable offence.

Perhaps the most well known example of the decriminalisation of Cannabis is the Netherlands who decriminalised soft drugs in 1976. Under Dutch law the country's 1,500 "coffee shops" can sell customers up to five grams of Cannabis as long as no nuisance is created. In Amsterdam, seeds and instructions for growing Cannabis are freely on sale and some shops have Cannabis plants growing hydroponically in their premises.

Belgium was the second European country to propose the decriminalisation of Cannabis. All possession for personal use, or the growing of Cannabis for personal use will be legal. Cannabis will be tolerated among those aged 18 or above unless it leads to "problematic" consumption; creates a social nuisance;

or poses risks to others by, for example, encouraging children to use the drug or people driving while under its effects.

The situation in the USA is more complicated because of its federal nature. In 1996 California passed a law allowing state residents to grow and use Cannabis. Since then, eight other states have passed laws allowing Cannabis to be used for medical purposes. However, in 2001, the US Supreme Court ruled that there is no medicinal exception to federal law prohibiting the sale of cannabis because it has no legitimate medical use.

Canada is probably the country that has made the greatest changes to its legislation. On July 31 2000 the Court of Appeal for Ontario rendered its decision in the case of Terrance Parker who used Cannabis to help control his epilepsy. It declared the prohibition on the possession of Cannabis in their Controlled Drugs and Substances Act to be unconstitutional and of no force and effect. After that ruling, patients could apply for an exemption for medicinal purposes under Section 56 of the Act with the support of their medical practitioner. However, Cannabis was still prohibited for recreational purposes. The law was then changed countrywide and from 30 July 2001, patients with terminal or chronic conditions can use Cannabis for medical purposes. A disused mineshaft in Manitoba is being used to grow the plants under a special licence. The new regulations also allow those who are granted permission for its use to grow it at home or designate others to supply it.

Drug Delivery

However the laws are changed, there will be the need for Cannabis (or cannabinoids) to be formulated in a suitable manner. Smoking is a dangerous way of using it because of the risks of cancer. It is unlikely that standardised tinctures or extracts will be used on their own as they used to be, and it is more likely that oral preparations such as Cannador and Marinol will be used. However, the bioavailability of cannabinoids by the oral route is poor (6-10%) and variable, and other routes of delivery are being investigated. GW Pharmaceuticals are using a sub-lingual spray which has the advantage that it has a fast absorption and is not subject to first-pass metabolism by the liver. It would be especially useful for the treatment of acute pain and spasticity. Other companies are investigating the pulmonary delivery of cannabinoid solutions via metered dose inhalers. Patches may also be a suitable delivery form if constant blood concentrations are required, e.g., in the treatment of chronic pain.

Conclusion

As we move forward in the medicinal use of Cannabis there will still be the need for good scientific evidence for its use and much research still needs to be undertaken to provide patients with a medicine that is safe, efficacious and of the appropriate quality.