REVIEW OF PHARMACOLOGY

Herbal cannabis contains over 400 compounds including over 60 cannabinoids, which are aryl-substituted meroterpenes unique to the plant genus Cannabis. The pharmacology of most of the cannabinoids is largely unknown but the most potent psychoactive agent, â–µ9-tetrahydrocannabinol (â–µ9-THC, or THC), has been isolated, synthesised and much studied. Other plant cannabinoids include â–µ8-THC, cannabinol and cannabidiol (Fig. 1, Table 1). These and other cannabinoids have additive, synergistic or antagonistic effects with THC and may modify its actions when herbal cannabis is smoked. Synthetic cannabinoids such as nabilone and others are also available for therapeutic and research purposes. Non-cannabinoid constituents of the plant are similar to those found in tobacco (with the exception of nicotine). Recent research on the pharmacology and effects of cannabis and cannabinoids is briefly reviewed here. Î”9-tetrahydrocannabinol (Î”9-THC) Natural plant cannabinoid Main psychoactive cannabinoid in Cannabis sativa; largely responsible for psychological and physical effects Available in synthetic form as dronabinol (THC in sesame oil) Î”8-tetrahydrocannabinol (Î”8-THC) Natural plant cannabinoid Slightly less potent than Î”9-THC but otherwise similar. Only small amounts present in plant. Also available in synthetic form Appears to have few psychoactive effects in children Cannabinol Natural plant cannabinoid Less potent than Î”9-THC Cannabidiol Natural plant cannabinoid Does not interact with cannabinoid receptors. Lacks psychotropic and most other effects of Î”9-THC, but has anticonvulsant activity. May attenuate some unwanted psychological effects of THC Cannabichromene Natural plant cannabinoid Does not interact with cannabinoid receptors. Not psychoactive but may enhance some effects of THC II-hydroxy-Î”9-THC Natural metabolite of Î”9-THC in the body Psychoactive; may be responsible for some of the psychological effects of cannabis (â€”)-Î”8-THC-II-oic acid Natural metabolite of Î”8-THC in the body Does not interact with cannabinoid receptors; not psychoactive but has analgesic activity Anandamide (arachidonyl ethanolamide) Endogenous ligand for mammalian cannabinoid receptors Not structurally similar to cannabinoids; related to prostaglandins. Appears to mimic actions of THC and other cannabinoids that interact with cannabinoid receptors

SOURCES OF CANNABINOIDS Cannabinoids are present in the stalks, leaves, flowers and seeds of the plant, and also in the resin secreted by the female plant. The THC content varies tremendously between different sources and preparations of cannabis (Table 2). Over the past 20 years, sophisticated cultivation (such as hydroponic farming) and plant-breeding techniques have greatly increased the potency of cannabis products. In the â€˜flower powerâ€™ days of the 1960s and 1970s an average reefer contained about 10 mg of THC. Now a joint made out of skunkweed, netherweed and other potent subspecies of Cannabis sativa may contain around 150 mg of THC, or 300 mg if laced with hashish oil. Thus, the modern cannabis smoker may be exposed to doses of THC many times greater than his or her counterpart in the 1960s and 1970s (Reference Mendelson and MeltzerMendelson, 1987; Reference Gold and MillerGold, 1991; Reference Schwartz, Nahas and LatourSchwartz, 1991; World Health Organization, 1997; Reference SolowijSolowij, 1998). This fact is important since the effects of THC are dose-related and most of the research on cannabis was carried out in the 1970s using doses of 5-25 mg THC (World Health Organization, 1997). Gold (Reference

Gold and Miller1991, p. 356) remarks: â€œ This single fact has made obsolete much of what we once knew about the risks and consequences of marijuana useâ€•. Form Source THC content (this is extremely variable and the figures are approximate) Marijuana (USA) Dried leaves/stalks/flowers/seeds Cannabis (UK) (Herbal cannabis) Traditional cigarette (reefer) of 1960s and 1970s 1-3% THC (âˆ¼10 mg/reefer) Modern cigarette (joint) of 1980s-1990s; result of intensive cultivation and more potent subspecies (sinsemilla, skunkweed, netherweed and others) 6-20% THC (60-200 mg/joint, over 300 mg if laced with hashish oil) Hashish (USA) Resin, secreted by plant Cannabis resin (UK) Bricks, cakes, slabs 10-20% THC Hashish oil Product of extraction by organic solvents 15-30% THC (sometimes up to 65%) In the UK at present, many recreational users grow their own supplies of high-potency cannabis (exact details of how to grow it can be obtained on the internet). Another main source is imports from Holland (also high-potency) and home growers can obtain seeds in Amsterdam at Â£10-Â£50 for 10 seeds, depending on potency. Cannabis can be smoked as joints, from pipes, or from â€˜bucketsâ€™, by inhaling from a mass of plant or resin ignited in a sawn-off plastic bottle. It can also be eaten, baked into cookies or cakes or occasionally drunk as an extract. It is unsuitable for intravenous use as it is relatively water insoluble, although it has been dissolved in alcohol and delivered as a fast-flowing saline infusion for research purposes.

PREVALENCE OF CANNABIS USE The prevalence of cannabis use has increased markedly over the past decade in young people in the UK, although patterns of consumption vary between different social groups. A survey of 3075 university students from 10 UK universities (Reference Webb, Ashton and KellyWebb et al, 1996) found that about 60% had some experience with cannabis; nearly 25% had tried it more than once or twice and 20% of students reported regular use (weekly or more frequently). Experience with cannabis had usually started at school, and other surveys have shown that 30-40% of 15- to 16-year-olds have tried it (Reference Miller and PlantMiller & Plant, 1996). Among 785 second-year medical students from seven UK medical schools surveyed in 1996, 46% reported cannabis use and 10% were taking it at least once a week (Reference Webb, Ashton and KellyWebb et al, 1998). A survey of 90 house officers found that nearly 30% reported current cannabis use and 11% used it weekly or monthly (Reference Birch, Ashton and KamaliBirch et al, 1998). These users are fairly moderate compared with some others. Some users report daily cannabis use, smoking up to 15 or

more joints daily. Many of these are unemployed youths who smoke to obtain a high level of intoxication and may be exposed to several hundreds of milligrams of THC daily. Other groups with a high prevalence of cannabis use are alcohol and polydrug misusers and psychiatric patients.

PHARMACOKINETICS OF CANNABINOIDS The pharmacokinetics of cannabinoids are reviewed by Agurell et al (Reference Agurell, Halldin and Lindgren1986) and Maykut (Reference Maykut1985) and others. About 50% of the THC in a joint of herbal cannabis is inhaled in the mainstream smoke; nearly all of this is absorbed through the lungs, rapidly enters the bloodstream and reaches the brain within minutes. Effects are perceptible within seconds and fully apparent in a few minutes. Bioavailability after oral ingestion is much less; blood concentrations reached are 25-30% of those obtained by smoking the same dose, partly because of first-pass metabolism in the liver. The onset of effect is delayed (0.5-2 hours) but the duration is prolonged because of continued slow absorption from the gut. Once absorbed, THC and other cannabinoids are rapidly distributed to all other tissues at rates dependent on the blood flow (Fig. 2). Because they are extremely lipid soluble, cannabinoids accumulate in fatty tissues, reaching peak concentrations in 4-5 days. They are then slowly released back into other body compartments, including the brain. Because of the sequestration in fat, the tissue elimination half-life of THC is about 7 days, and complete elimination of a single dose may take up to 30 days (Reference MaykutMaykut, 1985). Clearly, with repeated dosage, high levels of cannabinoids can accumulate in the body and continue to reach the brain. Within the brain, THC and other cannabinoids are differentially distributed. High concentrations are reached in neocortical, limbic, sensory and motor areas. Cannabinoids are metabolised in the liver. A major metabolite is 11-hydroxy-THC which is possibly more potent than THC itself and may be responsible for some of the effects of cannabis. More than 20 other metabolites are known, some of which are psychoactive and all of which have long half-lives of several days. The metabolites are partly excreted in the urine (25%) but mainly into the gut (65%) from which they are reabsorbed, further prolonging their actions. Because of the pharmacokinetic characteristics of cannabinoids â€” both the sequestration in fat and the presence of active metabolites â€” there is a very poor relationship between plasma or urine concentrations and degree of cannabinoid-induced intoxication.

PHARMACODYNAMICS OF CANNABINOIDS Cannabinoids exert their effect by interaction with specific endogenous cannabinoid receptors, discovered by Devane et al (Reference Devane, Dysarz and Johnson1988). Neuronal cannabinoid receptors are termed CB 1 receptors and have been found in rat, guinea pig, dog, monkey, pig and human brains and peripheral nerves. A second cannabinoid receptor, the CB 2 receptor, was identified by Munro et al (Reference Munro, Thomas and Abu-Shaar1993) in macrophages in the spleen and is also present in other immune cells. The distribution of CB 1

receptors is very similar to that of injected THC and includes cerebral cortex, limbic areas (including hippocampus and amygdala), basal ganglia, cerebellum, thalamus and brainstem (Reference Herkenham and PertweeHerkenham, 1995). The discovery of cannabinoid receptors naturally stimulated a search for an endogenous ligand with which the receptors naturally interact. Such a substance was isolated from the pig brain by Devane et al (Reference Devane, Hanus and Breuer1992). It was found to be chemically different from plant cannabinoids: it is a derivative of the fatty acid arachidonic acid (arachidonyl ethanolamide) related to the prostaglandins (Fig. 3). This endogenous substance was named anandamide after the Sanskrit word for bliss, ananda. It has a high affinity for CB 1 receptors and has most of the actions of THC. Thus, the story of opium, opioid receptors and endogenous opioids is now repeated with cannabis, cannabinoid receptors and anandamides. Two similar endogenous fatty acids have since been isolated (Fig. 3) and it now appears that there may be a whole system of multiple cannabinoid receptors and anandamide-related substances. Their physiological function has yet to be elucidated (see Reference Pertwee and PertweePertwee, 1995, for a review). It appears that both anandamides and their receptors reside within neuronal lipid membranes and act as neuromodulators through intracellular G-proteins controlling cyclic adenosine monophosphate formation and Ca2+ and K+ ion transport. In this role the system may have important interactions with other neurotransmitters, including Î³ -aminobutyric acid, opioid systems and monoamines. In particular, THC has been shown to increase the release of dopamine from the nucleus accumbens and prefrontal cortex (Reference Tanda, Pontieri and Di ChiaraTanda et al, 1997). This effect, which is common to many drugs of misuse (including heroin, cocaine, amphetamine and nicotine), may be the basis of its reinforcing properties and its recreational use. It is reversed by naloxone, suggesting an opioid link.

Reference

Dosage Calculations: A Multi-Method Approach

Study Guide for Pharmacology and the Nursing Process