Essentials of Medicinal Cannabis Pre-Reading

Medicinal Cannabis - Potential Drug Interactions

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Introduction

Drug interactions can occur when two or more drugs/substances with similar or different actions (including herbal substances) are co-administrated, such as warfarin with aspirin, and cyclosporine A with St John's Wort. Drug interactions may result from chemical reactions between different components or modifications by certain components of certain biochemical pathways involved in the action or metabolism of related drugs (Li *et al*., 2007). Drug interactions can be affected by various factors, including disease and patient conditions, as well as the nature of compounds involved. The potential outcome of a drug interaction can be additive (1+1=2), synergistic (1+1>2), or antagonistic (1+1<2). Therefore, a drug interaction may lead to an enhanced drug response or unexpected side effect.

Generally speaking, drug interactions are mediated by pharmacodynamic and/or pharmacokinetic mechanisms. Pharmacodynamic interactions involve synergistic or antagonistic interactions on the same drug targets, e.g. receptors, which can often be predicted and avoided. Pharmacokinetic interactions involve alterations of the drug's absorption, distribution, metabolism and excretion. Most reported drug interactions are pharmacokinetic interactions, eg. through affecting drug metabolism enzymes such as cytochrome P450 (CYP450). CYP450 may be changed by interacting components through induction and inhibition. The induction of CYP450 usually requires a longer period of time (e.g. several days), which may lead to decreased drug plasma levels (through increased drug metabolism), and consequently reduced drug effects. Conversely, the inhibition of CYP450 is usually immediate and may lead to increased drug plasma levels (through decreased drug metabolism), and thus increased drug effects, which may result in significant adverse reactions or toxicities (Li et al., 2007).

Cannabis has been used in various forms as crude extracts or purified ingredients (with different THC/cannabinoids ratios), therefore drug interactions caused by cannabis depend

not only on the drugs involved but also the chemical components/profiles of the cannabis preparations used.

Effects of cannabis on drug metabolizing enzymes and related drug interactions

There are experimental *in vitro* and *in vivo* findings indicating that cannabinoids may act on P450 isoenzymes to affect the metabolism of various drugs. A systematic review by Stout & Cimino (2014) showed that P-450 is involved in metabolising several exogenous cannabinoids, for example tetrahydrocannabinol (THC; CYP2C9, 3A4), cannabidiol (CBD; CYPs 2C19, 3A4) and cannabinol (CBN; CYPs 2C9, 3A4), supported by clinical data on THC and CBD metabolism. The inhibition or induction of CYP by cannabis compounds, eg THC as CYP 1A2 inducer and CBD as 3A4 inhibitor, may potentially affect the metabolism of many drugs metabolised by these CYPs. However, in many cases, the relevance of research findings in cells or animals to humans has yet to be established. Specific clinical studies are often needed before a conclusion can be drawn. For example, studies showed that medicinal cannabis did not affect the clinical pharmacokinetics of irinotecan and docetaxel (Engels *et al*., 2007), while co-administration of cannabidiol (CBD) and clobazam (CLB) increased blood CLB level in children with epilepsy (Geffrey et al., 2015). A similar recent study showed that concomitant administration of CBD significantly changed serum levels of clobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine in patients with treatment-resistant epilepsy (Gaston et al., 2017). Abnormal liver function test results were also noted in participants taking concomitant valproate, indicating the importance of monitoring serum levels of commonly used antiepileptic drugs and liver functions during treatment with CBD (Gaston et al., 2017). On the other hand, a study in healthy adults found that concomitant administration of fentanyl did not affect the plasma level of CBD, and the co-administration did not produce respiratory depression or cardiovascular complications during the test sessions and CBD did not potentiate fentanyl effects (Manini et al, 2015), but keloconazole (CYP3A4 inhibitor) was found to increase, and rifampin (CYP3A4 inducer) to reduce THC and CBD concentrations, (Stout & Cimino, 2014).

Other potential drug interactions

A study in 21 individuals showed that vaporized cannabis increased the analgesic effects of opioids without altering plasma opioid levels (Abrams et al., 2011). A non-controlled, prospective open-label study in 274 participants found that medicinal cannabis reduced the consumption of opioids (Haroutounian S *et al*, 2015). The current research generally supports

the use of medical cannabis as an adjunct or opioid substitute. On the other hand, it should be noted that a recent survey in US indicates that cannabis may increase the risk of developing nonmedical prescription opioid use (Olfson et al 2018). Thus, it is important to develop a program at state or national level to monitor the use of different forms of cannabis and their associations to different medical conditions.

A study in 32 adult cannabis smokers found that low dose alcohol (approximately 0.065% peak breath alcohol concentration) increased blood levels of THC which may explain the performance impairment observed from cannabis-alcohol combination (Heatman *et al*, 2015; Ronen et al., 2010).

In addition, there are early studies or case reports indicating potential drug interactions with warfarin, oxymorphone, pentobarbital, cocaine, sympathomimetic amines, disulfiram, disulfiram etc, but further research is needed. Interestingly, Russo (2016) mentioned that in extensive clinical application including complex drug regimens with opioids, tricyclic antidepressants, anticonvulsants etc, no drug interactions have been observed that would contraindicate or preclude use of nabiximols with any specific pharmaceutical, although additive sedative effects are always possible. MacCallum & Russo (2018) recently pointed out that there is no drug that cannot be used with cannabis, if necessary.

Conclusion

There is still limited data on significant drug interactions caused by medicinal cannabis. Thus the evidence-based clinical guidelines on interactions of drugs with medicinal cannabis are still lacking. Nevertheless, caution should be undertaken to closely monitor the responses of cannabis users with certain drugs to guard their safety, especially for the elderly and people with chronic diseases or kidney and liver conditions.

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