Comparative Effects of Cannabinoids Alone And in Combination with Other Centrally Acting Drugs

By

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CHAPTER VI

SUMMARY

Marihuana, which is derived from the hemp plant, Cannabis sativa, has been noted for centuries to produce beneficial effects in man. Although the major pharmacologically active constituent of marihuana is delta-9-tetrahydrocannabinol (THC), in recent years major emphasis has been placed on the pharmacologic evaluation of naturally occurring cannabinoids other than THC and also a large number of unique synthetic cannabinoid compounds in the hopes of discovering drugs which will possess the beneficial effects of THC without the undesirable effects such as tachycardia and dysphoria.

Experiments were therefore conducted to evaluate and compare in normal male volunteers (1) the effects of THC and cannabichromene (CBC), a naturally occurring major cannabinoid which is relatively abundant in variants of Cannabis reputed to produce potent marihuana; (2) the effects of THC and nabilone, a synthetic cannabinoid which has proved to be a useful antiemetic agent for treating cancer chemotherapy patients; and (3) the effects of nabilone alone and nabilone administered in combination with some other centrally acting drugs which are likely to be prescribed concomitantly, specifically, ethanol, sodium secobarbital, diazepam, and

codeine. Effects on physiologic, subjective, and psychomotor responses were measured in each of these studies.

The effects of THC, CBC, and the combination of THC and CBC were compared following administration by smoking. The CBC response was found to be comparable to the placebo response. Although THC could not be distinguished statistically from placebo, THC did appear to impair mental and motor performance and increase heart rate. Also, in combination with THC, CBC appeared to potentiate the effects of THC on two performance tests, including standing steadiness and attentive motor performance.

When THC and nabilone were compared following both intravenous and oral administration, THC elicited a greater psychologic "high" than nabilone. However, when subjects ranked treatments in order of preference, there was no preference demonstrated statistically for either nabilone or THC. Each of these active treatments, though, was preferred over placebo. Statistically significant impairment in psychomotor performance was observed for all active treatments, although at different time periods. Furthermore, nabilone and its metabolites could not be detected in the urine of the subjects in this study by means of the enzyme multiplied immunoassay technique (EMIT) for THC and its metabolites, thereby demonstrating no cross-reactivity in this assay between nabilone and THC or their respective metabolites.

When nabilone was administered in combination with sodium secobarbital, diazepam, codeine, or ethanol, the peak effects produced by each drug combination were compared to the peak effects of each drug of the respective combination administered alone. The cardiovascular effects of each combination compared to those of nabilone alone were largely unremarkable, with one notable exception: the standing heart rate normally produced by nabilone was markedly attenuated when codeine was administered simultaneously. With regard to psychologic "high" and subjective effects, nabilone appeared to be the dominant partner in each combination. Additive euphoric effects, though, were noted for the combination of nabilone and sodium secobarbital. Additionally, additive decrements in mental performance were demonstrated for the combinations of nabilone plus sodium secobarbital and nabilone plus diazepam.

In conclusion, when nabilone was compared to THC in experienced marihuana smokers, an abuse potential for nabilone was clearly demonstrated. However, considering that cannabinoids as a class have markedly less abuse potential than other classes of drugs of abuse while also appraising the environment in which nabilone is intended for use, it is likely that this abuse potential is low. When nabilone was administered concomitantly with ethanol, sodium secobarbital, diazepam, or codeine, sufficient evidence was obtained to implicate nabilone as a potential interactant with other

centrally acting drugs which may be prescribed concomitantly in the treatment of the cancer chemotherapy patient. Nabilone, however, is not dissimilar from other antiemetic agents in this respect.

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