

Inhaled medicinal cannabis and the immunocompromised patient

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Abstract Medicinal cannabis is an invaluable adjunct therapy for pain relief, nausea, anorexia, and mood modification in cancer patients and is available as cookies or cakes, as sublingual drops, as a vaporized mist, or for smoking. However, as with every herb, various microorganisms are carried on its leaves and flowers which when inhaled could expose the user, in particular immunocompromised patients, to the risk of opportunistic lung infections, primarily from inhaled molds. The objective of this study was to identify the safest way of using medicinal cannabis in immunosuppressed patients by finding the optimal method of sterilization with minimal loss of activity of cannabis. We describe the results of culturing the cannabis herb, three methods of sterilization, and the measured loss of a main cannabinoid compound activity. Systematic sterilization of medicinal cannabis can eliminate the risk of fatal opportunistic infections associated with cannabis among patients at risk.

Keywords Cannabis · Immunocompromised host · Aspergillosis

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Abbreviations

M.C. Medicinal cannabis
 Δ^9 -THC Delta-9-tetrahydrocannabinol

Introduction

The use of medicinal cannabis (M.C.) has escalated in the past decade following FDA approval for its use in HIV-1 and cancer patients. M.C. has been recommended for the alleviation of pain, chemotherapy-induced refractory nausea, and vomiting, as a mood modifier, and for anorexia and can be used and combined in foods such as cookies, cakes, chocolate, sugar, and candy, in topical creams, suppositories, sublingual oil-like thick drops, by smoking, or by vaporizers. Parenteral administration by smoking or a vaporizer is reserved for patients who do not tolerate the oral or sublingual forms of cannabis [1].

Vaporizers have the advantage of delivering the active components of cannabis directly to the lungs without the by-products of smoking, such as tar. However, inhalation of smoke or vaporized cannabis buds may potentially expose the user to life-threatening pulmonary infections as a result of direct inhalation of bacteria and molds which are ubiquitous on the surface of plants. The danger is primarily to the immunocompromised host. Since the mid-1970s, there have been medical case reports [2, 3, 5–7, 9, 13, 15, 16, 18] describing the detrimental effects of inhaled *Aspergillus* via cannabis among patients, most of whom were immunocompromised. In some of those cases, the outcome was fatal.

Case

The potential infectious dangers of cannabis were illustrated by a recent 19-year-old male patient treated at Shaare Zedek Medical Center, who was immunosuppressed by intensive

chemotherapy for Burkitt's lymphoma/leukemia. He suffered from severe chemotherapy-induced nausea and vomiting refractory to ondansetron, aprepitant, and palonosetron. Cannabis prepared as cookies and sublingual drops were not tolerated, as the taste intensified his nausea and vomiting. Before proceeding to inhalation of M.C. either by vaporizer or smoking in his hospital isolation room, and out of concern that this may directly infect his lungs with potentially virulent pathogens, the cannabis was cultured. The culture yielded a massive growth of *Aspergillus*.

An initial endeavor at sterilization of the cannabis by three methods readily available in hospitals resulted in reduced effectiveness of the compound. In an attempt to find the optimal balance between sterilization and efficacy, we undertook to compare the three hospital-based sterilization methods for quantitative loss of the active compound delta-9-tetrahydrocannabinol (Δ^9 -THC).

Materials and methods

Medicinal cannabis was provided (with permission from The Israeli Ministry of Health) by The Israeli Society for Promoting the Use of Medical Cannabis and The Israeli *Cannabliss Company*, in the form of oil-like thick sublingual drops, dry cookies, and as dried buds. A *Digital Volcano* vaporizer device (Storz & Bickel America Inc. products, Oakland, CA, USA) was used to vaporize the cannabis buds [1]. The dried cannabis buds were cultured before and after evaporation by the Digital Volcano and after sterilization. The Digital Volcano blows 194 °C hot air through a grid, on which the lightly ground dry cannabis buds were placed. The hot air was collected in a balloon attached to this device, made by the same manufacturer. After the balloon was filled, the cannabis vapor was released onto blood, chocolate and Sabouraud agar plates, as well as on broth liquid medium which were incubated for bacterial and fungal cultures by standardized universal methods. Culture results were read after 48, 72, and 96 h. We applied three different methods of sterilizing the dried cannabis buds. Sterilization was initiated by autoclave (50-min steam cycle and 30-min drying cycle, temperature of 135 °C, pressure of 316 kPa/3160 mbar), by plasma H₂O₂ (STERRAD 100NX, ASP, Johnson & Johnson, USA; 49-min cycle, temperature of 51 °C, pressure of 30 Torr/40 mbar), and by ethylene oxide (The gas is made by 3 M Health Care, St. Paul, MN, USA; 165-min cycle, temperature of 55 °C, pressure of 892 mbar). Sterilization by gamma irradiation was not used, as this method requires a nuclear facility not readily available in hospitals worldwide.

Effect of sterilization on Δ^9 -THC content in M.C. buds The sample of M.C. was homogenized (by hands with rubber gloves) and partitioned into four equal samples. The first

one was analyzed as it was, and the other three were analyzed after their sterilization by ethylene oxide gas, plasma, and heat (autoclave). Each sample was weighed twice and analyzed thrice for accurate results.

Experimental procedure Twenty milligrams of a medicinal cannabis sample was extracted with an internal standard solution (50 µg tetracosane/ml ethanol) and filtered through cotton in a capillary tube. This filtrate was diluted twenty times with the same internal standard solution. One microliter of this sample was injected into a GC/MS for analysis.

Instrumentation For quantitative analysis, the samples were analyzed by GC/MS in a Hewlett Packard G 1800B GCD system with a HP-5971 gas chromatograph with electron ionization detector. The software used was GCD PLUS CHEMSTATION.

Conditions of the analysis Column: The column used was SPB-5 (30 m×0.25 mm×0.25 µm film thickness). Experimental conditions: The following were the experimental conditions in the study: inlet, 250 °C; detector, 280 °C; splitless injection/purge time, 1.0 min; initial temperature, 100 °C; initial time, 2.0 min; rate, 10 °C/min; and final temperature, 280 °C. The helium flow rate was 1 ml/min.

Standards and solutions Concentrations of ethanol from 25.0 to 100.0 µg/ml of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) were used for the calibration curve, together with 50.0 µg/ml tetracosane as an internal standard [11]. Quantification of THC content was measured as a percentage of THC in the plant material, such that 15 % THC content in 1 g of plant material would be equivalent to 150 mg THC. With regard to the safety of the sterilization methods, plasma sterilization has been used for years to purify water in municipalities mainly in Europe. It is primarily used to sterilize medical equipment such as non-lumen catheters. This method leaves residual hydrogen peroxide with average concentrations of 0.22 % by weight, which is within the accepted limits of the American Association for the Advancement of Medical Instrumentation; the FDA issued a warning only regarding high concentrations of hydrogen peroxide; therefore, we do not believe hydrogen peroxide was of concern. Gas sterilization in contrast leaves toxic residues of ethylene oxide and of its reaction products. As this method was only used to test the effect of sterilization on cannabis but not used for the patient, a discussion of the toxicity is not relevant for this paper.

Results

Cultures of M.C. dry buds before sterilization yielded mixed bacterial colonies, predominantly of *Enterobacteriaceae* in

large numbers and generated colonies of a mixture of molds, primarily *Aspergillus* (identified by morphology alone) in abundant numbers. Cultures of the sublingual M.C. oily drops also produced numerous colonies of bacteria and molds but substantially less than the dry buds. A possible explanation of these results could be due to the high viscosity of the oily drops interfering with diffusion on agar and as a result of residual alcohol in the extract.

Cultures of the Volcano balloon air after evaporating raw cannabis revealed a scanty mixture of several colonies of bacteria and molds. All three sterilization methods succeeded in completely sterilizing the M.C. cultures, with varying reductions in Δ^9 -THC activity, i.e., 12.6 % (plasma), 22.6 % (autoclave), and 26.6 % (ethylene oxide gas) (Fig. 1 and Table 1).

In accordance with these results, we subsequently supplied the patient with cannabis sterilized by the plasma method throughout the duration of chemotherapy. The sterilized cannabis significantly improved his well-being, nausea, and appetite, with no adverse effects.

Sterilization of cannabis by the above methods did not entail added costs to the treatment, as the small volumes of cannabis were added to the much larger loads of the routine hospital sterilization.

Discussion

Medicinal cannabis can benefit cancer patients and improve their quality of life. However, extreme caution must be

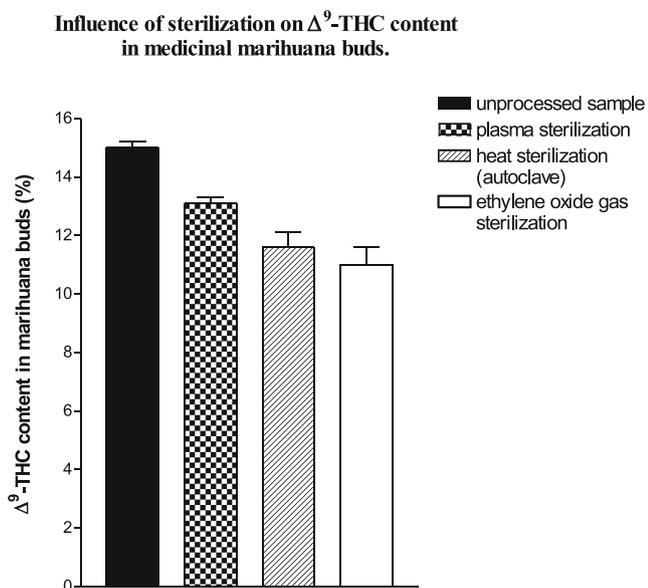


Fig. 1 Influence of sterilization on Δ^9 -THC content in medicinal marijuana buds. All three sterilization methods were effective in sterilizing the medicinal cannabis cultures, with varying reductions in the activity of the active compound Δ^9 -THC ranging from 12.6 to 26.6 %. The plasma sterilization method appeared to entail the least degradation of the cannabis Δ^9 -THC molecules

Table 1 Loss of Δ^9 -THC activity by sterilization

| Sample | Content of Δ^9 -THC | Decrease of Δ^9 -THC in % |
|----------------------------------|----------------------------|----------------------------------|
| Unprocessed | 15.0±0.2 | |
| Plasma sterilization | 13.1±0.2 | -12.6 |
| Autoclave sterilization | 11.6±0.5 | -22.6 |
| Ethylene oxide gas sterilization | 11.0±0.6 | -26.6 |

exercised in immunocompromised patients, in whom any gain may be offset by the risk of infection with potentially dangerous pathogens such as *Aspergillus*.

Aspergillus is a ubiquitous fungus found worldwide in water, soil, air, vegetation, and decaying matter. Infection is acquired by inhalation of conidia. While exposure in immunocompetent hosts may result in colonization without disease, immunocompromised patients are at risk to develop invasive pulmonary aspergillosis associated with significant morbidity and mortality. The risk of infection has been linked to the concentration of conidia in the patient's ambient air but requires both compromised cell-mediated immunity and macrophage and neutrophil function [9, 12, 16]. Marijuana smoke may damage alveolar macrophage function, further compromising the immunocompromised host [14].

Invasive aspergillosis has been described in immunocompromised patients in association with smoking marijuana following renal transplantation, leukemia, cancer patients undergoing chemotherapy, AIDS, and chronic steroid therapy [2, 4–6, 9, 16]. The mode of administration is of utmost importance in these patients. Cannabis in the form of cookies appears to be safe for immunocompromised patients, but these patients commonly suffer from intractable nausea, limiting their use. Inhalation of cannabis by smoking or by vaporization harbors a high risk for respiratory allergic reactions and severe or potentially fatal pulmonary infections particularly for immunocompromised patients. Heating of the cannabis buds by smoking or evaporation may not be sufficient for sterilization and is clearly not standardized to be safe for immunocompromised patients. Few publications have addressed this subject: Kagen et al. [7] showed the seroprevalence of various *Aspergillus* antigen species among 11 out of 21 cannabis smokers, implying previous exposure to *Aspergillus*. Verweij et al. [17] cultured 7 samples of marijuana and 98 cigarettes from 14 different commercial brands and found both to be heavily contaminated by fungal spores. They recommended that tobacco and cannabis should be eliminated from their patients' environments. Mechoulam et al. [10] in 1976 showed that home baking of cannabis does not considerably degrade Δ^9 -THC activity, but contamination by pathogens was not addressed. Levitz and Diamond [8] in 1991 attempted to solve the problem of cannabis contamination by home baking experiments using parsley, oregano, and tea

which are physically similar to cannabis as cannabis was not readily available. They recommended home baking the cannabis under dry heat of 150 °C (300 °F) for 50 min before smoking.

In the present study of the three common sterilization methods available in medical centers, we found all three methods to be effective in sterilizing the cannabis. The plasma sterilization method entailed the least degradation of the cannabis Δ^9 -THC molecules. The safety of sterilizing inhaled cannabis in immunocompromised patients needs to be confirmed in a large cohort of patients. To our knowledge, the Netherlands and Canada may be the only countries where there is strict central government control on medicinal cannabis. The Dutch Office of Medicinal Cannabis (OMC), a part of the Dutch Ministry of Health, is responsible for the production, processing, and distribution of M.C. for medical use; based on their findings, there is no degradation of the active cannabis molecules during the irradiation. However, this sterilization method is not routinely available.

Conclusions

Smoking or vaporization of medicinal cannabis may lead to life-threatening pulmonary infections including aspergillosis in immunocompromised patients as a result of direct inhalation of bacteria and molds ubiquitous on the surface of plants. Sterilization of cannabis in immunocompromised patients is therefore imperative before use.

We compared three different methods of sterilization and found plasma sterilization to be effective and cause the least quantitative loss of the active cannabis compound Δ^9 -THC. This method may allow for the optimal balance between the product activity and safety. We emphasize the hazard involved in smoking or vaporization of medicinal cannabis for immunosuppressed patients and suggest strict government control in each country worldwide over growing, processing, and sterilization of medicinal cannabis.

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Conflict of interest None.

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