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Research paper

Intranasal absorption of Δ^9-tetrahydrocannabinol and WIN55,212-2 mesylate in rats

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Abstract

The aim of this study was to examine the potential of the nasal route for systemic delivery of Δ^9-tetrahydrocannabinol (Δ^9-THC) and WIN55,212-2 mesylate. Anesthetized rats were surgically prepared to isolate the nasal cavity, into which Δ^9-THC (10 mg/kg) or WIN55,212-2 (150 μg/kg) in propylene glycol alone or propylene glycol and ethanol (9:1) were administered. Rats were also administered Δ^9-THC (1 mg/kg) and WIN55,212-2 (150 μg/kg) intravenously in order to determine absolute bioavailabilities of the nasal doses. Plasma Δ^9-THC and WIN55,212-2 concentrations were determined by liquid chromatography/mass spectroscopy (LC/MS). The pharmacokinetics of the drugs after intranasal administration was best described by a one-compartment model with an absorption phase. WIN55,212-2 was absorbed more rapidly ($T_{max} = 0.2$–0.3 h) than Δ^9-THC ($T_{max} = 1.5$–1.6 h) and to a higher extent than Δ^9-THC. Addition of ethanol (10%) to the formulations had no significant effect on the C_{max} after nasal administration ($p > 0.05$). Furthermore, it had no significant effect on the absolute bioavailability (F_{abs}): $F_{abs} = 6.4 \pm 2.4\%$ and $9.1 \pm 3.0\%$ for Δ^9-THC in propylene glycol, with and without ethanol, respectively. For WIN55,212-2, $F_{abs} = 49.9 \pm 6.9\%$ (propylene glycol alone) and $56.6 \pm 14.1\%$ (propylene glycol with 10% ethanol). The results of the study showed that systemic delivery of Δ^9-tetrahydrocannabinol and WIN55,212-2 could be achieved following nasal administration in rats.

Keywords: Δ^9-Tetrahydrocannabinol; Nasal delivery; Pharmacokinetics; Ethanol; Propylene glycol; Cannabinoids

1. Introduction

Δ^9-Tetrahydrocannabinol (Δ^9-THC), a cannabinoid, is used in the treatment of chemotherapy-induced nausea and vomiting in cancer patients and in AIDS cachexia [1]. The only currently approved dosage form of Δ^9-THC in the United States is the oral capsule dronabinol (Marinol®). Δ^9-THC has low oral bioavailability ($6 \pm 3\%$) due to extensive pre-systemic metabolism [2]. Alternative delivery methods, such as aerosols [3,4], rectal suppositories [5] and eye drops [6], have been reported in the literature.

R-(+)-WIN55,212-2[(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl carbonyl)-6*H* pyrrolo [3, 2, 1ij] quinolin-6-one] (R-(+)-WIN55,212-2), a synthetic cannabinoid, has been shown to have anti-inflammatory, immunosuppressive, analgesic and anti-tumor effects [7,8]. These positive preclinical data imply that the compound may be of future benefit for cancer treatment and other medical conditions involving inflammation and pain. R-(+)-WIN55,212-2 is also prone to hepatic first-pass metabolism and variable bioavailability following oral administration. *In vitro* metabolism studies in mouse liver microsomal preparations indicate that WIN55,212-2

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undergoes significant metabolism similar to that of the other cannabinoids [9].

During cancer chemotherapy, the oral route may not always be preferred over other routes of drug administration because of the nausea and vomiting side effects associated with some cancer chemotherapeutics. Depending on the potency and physicochemical properties of the drugs needed for supportive treatment during chemotherapy, the nasal route could be an alternative to the conventional oral route in treating cancer patients. Furthermore, the nasal route may be a suitable route for management of the acute pain in cancer or other medical conditions because of the faster absorption of the drug. The nasal route is an interesting portal for systemic drug delivery because it also circumvents pre-systemic metabolism associated with oral drug delivery. Several studies have shown improved bioavailability of many pre-systemically metabolized drugs delivered through the nasal route, including progesterone [10], propranolol [11,12], doxylamine succinate [13], oxymorphone [14], midazolam [15], budesonide [16], and anticonvulsants [17]. Furthermore, nasal drug delivery is an attractive alternative to injections, and is suitable for self-administration.

Unlike Δ^9-THC, where previous literature exists describing various drug administration routes, limited information exists on the systemic delivery of WIN55,212-2. One patent [18] describes the delivery of THC prodrugs intranasally. Besides this, there are no reports in the literature on the systemic delivery via the nasal route for both compounds. The aim of this study was to assess the feasibility of intranasal administration of Δ^9-THC and WIN55,212-2 (Fig. 1). The nasal absorption of lipophilic compounds like these cannabinoids involves concentration gradient-dependent permeation of epithelial cell membranes via the transcellular route, therefore a preliminary pharmacokinetic investigation was carried out using the anesthetized rat surgical model [19]. Both drugs are lipophilic compounds that require substantial solubilization formulation efforts for nasal administration, so appropriate preliminary cosolvents were used. Propylene glycol, polyethylene glycol, and ethanol have been used to formulate lipophilic drugs for nasal administration [17,20,21]. These initial studies with Δ^9-THC and WIN55,212-2 were completed using simple solvent systems including propylene glycol alone or in combination with ethanol (9:1), as has been described previously for a highly lipophilic compound, diazepam [17].

2. Materials and methods

2.1. Materials

Δ^9- THC in 95% ethyl alcohol was obtained from Sigma Chemical Co. (St. Louis, MO). Ethyl acetate (HPLC grade), acetonitrile (HPLC grade) and ammonium acetate (HPLC grade) were obtained from Fisher Scientific (Fairlawn, NJ). Ethanol (absolute, 200 proof) was purchased from the Aldrich Chemical Company, Inc. (Milwaukee, WI). WIN55,212-2 and propylene glycol (USP) were supplied by Sigma Chemical Co. (St. Louis, MO). All the glassware used in the study was silanized and siliconized microcentrifuge tubes were used (Fischer Scientific, Pittsburgh, PA).

2.2. Animal studies

Male Sprague–Dawley rats that weighed approximately 265 ± 30 g were purchased from Harlan Labs (Indianapolis, IN), and the studies were conducted at the University of Kentucky College of Pharmacy Animal Research Facility in accordance with institutional guidelines. The animals were prepared using a surgical procedure allowing intranasal and i.v administration. The animals were lightly sedated with a small amount of pre-anesthetic halothane, anesthetized with ketamine (100 mg/kg, IP) and xylazine (8 mg/kg, IP), and placed in the prone position. An incision was made in the neck, and the trachea was cannulated with an open glass tube (0.2 in, od) and ligated using 2-0 silk sutures. A closed glass tube (0.2 in, od) was inserted into the esophagus to the posterior part of the nasal cavity and ligated using 2-0 silk sutures preventing nasal drainage into the stomach. The nasopalatine passage was closed with cyanoacrylate glue preventing nasal drainage into the mouth. The right jugular vein (and left femoral vein when dosing intravenous) was cannulated with medical grade silastic

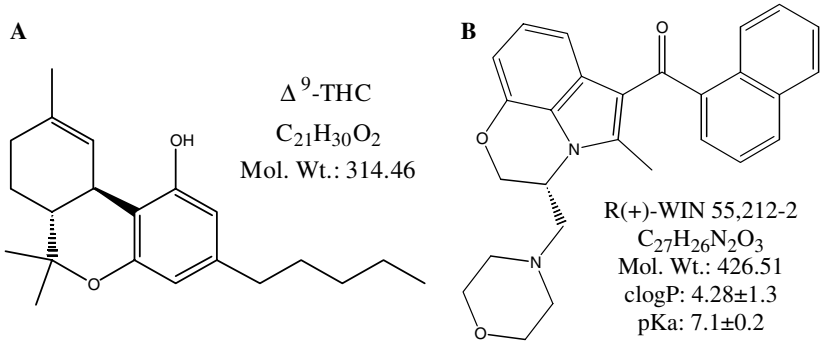

Fig. 1. Chemical structures of Δ^9-tetrahydrocannabinol (A) and WIN55,212-2 (B).

tubing (0.020 in, id × 0.037 in, od) ligated with 2-0 silk sutures and was anchored to the surrounding tissue with cyanoacrylate glue. The jugular and femoral catheters were flushed with 0.9% saline containing 10 U/mL of heparin to maintain patency. Each rat was administered 10 μL of a solution of Δ^9- THC (10 mg/kg) or WIN55,212-2 (150 μg/kg) in propylene glycol alone or in propylene glycol and ethanol (9:1) into each nostril using a 25 μL gas-tight Hamilton syringe with PE-50 tubing. For intravenous administration, 2.5μL of Δ^9-THC (1 mg/kg) or WIN55,212-2 (150 μg/kg) was given as a femoral bolus (30-s bolus by hand push) using a 10 μL gas-tight Hamilton syringe with a sterile 25-gauge needle. Δ^9- THC and WIN55,212-2 were prepared in sterile saline containing 5% v/v propylene glycol and 3% v/v Tween 80. Solutions were prepared immediately before each experiment. After dosing the animal, the femoral line was flushed with 0.2 mL of drug vehicle followed by a 0.2 mL flush of 0.9% saline. Each experiment was conducted in triplicate. Blood samples (300 μL) were collected from a cannula inserted in the jugular vein at 0, 0.5, 5, 15, 30, 60, 120, 160 (or 180 WIN55,212-2) and 240 min after administration. The blood sample at 0.5 min was withdrawn 30 s after the completion of the bolus dose administration. Each blood sample was obtained from a heparin lock. Heparinized plasma was separated immediately by centrifugation and frozen (−70 °C) in silanized vials until LC/MS analysis.

2.3. LC/MS analysis of plasma samples

2.3.1. Plasma sample extraction procedure

Exactly 500 μL of acetonitrile:ethyl acetate (1:1, v/v) was added to 50 μL of plasma sample in a 1.5-mL siliconized microcentrifuge tube, the mixture was vortexed for 30 s and centrifuged at 10,000*g* for 20 min. The supernatant was decanted into a clean silanized test tube and evaporated under nitrogen at 37 °C. The residue was reconstituted with 200 μL of acetonitrile, vortexed, and sonicated for 5 min. The clear solution was placed into a clean HPLC vial containing silanized low volume inserts and 20 μL of the sample was injected into the LC/MS system. The extraction efficiency was 96 ± 9% for THC and 95 ± 6% for WIN55,212-2.

2.3.2. LC/MS analysis of Δ^9-THC in plasma samples

Chromatography was performed on a Waters Symmetry® C_{18} (2.1 × 150 mm, 5 μm) column at 35 °C with a mobile phase consisting of ammonium acetate (2 mM)/acetonitrile (30:70, v/v) at a flow rate of 0.25 mL/min. A Waters Symmetry® C_{18} (2.1 × 10 mm, 3.5 μm) guard column was used.

The LC/MS system consisted of a Waters Alliance 2690 HPLC pump (Waters, Milford, MA, USA), a Waters Alliance 2690 autosampler, and a Micromass ZQ detector (Waters, Milford, MA, USA) using electrospray ionization (ESI) for ion production. Selected ion monitoring (SIM) was performed in negative mode for ion *m*/*z* 313 [THC-H]-(dwell time 0.30 s). Capillary voltage was 3.0 kV and cone voltage was 30 V. The source block and desolvation temperatures were 120 and 250 °C, respectively. Nitrogen was used as a nebulization and drying gas at flow rates of 50 and 450 L/h, respectively. Studies were carried out to find the inter- and intra-day variation and accuracy. The retention time for Δ^9-THC was 20.14 ± 0.18 min. A calibration curve was prepared with each assay at a concentration range of 5–200 ng/mL, and the observed correlation coefficient was 0.998 or better. The limit of detection was 5 ng/mL.

2.3.3. LC/MS analysis of WIN55,212-2 in plasma samples

The liquid chromatograph was a Waters Alliance 2690 HPLC pump (Waters, Milford, MA, USA) with a Waters Alliance 2690 autosampler and column heater. The analytical column used was a Waters Symmetry®C_{18} (2.1 × 150 mm, 5 μm) and guard column (2.1 × 10 mm, 3.5 μm). The chromatography was performed with a mobile phase consisting of ammonium acetate (2 mM)/acetonitrile (20:80 v/v) at a flow rate of 0.20 mL/min. The temperature of the column was maintained at 35 °C. The total run time was 15 min.

The detector was a Micromass ZQ detector (Waters, Milford, MA, USA) equipped with an electrospray ionization (ESI) probe. Selected ion monitoring (SIM) was performed in positive mode for *m*/*z* 427 $[M+1]^+$. The capillary voltage was 3500 V and the cone voltage was 40 V. The source block and desolvation temperatures were 120 and 250 °C, respectively. Nitrogen was used as a nebulization and drying gas at flow rates of 50 and 450 L/hr, respectively. The required studies were carried out to find the inter- and intra-day variation and accuracy. The retention time for WIN 55,212-2 was 3.92–4.12 min. A calibration curve was prepared with each assay at a concentration range of 1.25–200 ng/mL, and the observed correlation coefficient was 0.999. The limit of detection was 1.25 ng/mL.

2.4. Pharmacokinetic analysis

Pharmacokinetic analysis of the plasma concentration-time profiles after i.v. bolus injection was conducted by fitting the data to a two-compartment pharmacokinetic model using WinNonlin® Professional Version 4.0 (Pharsight Corporation, Mountain View, California) according to the equation:

$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (1)$$

After intranasal administration, the data generated were also analyzed with WinNonlin® using a one-compartment pharmacokinetic approach (Model 3, first order absorption/first order elimination).

The absolute bioavailability (F_{abs}) of the drugs after a single intranasal dose was calculated using the following equation:

$$F(\%) = [(AUC_{0-t\ IN} \times Dose_{IV})/(AUC_{0-t\ IV} \times Dose_{IN})] \times 100$$

Statistical analysis was performed utilizing standard methods. A Student's *t*-test was employed for calculating the level of significance with respect to the two propylene glycol-based formulations prepared. A value of $p < 0.05$ was considered statistically significant.

3. Results and discussion

To investigate the feasibility of the nasal route for systemic delivery of cannabinoids, the pharmacokinetics of Δ^9-THC and WIN55,212-2 were compared following intranasal and intravenous dosing in male Sprague–Dawley rats.

The mean observed and predicted plasma concentration–time profiles following Δ^9-THC formulation treatments are shown in Fig. 2. The predicted plasma concentrations for intravenous and intranasal dosing were obtained by fitting the observed data to a two-compartment model and one-compartment model with absorption phase, respectively. As can be seen from the figure, the predicted values fit the observed plasma concentrations very well. Intravenous bolus injection of 1 mg/kg Δ^9-THC caused instant and pronounced high plasma levels, with a C_{max} of 327 ± 126 ng/mL. The plasma drug levels fell rapidly to an average of 73 ± 40 ng/mL at 15 min, and then to 24 ± 13 ng/mL at 2 h. After intranasal administration (10 mg/kg), detectable drug levels were not observed until the 15 min time-point. The inter-animal variability in plasma drug concentrations following the intranasal doses was similar to that observed with the intravenous dose, indicating relatively consistent absorption without increased variation from the absorption step. The formulation containing propylene glycol and 10% ethanol increased the peak plasma levels (66 ± 30 ng/mL) as compared to the formulation with only propylene glycol (49 ± 24 ng/mL), although the difference did not reach statistical significance ($p > 0.05$) (Fig. 1 and Table 1). The same effect was seen when Li et al. [17] studied the effect of ethanol and propylene glycol on the intranasal pharmacokinetics of diazepam. It was found that the peak plasma concentration of diazepam was increased after intranasal administration with increasing ethanol concentrations in the formulations (20–60%). In our studies, ethanol may have had no significant effect because a more conservative concentration was used (less than 20%). It appears that the peak plasma levels of lipophilic drugs might be controlled by changing the ethanol/propylene glycol ratios of the nasal formulations. However, this needs to be done with caution to avoid possible epithelial irritation or damage due to high concentrations of ethanol.

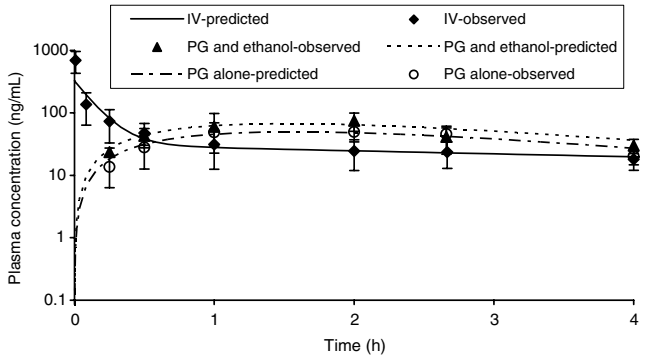

Fig. 2. Mean (±SD) Δ^9-tetrahydrocannabinol plasma concentration vs. time profiles after intranasal (10 mg/kg) ($n = 3$) and intravenous (1 mg/kg) ($n = 3$) administration in rats.

The mean observed and predicted plasma WIN55,212-2 concentration-time profiles after intranasal and intravenous administration are shown in Fig. 3. The predicted values were obtained with the same models as described for Δ^9-THC, and were a good fit for the observed concentrations. The pharmacokinetic parameters determined from these concentration-time profiles are listed in Table 1. After intravenous administration of WIN55,212-2, the C_{max} and AUC were 234 ± 186 ng/mL and 59 ± 30 ng/mL*h, respectively. The steady-state volume of distribution was high (11.08 ± 9.52 L/kg), but not as high as the more hydrophobic Δ^9-THC (32.20 ± 18.94 L/kg), as expected. The clearance (CL) was 3.38 ± 2.08 L/h. The intranasal application of the WIN55,212-2 formulations resulted in rapid and significant absorption of WIN55,212-2 from the nasal cavity compared to Δ^9-THC. The T_{max} and absolute bioavailability of WIN55,212-2 were statistically significantly different ($p < 0.05$) when compared to Δ^9-THC. There was a very sharp decline in plasma drug levels following attainment of the C_{max} in the two formulations tested, as compared to Δ^9-THC. There were no statistically significant differences in AUC, C_{max} and T_{max} between the propylene glycol-based formulation alone and the formulation containing 10% ethanol. Similarly, systemic clearance following nasal administration (5.19 ± 0.73 L/h without ethanol and 4.68 ± 1.03 L/h with ethanol) and absolute bioavailability ($49.9 \pm 6.9\%$ without ethanol and $56.6 \pm 14.1\%$ with ethanol) were comparable. Similar results were obtained for Δ^9-THC, where the presence of ethanol in the formulations had no significant effect on the pharmacokinetic parameters.

Although the T_{max} for Δ^9-THC (1.64 ± 0.23 h without ethanol and 1.52 ± 0.07 h with ethanol) was longer than expected for nasal absorption of small molecular weight lipophilic compounds, the Δ^9-THC plasma levels in the intranasal rat groups were significant and high enough to cause a pharmacologic effect [22]. However, the absolute bioavailability of Δ^9-THC after intranasal administration (6–9%) was lower than reported for Δ^9-THC smoking in humans, $18 \pm 6\%$ [2]. The increased surface area of the lungs could be the main factor responsible for higher bioavailability values following inhalation. Surprisingly, the absolute bioavailability of Δ^9-THC following nasal administration in rats was approximately equivalent to the bioavailability after oral drug administration in humans.

Table 1
Pharmacokinetic parameters of intravenous and intranasal administrations of Δ^9-tetrahydrocannabinol and WIN55,212-2 in rats

Pharmacokinetic parameter	Intravenous		Intranasal			
	Δ^9-THC	WIN55,212-2	Δ^9-THC (PG alone)	Δ^9-THC (PG/ethanol, 9:1)	WIN55,212-2 (PG alone)	WIN55,212-2 (PG/ethanol, 9:1)
AUC (ng/mL*h)	331 ± 119	58.69 ± 30.36	212 ± 79	301 ± 100*	29 ± 4	33 ± 8*
α (h^{-1})	7.17 ± 0.86	15.41± 3.27	–	–	–	–
β (h^{-1})	0.10 ± 0.03	0.37 ± 0.18	0.61 ± 0.09	0.46 ± 0.20*	1.14 ± 0.096	0.99 ± 0.17*
k_a (h^{-1})	–	–	0.62 ± 0.09	0.96 ± 0.25*	8.77 ± 1.41	9.53 ± 1.8*
$t_{1/2}$ (α) (h)	0.10 ± 0.01	0.08 ± 0.06	–	–	–	–
$t_{1/2}$ (β) (h)	7.27 ± 1.95	3.03 ± 3.22	1.11± 0.13	1.70 ± 0.59*	0.61 ± 0.05	0.71 ± 0.13*
$t_{1/2}$ (k_a) (h)	–	–	1.13 ± 0.15	0.76 ± 0.23*	0.08 ± 0.014	0.07 ± 0.013*
C_{max} (ng/mL)	327 ± 126	234 ± 186	49± 24	66 ± 30*	24 ± 4	25 ± 3*
T_{max} (h)	–	–	1.64 ± 0.23	1.52 ± 0.07*	0.27 ± 0.02	0.27 ± 0.03*
CL (L/h)	3.37 ± 1.47	3.38 ± 2.08	5.07 ± 1.90	3.60 ± 1.30*	5.19 ± 0.73	4.68 ± 1.03*
V_{ss} (L/kg)	32.20 ± 18.94	11.08 ± 9.52	–	–	–	–
F_{abs} (%)	100	100	6.4 ± 2.4	9.10 ± 3.00*	49.85 ± 6.91	56.63 ± 14.09*

Data represent means ± SD, $n = 3$. AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time of peak concentration; Δ^9- THC, delta-9-tetrahydrocannabinol; α, distribution rate constant; β, elimination rate constant; k_a, absorption rate constant; CL, clearance; F_{abs}, absolute bioavailability; PG, propylene glycol; V_{ss}, apparent volume of distribution at steady state; *, not significantly different from formulations without ethanol.

Discounting differences in species and experimental design, the lack of improved Δ^9-THC bioavailability via the nasal route seen in this study might be related to formulation issues, especially with respect to the solvent systems used. Better bioavailability may be possible through other formulation strategies that would increase the polarity of the cannabinoids or include various permeation enhancers. The increased Δ^9-THC bioavailability seen with ethanol addition is a positive encouragement for further formulation efforts. The comparatively lower bioavailability of Δ^9- THC compared to WIN55,212-2 may be ascribed to differences in polarity between the compounds. Although Δ^9-THC is more lipophilic than WIN55,212-2, this can sometimes be a disadvantage for epithelial permeation, especially in the presence of epithelial mucus and other secretions which are polar in nature.

The slow absorption of these drugs from nasal cavity might be due to the formulation in highly viscous propylene glycol together with the extreme lipophilic nature of these compounds which might interfere with the permeation of the drugs through nasal epithelium as described above. In our rat model, esophagus was ligated preventing nasal drainage into the stomach and the nasopalatine passage was closed preventing nasal drainage into the mouth, thus making it unlikely that the drugs would have been absorbed from the stomach.

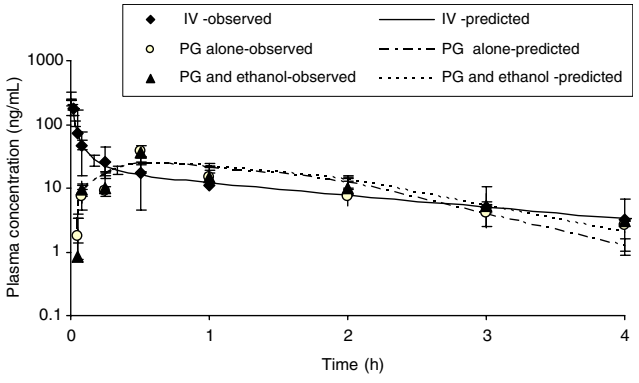

Fig. 3. Mean (±SD) WIN55,212-2 plasma concentration vs. time profiles after intranasal (150 μg/kg) ($n = 3$) and intravenous (150 μg/kg) ($n = 3$) administration in rats.

In the present study, the anesthetized rat model was used to investigate the nasal absorption of the cannabinoids. Because of the anesthetic condition, which also impairs the mucociliary clearance to some extent, the liquid formulation was in contact with the nasal mucosa for a longer period of time than would be normally expected without anesthesia. In an awake animal or human, mucociliary clearance would be more active and the absolute bioavailability might be somewhat lower than estimated when the subject is under anesthesia. However, this experimental model can still give valuable comparative bioavailabilities of Δ^9-THC and WIN55,212-2. A formulation strategy that would decrease normal mucociliary drug clearance would be required in a conscious subject, to ensure a longer contact time to get the equivalent bioavailability obtained in these anesthetized rats. The high proportion of propylene glycol used in this formulation would also be replaced with other solvents or permeation enhancers, because of the potential risks in clinical application of 100% propylene glycol formulations. Other glycols could be used, for example, polyethylene glycol could be substituted for a portion of the solvent used in this study.

4. Conclusions

The results of this study indicated that systemic delivery of cannabinoids is possible through the nasal route. Given the lipophilic nature of Δ^9-THC and WIN55,212-2, future work with respect to improving their bioavailability after nasal administration should focus on improving their aqueous solubility. Furthermore, the use of absorption

enhancers in the nasal formulations may increase the bioavailability values significantly.

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References

[1] PDR Generics, Medical Economics, second ed., New Jersy, 1996, pp. 1083–1086.
[2] A. Ohlsson, J.-E. Lindgren, A. Wahlen, S. Agurell, L.-E. Hollister, H.-K. Gillespie, Plasma delta-9-tetrahydrocannabinol concentration and clinical effects after oral and intravenous administration and smoking, Clin. Pharmacol. Ther. 28 (1988) 409–416.
[3] S.-J. Willaims, J.-P. Hartley, J.-D. Graham, Bronchodilator effect of delta-9-THC administered by aerosol to asthmatic patients, Thorax 31 (1976) 720–723.
[4] D.-P. Tashkin, S. Reiss, B.-J. Shapiro, B. Calvarese, J.-L. Olsen, J.-W. Lodge, Bronchial effects of aerosolized detla-9-THC in healthy and asthmatic patients, Am. Rev. Respir. Dis. 115 (1997) 57–65.
[5] R.-D. Mattes, K. Engelman, L.-M. Shaw, M.-A. Elsohly, Cannabinoids and appetite stimulation, Pharmacol. Biochem. Behav. 49 (1994) 187–195.
[6] W.-M. Jay, K. Green, Multiple drop study of topically applied 1% delta-9-THC in human eyes, Arch. Opthalmol. 101 (1983) 591–593.
[7] A. Arevalo-Martin, J.-M. Vela, E. Molina-Holgado, J. Borrell, C. Guaza, Therapeutic action of cannabinoids in a murine model of multiple sclerosis, J. Neurosci. 23 (2003) 2511–2516.
[8] A.-R. Gingold, N.-V. Bergasa, The cannabinoid agonist WIN55,212-2 increases nociception threshold in cholestatic rats: implications for the treatment of the pruritus of cholestasis, Life Sci. 73 (2003) 2741–2747.
[9] Q. Zhang, P. Ma, M. Isard, R.-B. Cole, W. Wang, G. Wang, In vitro metabolism of *R*(±)-[2,3-dihydro-5-methyl-3- [(morpholinyl)methyl]pyrrolo [1,2,3-de]1,4 benzoxazinyl]-(1- naphthalenyl) methanone mesylate, a cannabinoid receptor agonist, Drug Metab. Dispos. 30 (2002) 1077–1086.
[10] D.-C. Corbo, Y.-C. Haung, Y.-W. Chein, Nasal delivery of progestational steroids in overiectomized rabbits I, Progesterone-comparison of pharmacokinetics with intravenous and oral administration, Int. J. Pharm. 46 (1988) 133–140.
[11] A.-A. Hussain, S. Hirai, R. Bawarshi, Nasal absorption of propranolol in rats, J. Pharm. Sci. 68 (1979) 1196.
[12] A.-A. Hussain, S. Hirai, R. Bawarshi, Nasal absorption of propranolol from different dosage forms by rats and dogs, J. Pharm. Sci. 69 (1980) 1411.
[13] A. Pelser, D.-G. Muller, J.-D. Plessis, J.-L. Preez, C. Goosen, Comparative pharmacokinetic of single doses Doxylamine succinate following intranasal, oral and intravenous administration in rats, Biopharm. Drug Dispos. 23 (2002) 239–244.
[14] M.-A. Hussain, B.-J. Aungst, Intranasal absorption of oxymphone, J. Pharm. Sci. 86 (1997) 975–976.
[15] A.-H. Burstein, R. Modica, M. Hatton, A. Forrest, F.-M. Gengo, Pharmacokinetics and pharmacodynamics of midazolam after intranasal administration, J. Clin. Pharmacol. 37 (1997) 711–718.
[16] S. Edsbacker, K.-E. Anderson, A. Ryrfeldt, Nasal bioavailability and systemic effects of glucorticoid budesonide in man, Eur. J. Clin. Pharm. 29 (1985) 477–481.
[17] L. Li, S. Gorukanti, Y.-M. Choi, K.-H. Kim, Rapid-onset intranasal delivery of anticonvulsants: pharmacokinetic and pharmacodynamic evaluation in rabbits, Int. J. Pharm. 199 (2000) 65–76.
[18] A.-A. Hussain, L.-W. Dittert, A.-M. Qaisi, A. Traboulsi, Method for enhancement of delivery of THC by the administration of its prodrugs via the nasal route, New Millennium Pharmaceutical Research US Patent 6,380,175 (2001).
[19] A.-A. Hussain, A. Dakkuri, S. Itoh, Nasal absorption of ondansetron in rats: an alternative route of drug delivery, Cancer Chemother. Pharmacol. 45 (2000) 432–434.
[20] E. Bechgaard, S. Gizurarson, R.-K. Hjortkjaer, Pharmacokinetic and pharmacodynamic response after intranasal administration of diazepam to rabbits, J. Pharm. Pharmacol. 49 (1997) 747–750.
[21] K. Lindhardt, D.-R. Olafsson, S. Gizurarson, E. Bechgaard, Intranasal bioavailability of diazepam in sheep correlated to rabbit and man, Int. J. Pharm. 231 (2002) 67–72.
[22] M.-E. Wall, B.-M. Sadler, D. Brine, H. Taylor, M. Perez-Reyes, Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women, Clin. Pharmacol. Ther. 34 (1983) 352–363.