Pharmacokinetic Interactions of Cannabidiol and Oxycodone after oral administration in Rats

A.S. Senetra[1,2], M.A. Kuntz[1,2], S.R.R. Kanumuri[1,2], Y. Chiang[1,2], A.C. Brice-Tutt[4], N.P. Murphy[4], A.W. Bruijnzeel[5], M. Febo[5], B. Setlow[5], J.K. Neubert[4,6], C.R. McCurdy[1,2,3], A. Sharma[1,2]

[1]Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL, USA, [2]Translational Drug Development Core, Clinical and Translational Science Institute, University of Florida, Gainesville, FL, USA, [3]Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, FL, USA, [4]Department of Orthodontics, College of Dentistry, University of Florida, Gainesville, FL, USA, [5]Department of Psychiatry, College of Medicine, Gainesville, FL, USA, [6]Department of Neuroscience, College of Medicine, Gainesville, FL, USA

COLLEGE OF PHARMACY 100 YEARS 1923 UF 2023

INTRODUCTION

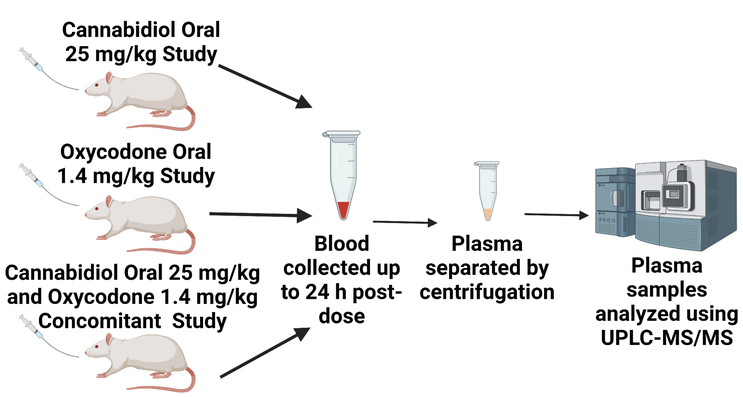
Cannabinoids and opioids share many pharmacologic properties and may act synergistically[1]. Cannabidiol (CBD) exhibits analgesic and anti-inflammatory properties, but a major concern is its potential to interact with prescription drugs, specifically, opioids[2]. Oxycodone (OXY) is a commonly prescribed opioid used to treat moderate to severe pain. Recent studies show patients using both CBD and OXY concomitantly report greater analgesia[3]. Cannabinoid consumption has been shown to cause impairment of a wide range of cognitive functions in a dose-related manner[6], along with exhibiting adverse effects in the cardiovascular, respiratory, neural, and psychological systems[7]. Due to the depressant effects of both CBD and opioids[4], co-administration of these substances can suppress the central nervous system to dangerous levels, as well as increase the risk of opioid use disorder[5]. To date, there have been no studies to assess the pharmacokinetic interactions of opioids and CBD.

OBJECTIVE

This study was performed to investigate the potential interactions of CBD and OXY in male Sprague-Dawley rats.

METHODS

A single oral dose of CBD (25 mg/kg), OXY (1.4 mg/kg), or a combination of both was administered to male rats (N=4). Blood samples were collected up to 24 h post administration. The TargetLynx™ application of MassLynx™ 4.2 was used for data processing and quantification of the UPLC-MS/MS data (Waters, Milford, MA, USA). Phoenix Version 6.4 (Certara, Princeton, NJ, USA) was used for the non-compartmental analysis. Graphpad Prism Version 8 (GraphPad Software, San Diego, CA, USA) was used to generate figures.



RESULTS

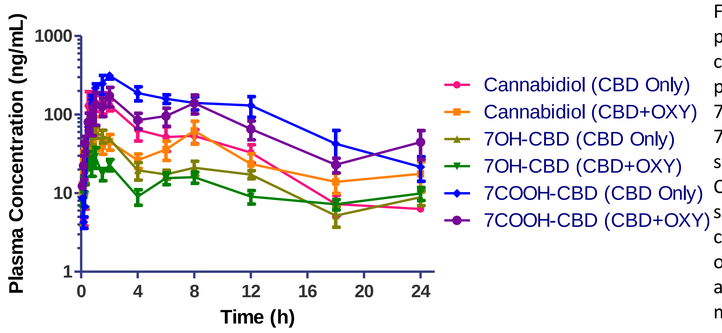


Figure 1: Mean plasma-concentration-time profiles of CBD, 7OH-CBD, and 7COOH-CBD after a single oral dose of CBD (25 mg/kg or a single oral concomitant dose of CBD (25 mg/kg) and OXY (1.4 mg/kg)

Table 1: Pharmacokinetic parameters of CBD after single oral dose of CBD (25 mg/kg) alone and concomitant with OXY (1.4 mg/kg) in male Sprague-Dawley Rats[a]

Parameter	CBD Alone	CBD + OXY
CBD		
C_{max} (ng/mL)	201.4 ± 105.3	101.1 ± 32.4
T_{max} (h)	1.2 ± 0.7	3.9 ± 3.6
AUC (h*ng/mL)	921.8 ± 267.3	698.2 ± 195.3
CL/F (L/h/kg)	26.1 ± 7.2	21.2 ± 9.5
V_z/F (L/kg)	180.7 ± 105.4	526.8 ± 361.1
7OH-CBD		
C_{max} (ng/mL)	70.3 ± 16.9	36.4 ± 10.3
T_{max} (h)	1.5 ± 0.4	2.1 ± 2.6
AUC (h*ng/mL)	3027.6 ± 766.2	2467.2 ± 498.9
AUC Ratio 7OHCBD:CBD	3.2	3.5
7COOH-CBD		
C_{max} (ng/mL)	332.5 ± 79.0	225.1 ± 72.2
T_{max} (h)	1.8 ± 0.3	3.3 ± 3.2
AUC (h*ng/mL)	21882.5 ± 9422.8	15409.9 ± 6752.8
AUC Ratio 7COOHCBD:CBD	23.7	22.1
AUC Ratio 7COOHCBD:7OHCBD	7.2	6.2

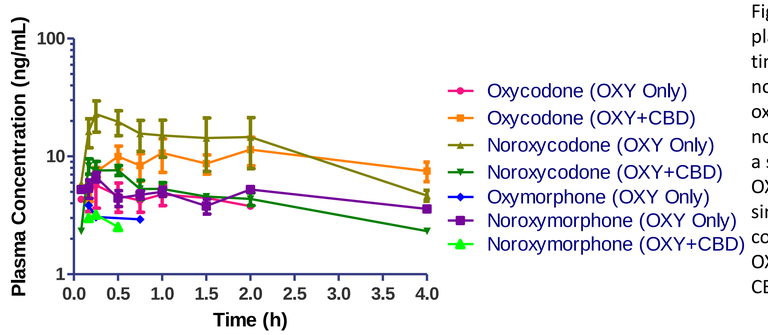


Figure 2: Mean plasma-concentration time profiles of OXY, noroxycodone, oxymorphone, and noroxymorphone after a single oral dose of OXY (1.4 mg/kg) or a single oral concomitant dose of OXY (1.4 mg/kg) and CBD (25 mg/kg)

Table 2: Pharmacokinetic parameters of oxycodone after single oral dose of OXY (1.4 mg/kg) alone and concomitant with CBD (25 mg/kg) in male Sprague-Dawley Rats[a]

Parameter	OXY Alone	OXY + CBD
OXY		
C_{max} (ng/mL)	5.9 ± 4.7	14.8 ± 4.8
T_{max} (h)	0.2 ± 0.1	2.9 ± 3.5
AUC (h*ng/mL)	25.2 ± 5.3	604.0 ± 646.7
CL/F (L/h/kg)	56.9 ± 11.9	4.7 ± 3.4
V_z/F (L/kg)	254.3 ± 141.6	141.5 ± 55.0
Noroxycodone		
C_{max} (ng/mL)	23.9 ± 14.1	8.5 ± 2.3
T_{max} (h)	0.3 ± 0.1	0.3 ± 0.1
AUC (h*ng/mL)	859.8 ± 510.0	289.2 ± 349.7
AUC Ratio Noroxycodone:OXY	34.1	0.48
Noroxymorphone		
C_{max} (ng/mL)	6.2 ± 2.2	3.2 ± 0.4
T_{max} (h)	0.3 ± 0.1	0.2 ± 0.0
AUC (h*ng/mL)	398.3 ± 452.1	0.3 ± 0.2
AUC Ratio Noroxymorphone:OXY	15.8	0.0005

[a] N = 4, values are mean ± SD; *Abbreviations*: AUC = area under the plasma concentration-time curve, Cl/F= clearance, C_{max} = peak plasma concentration, F=bioavailability fraction, V_z/F= volume of distribution, T_{max} = time to reach C_{max}

SUMMARY

- When CBD and OXY are co-administered, CBD has a 1.3-fold lower exposure (AUC), while OXY has a 24-fold higher exposure (AUC), than when administered alone
- The metabolites, 7OH-CBD, 7COOH-CBD, noroxycodone, and noroxymorphone have a 1.2-, 1.4-, 2.9-, and 1328-fold lower AUC, respectively with concomitant administration
- In addition, a delayed absorption phase for both CBD and oxycodone, is evident in rats when dosed with both CBD and OXY

CONCLUSIONS

Due to the depressant effects of both cannabidiol and opioids[4], co-administration of these substances can suppress the central nervous system to dangerous levels, as well as increase the risk of opioid use disorder[5]. These results reveal the pharmacokinetic interactions between CBD and oxycodone that could manifest as interactions at a physiological level, which may extend to other prescription opioids.

FUNDING

Funding provided by NIDA. Grant: 1R01DA049470-01A1.

REFERENCES

1. Vázquez, M., Guevara, N., Maldonado, C., Cáceres Guido, P., & Schaiquevich, P. (2020). *BioMed Research International*, *2020,* 1-9.
2. Mlost, J., Bryk, M., & Starowicz, K. (2020). *International journal of molecular sciences*, *21*(22), 8870.
3. Balachandran, P., Elsohly, M., & Hill, K. P. (2021). *Journal of general internal medicine*, 36(7), 2074–2084.
4. Rogers, A.H., Bakhshaie, J., Buckner, J.D., Orr, M.F., Paulus, D.J., Ditre, J.W., & Zvolensky, M.J. (2019). *Journal of Addiction Medicine, 13(4)*, 287-294.
5. Olfson, M., Wall, M.M., Liu, S.M., & Blanco, C. (2018). *The American Journal of Psychiatry, 175(1)*, 47-53.
6. Lorenzetti, V., Solowij, N. & Yücel, M. (2015). *Biol. Psychiatry*, *79*, 17-31.
7. Cohen, K., Weizman, A., & Weinstein, A. (2019). *Clinical Pharmacology & Therapeutics, 105(5),* 1129-1147.