In Vitro Dermal Absorption of Carfentanil

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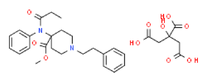
BACKGROUND

- Synthetic analogue of fentanyl
- μ-opioid agonist
- Acts on central nervous system
- One of most potent opioids in animals
- Potency in humans unknown
  - Est. 100X fentanyl; 10,000X morphine
  - Est. lethal human dose of 20 μg (0.286 μg/kg)
- Illicit drug market
  - Adulterant in heroin, cocaine, and methamphetamine
  - Among the 11,045 opioid overdose deaths reported between July 2016 and June 2017 in 10 states, 1,236 (11.2%) were positive for carfentanil[1]
- Potential exposure of law enforcement and emergency personnel
- Risk associated with dermal exposures unknown

[1]CDC, 2018. Rising Numbers of Deaths Involving Fentanyl and Fentanyl Analogs, Including Carfentanil, and Increased Usage and Mixing with Non-Opioids. Centers for Disease Control. https://emergency.cdc.gov/han/han00413.asp.

TEST MATERIAL

- Carfentanil citrate



TEST SYSTEM

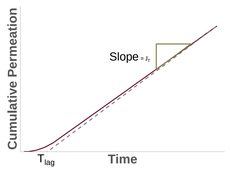
- Reconstructed human epidermal tissues (EpiDerm®, MatTek®, Ashland, MA, USA)
- Highly differentiated 3D tissue model
- Normal, human-derived epidermal keratinocytes (NHEK)
- 8-12 cell layers plus stratum corneum (basal, spinous, and granular layers)

METHODS

1. *In vitro* static diffusion cell system (Logan Instruments, Somerset, NJ, USA)
   a. Krebs Ringer buffer
   b. 37±0.1°C
   c. continuously stirred 500-600 rpm
2. Franz cells
   a. water jacketed
   b. 12 ml receiver volume
   c. 15 mm orifice
3. Carfentanil citrate dissolved in 3 vehicles:
   a. Water
   b. Ethanol
   c. Hand sanitizer (2 brands)
4. Infinite dose carfentanil exposures:
   a. 5.3 μg/ml
   b. 50.6 μg/ml
5. Caffeine as internal standard
   a. 500 μg/ml
6. Sampled 7 times over 6-hours
7. Analyzed by UPLC® with quadrupole-ion mass spectrometry

DATA ANALYSIS

1. Plotted as cumulative amount permeated over time
2. Calculated:
   a. Flux, J_T, at steady state
      $J_T = V\ dC/dt$
   b. Apparent permeability coefficient, K_p
      $K_P = J_T / A\,\Delta C$
   c. Lag-time

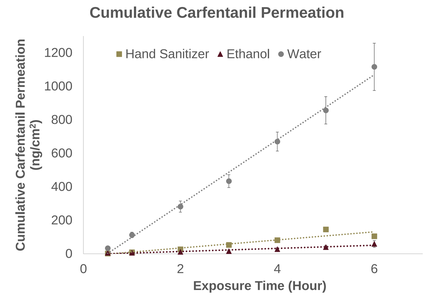


Use of alcohol-based hand sanitizers following exposure to carfentanil may not pose the degree of threat previously suspected

Small skin exposures may not result in rapid, significant toxicity as previously reported

RESULTS

1. The permeation rate was fastest for carfentanil in water, followed by hand sanitizer, and slowest for carfentanil in ethanol.
2. In both ethanol and hand sanitizer, a lag-time between exposure and permeation of approximately 1.5 hours was observed, while the lag-time in water was 30 minutes.



EpiDerm (EPI-606-X) dermal permeation assay results. Mean flux, permeability coefficient (K_p), and lag-time at 6 hours for carfentanil.

Vehicle - Test Substance	Flux (ng/cm²/hr) mean ± SD	K_p (10^{-3} cm/hr) mean ± SD	Lag time (hours) mean ± SD
Water			
Carfentanil 5.3 μg/ml	15.7 ± 3.4[a]	3.8 ± 0.9	0.7 ± 0.2
Carfentanil 50.6 μg/ml	162.1 ± 35.8[x]	3.9 ± 1.0	0.6 ± 0.1
Carfentanil - mean	**82.2 ± 79.8**	**3.9 ± 0.9[a]**	**0.6 ± 0.2[a]**
Ethanol			
Carfentanil 5.3 μg/ml	0.4 ± 0.3[b]	0.1 ± 0.1	1.5 ± 0.9
Carfentanil 50.6 μg/ml	7.0 ± 5.4[y]	0.2 ± 0.2	1.6 ± 0.3
Carfentanil - mean	**4.0 ± 5.2**	**0.2 ± 0.2[b]**	**1.6 ± 0.6[b]**
Hand Sanitizer 50.6 μg/ml carfentanil			
Carfentanil – Hand sanitizer 1	41.5 ± 8.1	1.7 ± 0.4	1.8 ± 0.2
Carfentanil – Hand sanitizer 2	20.1 ± 2.5	0.7 ± 0.1	1.1 ± 0.1
Carfentanil - mean	**30.8 ± 12.5[y]**	**1.2 ± 0.6[c]**	**1.4 ± 0.4[b]**

Vehicle means with different letters are significantly different (Tukey HSD p<0.05). For flux, letters denote comparisons made among vehicles, within carfentanil concentration.

DISCUSSION

Dermal exposure risk based on present carfentanil study compared to published fentanyl dermal risk calculations.

	absorption rate (ng/cm²/hr)	palmar surface area (cm²)	μg/min	min to lethal dose (20 μg, 2 mg)	min to analgesic dose (1 μg, 100 μg)
carfentanil water	162.1	170	0.459	44	2
carfentanil ethanol	7.0	170	0.020	994	50
carfentanil hand sanitizer 1	41.5	170	0.118	169	8
carfentanil hand sanitizer 2	19.6	170	0.056	360	18
fentanyl[2]	2500.0	170	7.083	282	14

[2]Moss et al. 2018. ACMT and AACT position statement: preventing occupational fentanyl and fentanyl analog exposure to emergency responders. Clinical Toxicology 56:297-300.

- Likely an overestimation
  - Steady state = highest flux
  - Occupational exposures = early exposure and lower flux
  - Dissolved in vehicle - ↑ absorption relative to powder
- Incidental dermal contact with carfentanil is unlikely to cause rapid, significant toxicity
- Alcohol-based hand sanitizers do not increase the absorption of carfentanil compared to when it is dissolved in water
- Hand sanitizers should not be used for decontamination because they do no remove carfentanil from the skin

FUTURE DIRECTIONS

1. Carfentanil absorption using an *in vitro* wounded skin model.
2. Carfentanil absorption following application of several military and commercially available decontamination agents.
3. Optimal timing of application of decontamination agents.