

Population Pharmacokinetics of Two Volatile Markers Used for Assessment of Definitive Adherence

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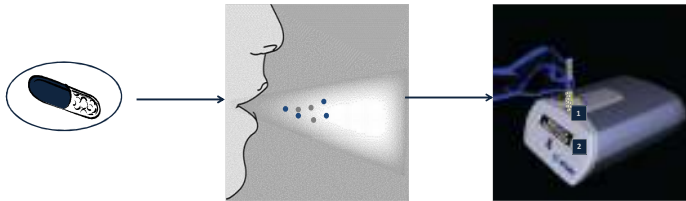
INTRODUCTION

Poor medication adherence results in pharmacokinetic variability and an increased risk for treatment failure. In practice, obtaining an accurate assessment of medication adherence is difficult and frequently employed measures (e.g., prescription fills, medication diaries) have numerous drawbacks. Methods available to determine definitive adherence (e.g., directly observed therapy) are costly and impractical for most disease states. The availability of a breath test to measure medication adherence in real-time, either at home or in a clinic, may facilitate medical decision making and improve therapeutic outcomes.

Recent studies have shown that 2-butyl acetate and 2-pentyl acetate, both safe food chemicals, are each rapidly converted to volatile alcohol and ketone metabolites which can be measured in breath.^{1,2} Both these inactive ingredients can be compounded in various dosage forms and provide an accurate assessment of medication adherence. Moreover, a validated system (Xhale, Inc., Gainesville, FL) allows for the measurement of metabolite levels using a portable, internet- and/or telephone-enabled, miniature gas chromatograph. The goal of the analyses described herein was to conduct a pharmacokinetic analysis for these volatile markers and their metabolites in breath.

METHODS

- Five fasting, healthy subjects were administered a size zero hard gel capsule (Capsugel, Inc., Greenwood, SC) containing 2-butanol (60 mg), 2-pentanone (60 mg), and L-carvone (30 mg) on six different occasions (replicates). Subjects directly exhaled into a miniature gas chromatograph (Xhale, Inc., Gainesville, FL), which requires only 10 ml of human breath for analysis. Breath concentrations of 2-butanone and 2-pentanone were determined at 0, 5, 10, 15, 20, 30, 45, and 60 minutes post-ingestion of the capsule. The study was approved by the Western Institutional Review Board (Olympia, WA).
- Breath concentrations of 2-butanone and 2-pentanone were measured in "real-time" using a miniature gas chromatograph (Xhale, Inc., Gainesville, FL, USA).



- Analyte breath concentrations reported in parts by billion (ppb) were converted to ng/ml by multiplying each concentration by the molecular weight of the respective molecule. All results presented herein are reported in $\mu\text{g/ml}$ units.
- A population pharmacokinetic analysis was conducted to describe the inter- and intra-individual variability, as well as the inter-occasion variability using the software NONMEM (Version 7.2, Icon Development Solutions, Ellicott City, Maryland). A one-compartment body model with first-order absorption and elimination was fitted to the data for both metabolites. All models were fitted using a first-order conditional estimation method with interaction. Perl-speaks-NONMEM (PsN, Version 3.4.2) was used for NONMEM submission and for generation of visual predictive checks, while Wings for NONMEM (Version 720) facilitated bootstrapping of the final model.³ Last, the lattice and Xpose packages in the software R (Version 2.12.2) were used for generation of graphics and for model diagnostic purposes.⁴

RESULTS

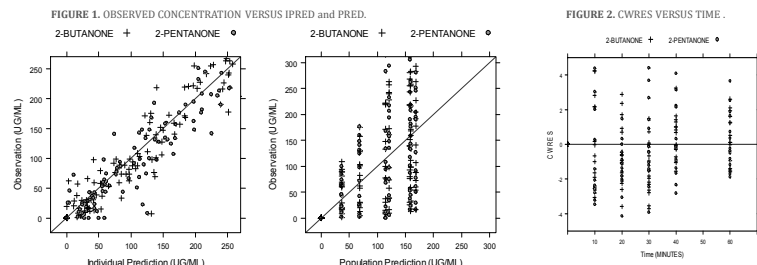


TABLE 1. POPULATION PARAMETER ESTIMATES FROM FINAL MODEL AND BOOTSTRAP ANALYSIS.

PARAMETER AND MODEL	2-BUTANONE		2-PENTANONE	
	ESTIMATE (SD SCALE) ± SE FROM FINAL MODEL	BOOTSTRAP ESTIMATE (95% CI) ^a	ESTIMATE (SD SCALE) ± SE FROM FINAL MODEL	BOOTSTRAP ESTIMATE (95% CI) ^a
STRUCTURAL MODEL				
K1 (MIN ⁻¹)	0.129 ± 0.043	0.133 (0.065-0.253)	0.078 ± 0.017	0.076 (0.049-0.113)
K2 (MIN ⁻¹)	0.035 ± 0.008	0.035 (0.007-0.062)	0.061 ± 0.020	0.066 (0.039-0.110)
V (L) ^b	0.150 ± 0.017	0.177 (0.119-0.329)	0.193 ± 0.038	0.202 (0.159-0.265)
VARIANCE MODEL				
ω^2 (K1)	0.543 (73.7%) ± 0.307	0.546 (0.003-0.886)	0.319 (56.5%) ± 0.235	0.484 (0.003-0.702)
ω^2 (K2)	0.152 (39%) ± 0.137	0.458 (0.003-1.631)	0.15 (38.7%) ± 0.118	0.268 (0.003-0.595)
IOV (K1)	0.077 (27.7%) ± 0.643	0.283 (0.113-0.545)	0.132 (36.3%) ± 0.096	0.370 (0.199-0.541)
IOV (K2)	0.387 (62.2%) ± 0.203	0.709 (0.394-1.435)	0.733 (85.6%) ± 0.294	0.864 (0.401-1.530)
RESIDUAL ERROR (UG/ML)	19.1 ± 4.4	18.5 (10.6-26.6)	19.2 ± 3.02	18.8 (12.6-24.3)

^a2-BUTANONE: 1,000 runs; 98.8% of runs with successful minimization; 53.5% of runs with successful covariance step.

^b2-PENTANONE: 1,000 runs; 98.3% of runs with successful minimization; 64.3% of runs with successful covariance step.

^cNo physiological meaning as drug concentrations were measured in breath.

FIGURE 3. INDIVIDUAL PLOTS FOR 2-BUTANONE.

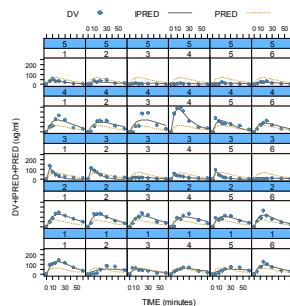


FIGURE 4. INDIVIDUAL PLOTS FOR 2-PENTANONE.

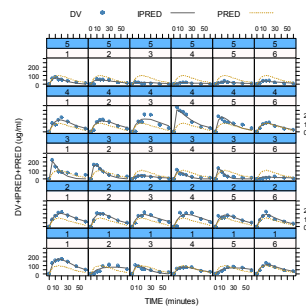


FIGURE 5. VISUAL PREDICTIVE CHECK FOR BUTANONE.

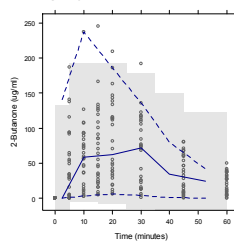
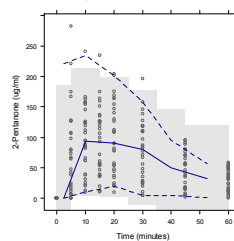


FIGURE 6. VISUAL PREDICTIVE CHECK FOR PENTANONE.



CONCLUSIONS

The results of this pilot study show that 2-butanone and 2-pentanone could be quantified in breath following oral administration. A one-compartment body model with first-order absorption and elimination described the pharmacokinetic data well. The availability of a validated method which uses a portable device for detection of these volatile markers can allow for a real-time assessment of medication adherence.

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