Development of a Mathematical Model for Detecting Hydrocodone Concentrations in Interstitial Fluid with Continuous Glucose Monitors

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ABSTRACT

This brief communication outlines a study of how combination opioids distort continuous glucose monitor (CGM) data readings. The glucose data collected by certain CGMs can be predictably distorted by hydrocodone/acetaminophen combinations, leading to the development of a mathematical model that can be used to determine the concentration of these metabolites within a patient's interstitial fluid (ISF). This research contains an analysis of published clinical data to develop the governing equations and validate the accuracy of the results within a 9% error. The resulting equations provide a basis for accurately detecting opioid concentrations in real time.

Keywords:
Opioid Monitoring, Hydrocodone, Combination Opioids, Continuous Glucose Monitors

INTRODUCTION

It is widely known that acetaminophen (APAP) can interfere with data collection of a continuous glucose monitoring (CGM) system, leading to erroneously high glucose readings [1,2,3]. Advances in CGM technology have taken such distortion into account, in order to output more accurate data for patient glucose levels [1,3]. Considering that the distortion effect is also present with opioid medications that include APAP as an ingredient, it is important to model the impact of such medications on the CGM readings of commercially-available CGM technology.

CGM monitoring systems operate by measuring the glucose concentration in the subcutaneous tissue by utilizing a needle electrode to exploit the glucose-oxidase reaction [4]. However, the presence of acetaminophen in a patient's system causes an interference with the patient's glucose monitor readings because of its

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interference with such reaction [5,6]. While this has long been considered a flaw in CGM technology, the advent of CGM sensors that are impervious to such interference opens the possibility for this phenomenon to be utilized for medication detection.

Studies investigating the APAP CGM distortion effect in novel CGM sensing technologies have shown that the latest cutting-edge technology exhibits insignificant distortion effects due to APAP [1]. While this is a favorable development for diabetic patients using CGM to control insulin intake, such technology also opens the possibility of this effect being harnessed for medication monitoring, particularly in the field of opioid monitoring. If the effect can be measured in real time, then it is possible for an algorithm to be developed that will determine the concentration of APAP in a patient's system, especially when compared to CGMs that exhibit a significant distortion effect.. Results of a research study suggest that such a model is able to reliably describe the mean APAP effect on CGM measurements [6].

Therefore, by measuring the effect of APAP on CGM readings, it is possible to derive the concentration of APAP present in a patient's system. Combination medications, such as vicodin or percocet, contain a combination of APAP and a high-strength opioid pain reliever [7]. The combination medication containing hydrocodone and APAP is the most commonly prescribed opioid, and also one of the most commonly prescribed medications in the United States [7,8,9,10]. Opioids have a high potential for addiction, so it is important to ensure that dosing is tightly controlled [10]. Therefore, it is important to develop methods to monitor the use of opioid combination pharmaceuticals that contain APAP. By understanding the disposition relationship between the active opioid ingredient and the APAP in a combination medication, it is possible to make better treatment decisions and detect opioid use patterns in at-risk patients.

APPROACH

The primary goal of this research is to investigate the phenomena of APAP-dependent CGM reading distortion and to develop a mathematical model to determine the plasma concentration of APAP with a measured distortion for further extension toward opioid detection. To obtain this goal, the researchers examined clinical plasma concentration data for APAP and glucose, as well as the associated CGM readings after administration of a single 1 gram dose of APAP [11]. This algorithm was developed using an analysis of this data containing actual glucose values from a calibrated glucometer contrasted with distorted CGM readings from the Medtronic (Minneapolis, MN) Sof-Sensor, and Dexcom (San Diego, CA) Seven Plus alongside measured APAP concentrations [5].

Using this clinical data, a relationship between APAP and glucose distortion was calculated for the two types of CGM sensors. Interpolant curve fitting was used to generate an equation for each sensor in the form of Equation 1 to develop algorithms for predicting the amount of APAP present in patients' plasma and interstitial fluid (ISF) based on each CGM sensor's glucose reading and the experimentally predetermined distortion amount by the sensor after ingestion of 1g of APAP. These values at specific intervals in time were used in order to develop a prediction curve for the concentration of APAP over time. The derived prediction was compared to a known APAP disposition curve to evaluate the accuracy of the mathematical model. These equations were further tested for accuracy against the clinical data for APAP concentrations [11]. The output of these equations represents the concentration of APAP in a patient's ISF.

RESULTS

In Equation 1, b_1, b_2, and b_3 represent experimentally determined constants. A represents the actual blood glucose reading (in mg/dl), and B is the measured value of the blood glucose obtained by the CGM in question. Finally, C is the mathematically determined APAP concentration (in µg/dl).

Equation 1. $$b_1A + b_2B + b_3 = C$$

Numerical values for each of the constants were determined and used to generate a predictive model of the concentration of APAP in ISF. The mathematical model for APAP based on the Medtronic Sofsensor is shown as the dashed line in Figure 1 below. The model is visibly inaccurate before medication reaches its peak concentration around 150 minutes after the administration of the initial dose of medication. The accuracy of the mathematical model improves substantially after this point, making it possible to detect the concentration of APAP with an error of only 9% between 3-6 hours after the initial dose.

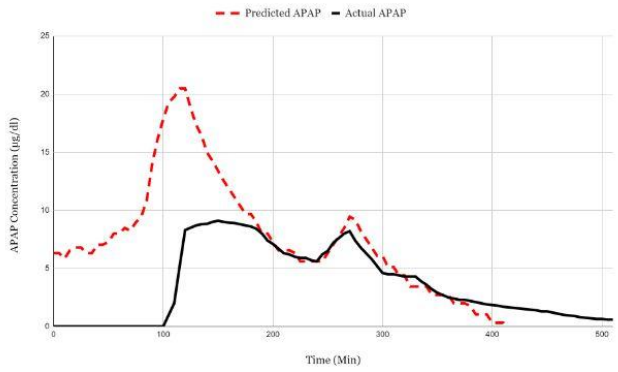

Figure 1. Medtronic Sofsensor Predicted APAP vs. Actual APAP Concentration

Examining the mathematical model of APAP concentrations using the Dexcom Seven Plus in Figure 2, the sensors are accurate within a similar range to the Medtronic Sofsensor, with an average error of 12% between 3-6 hours after the initial dose.

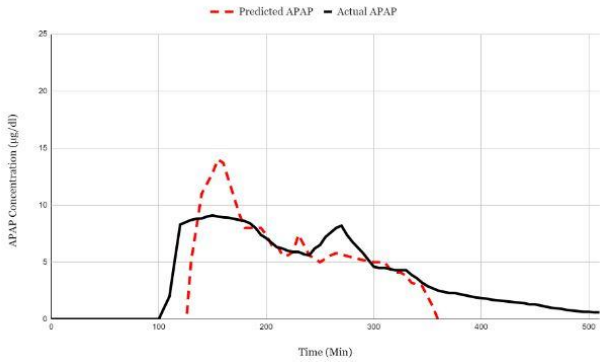

Figure 2. Dexcom Seven Plus Predicted APAP vs. Actual APAP Concentration

An additional step was required to determine the concentration of hydrocodone present in the patient's system at any given time. This is accomplished due to the combination of hydrocodone with APAP in known ratios in medically-available opioid medications, such as Vicodin. Another important consideration is the rate of decay and metabolic differences between APAP and hydrocodone. Despite being administered in combination, each component undergoes its own metabolism with a separate disposition curve. The relationship between the two must be known in order to accurately calculate concentrations of hydrocodone based on the amount of APAP present. It should be noted that both APAP and hydrocodone reach their peak concentrations at approximately the same time after administration [12,13]. For this study, a single 22.5/975 mg dose of immediate release (IR) combination hydrocodone bitartrate (HB)/APAP was used to determine the rate of decay of both components.

The rate of decay following the peak of each component medication reveals some differences that must be considered when developing governing equations to describe the relationship between the metabolization of these two medications. Using the calculated APAP concentration and the pre-existing dosage ratios between APAP and hydrocodone in medication

in order to determine the hydrocodone concentration at a given point in time, it was found that the relationship between the rates of decay between the two medications can be approximated by a constant, α. It is also critical to include the ratio of APAP to hydrocodone, as several formularies are commercially available. This ratio is represented by the symbol φ in Equation 2. Combining this research into a single equation to determine the concentration of hydrocodone, H, in a patient's ISF in real time, Equation 2 is presented.

Equation 2. $$\alpha\varphi\left(b_1 A + b_2 B + b_3\right) = \mathrm{H}$$

This equation allows for accurate detection of hydrocodone concentrations with the input of glucose data from a CGM and a glucometer

DISCUSSION

The research herein reveals a model that can be used to determine the plasma concentration of APAP in a patient. This principle can be extended to accurately determine the concentration of medications that are co-administered with APAP and/or have APAP as a primary ingredient in the formulation. Through Equation 2, the concentration of hydrocodone co-administered with APAP is determined. Because this process was built into a mathematical formula, it is possible that, with proper inputs, software can be developed to detect the opioid concentration in real time. This software could then be utilized to determine more accurate dosing for patients taking combination opioids.

This study is limited by the fact that the formulae utilized for this model are applied against retrospective data and not validated against prospective data. Also, the formulae are dependent on data from specific sensor types and patient population(s) utilized within original studies. As such, it's possible that these formulae may not be applicable to all populations. While we acknowledge, also, that the method may not be applicable to all sensor types, we believe that the method and formulae can be revised to account for sensor-specific differences if/when said sensors meet certain criteria.

Future work on this topic will include a qualitative study to determine the approximate quantity and timing of doses in patients taking combination prescription opioids. Future work could also include a quantitative analysis using calculated expected serum opiate concentration based on patient characteristics like height, weight, sex, etc. for further validation of this method and improvement of the results to be more adaptable to individual patient metabolisms.

Future analysis and optimization of Equation 2 will allow for the development of real-time opioid monitoring software. Additionally, the accurate real-time monitoring of hydrocodone in a patient's interstitial fluid could be further integrated into a fully-automated opioid delivery system.

REFERENCES

1. Calhoun P, Johnson TK, Hughes J, et al.: Resistance to Acetaminophen Interference in a Novel Continuous Glucose Monitoring System. *Journal of Diabetes Science and Technology*. 2018; 12(2):393-396.

2. Maahs DM, DeSalvo D, Pyle L, et al.: Effect of Acetaminophen on CGM Glucose in an Outpatient Setting. *Diabetes Care.* 2015; 38(10):e158–e159.

3. Zhang Y, Hu Y, Wilson GS, et al.: Elimination of the Acetaminophen Interference in an Implantable Glucose Sensor. *Analytical Chemistry.* 1994; 66(7):1183–1188.

4. McGarraugh G: The Chemistry of Commercial Continuous Glucose Monitors. *Diabetes Technology & Therapeutics*. 2009; 11(Supplemental):S17-24.

5. Basu A, Slama MQ, Nicholson WT, et al.: Continuous Glucose Monitor Interference with Commonly Prescribed Medications: a Pilot Study. *Journal of Diabetes Science and Technology.* 2017; 11(5):936–941.

6. Schiavon M, Acciaroli G, Vettoretti M, et al.: A Model of Acetaminophen Pharmacokinetics and its Effect on Continuous Glucose Monitoring Sensor Measurements. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society.* 2018; 1:159-162.

7. Singla A, Sloan P: Pharmacokinetic evaluation of hydrocodone/acetaminophen for pain management. *Journal of Opioid Management.* 2013; 9(1):71-80.

8. Fuentes AV, Pineda MD, & Nagulapalli Venkata KC: Comprehension of Top 200 Prescribed Drugs in the US as a Resource for Pharmacy Teaching, Training and Practice. *Pharmacy.* 2018; 6(2):43.

9. ClinCalc: Top 300 Drugs. Available at *https://clincalc.com/DrugStats/Top300Drugs.aspx*. Accessed July 7, 2022.

10. Habibi M, Kim PY: Hydrocodone and Acetaminophen. In *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing, 2022.

11. Basu A, Veettil S, Dyer R, et al.: Direct Evidence of Acetaminophen Interference with Subcutaneous Glucose Sensing in Humans: A Pilot Study. *Diabetes Technology & Therapeutics.* 2018; 18(Suppl 2): S243-S247.

12. Devarakonda K, Kostenbader K, Giuliani MJ, et al.: Single- and multiple-dose pharmacokinetics of biphasic immediate-release/extended-release hydrocodone bitartrate/acetaminophen (MNK-155) compared with immediate-release hydrocodone bitartrate/ibuprofen and immediate-release tramadol HCl/acetaminophen. *Journal of Pain Research.* 2015; 8:647-656.

13. Yue Y, Liu DJ: Selection of 12‐Hour Sustained‐Release Acetaminophen (Paracetamol) Formulation Through Comparison of Pharmacokinetic Profiles of 4 Sustained‐Release Prototype Formulations and Standard Acetaminophen Formulation. *Clinical Pharmacology in Drug Development.* 2017; 7(12):87-94.