Modeling Effects of Exenatide on the Pharmacokinetics of Acetaminophen, Digoxin, and Warfarin

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Objectives

Exenatide, a 39-amino acid peptide used for treatment of type 2 diabetes, is known to inhibit gastric emptying and as a result to alter the absorption of orally administered concomitant medications. After subcutaneous administration, exenatide is rapidly absorbed, usually reaching peak concentrations 2 hours postadministration. It is eliminated renally with a 2.5 hr half-life. The aim of our study was to build a model of delayed gastric emptying caused by exenatide that could be applied to any drug co-administered with it, and would allow predicting its effect on the drug's pharmacokinetics.

Methods

GastroPlus™ (Simulations Plus, Inc.) was used to build absorption models for acetaminophen, digoxin, and warfarin. ADMET Predictor™ (Simulations Plus, Inc.) was used to predict human intestinal permeability for the studied compounds. Internal Roche data for warfarin and digoxin, and literature data for acetaminophen were used to construct absorption models for these drugs. Published studies of exenatide effect on all the three compounds were used to simulate this effect using GastroPlus.

Results

A Weibull Function representing a gastric release profile with a two-hour time lag, together with two-hour stomach retention time, provided a quick and reasonable estimation of changes in C_{max}, T_{max} and AUC observed for digoxin and warfarin when co-administered with exenatide; however, it did not account for the small release of the stomach contents prior to two hours. The best simulation of the Cp-time curves after exenatide administration was achieved with a hypothetical release profile that included slower release (~ 20 % at 2.5 hrs) of the drug from stomach for the first 2.5 hrs, and after that time, regular release from the stomach dictated by the drug's dissolution. The same result could be achieved by using 7 hrs stomach transit time for the first 2.5 hrs, and then standard stomach transit time after that. Unlike warfarin and digoxin, acetaminophen was administered as an oral solution. In order to simulate the exenatide effect on pharmacokinetics of this drug, increasing the stomach transit time to 7 hr for the first 2 hrs and to 2.5 hrs after that time produced an almost perfect match to the Cp-time profile observed for acetaminophen when exenatide was injected 1 hr before. When exenatide was injected 2 hrs before acetaminophen's administration, stomach transit time of 5 hrs for the first hour and 1.75 hrs after that allowed to simulate the experimental plasma concentration of acetaminophen.

References

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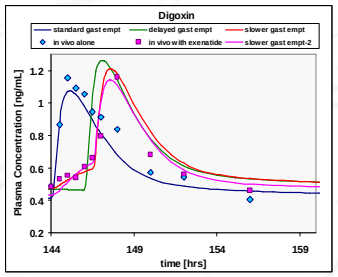
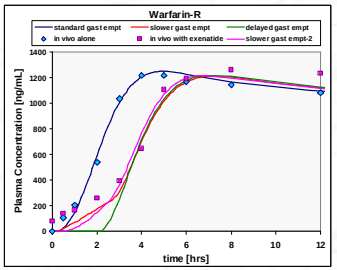
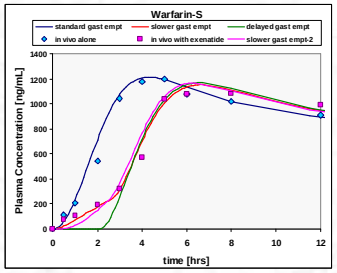


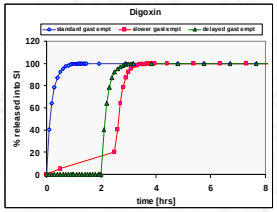
Exenatide effect on the C_p- time profile of 0.25 mg oral dose of digoxin.



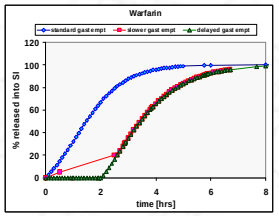
Exenatide effect on the C_p- time profile of 0.25 mg oral dose of R-warfarin.



Exenatide effect on the C_p- time profile of 0.25 mg oral dose of S-warfarin.

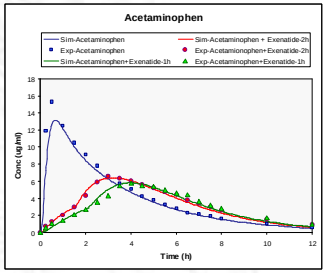


Gastric release profiles used in simulations in order to account for the exenatide effect on digoxin: immediate release with standard gastric emptying, 2 hrs delayed gastric emptying, and slower gastric emptying for the first 2.5 hrs.



Gastric release profiles used in simulations in order to account for the exenatide effect on warfarin: immediate release with standard gastric emptying, 2 hrs delayed gastric emptying, and slower gastric emptying for the first 2.5 hrs.

Drug	Dose time after Exenatide (h)	Slow Phase Length (h)	STT Phase I (h)	STT Phase II (h)
Digoxin	0.5	2.5	7	0.25
Warfarin	0.5	2.5	7	1
Acetaminophen	1	2	7	2
Acetaminophen	2	1.5	5	1.75



Exenatide effect on the absorption profile of 1000 mg oral acetaminophen administered as a solution 1 hr and 2 hrs after exenatide injection. As in the case of Digoxin and Warfarin, two different stomach transit times were necessary in order to simulate the exenatide effect on acetaminophen.

Conclusions

- It was not possible to build one model that could simulate the exenatide effect on all three drugs' pharmacokinetics. This is due to different physicochemical properties, formulations, and dissolution profiles of these compounds.
- The models generated for the studied drugs provided an insight into exenatide's mechanism of inhibiting stomach emptying. They revealed that the stomach transit time is significantly slowed for about the first 2.5 hrs after exenatide injection and returns to normal function after that time. This was not valid for acetaminophen, in which case the stomach transit time decreased after the exenatide effect ceased but did not appear to return to the standard value.
- A Weibull function with a two-hour lag time and a time scale equal to the time needed to dissolve 50% of the dose gave a reasonable prediction of the exenatide effect for drugs given as tablets or capsules.
- For Digoxin and Warfarin, a specially constructed controlled release profile that included a slow release (~ 20%) of the drug from the stomach for the first 2.5 hrs, and after that a Weibull Function representing the standard dissolution curve of the drug, provided the best simulations of the exenatide effect. The same good results could be obtained with two stomach transit times: 7 hrs for the first 2.5 hrs and the standard STT after that time.

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