Transdermal Exenatide Delivery in Patients with Type 2 Diabetes: Pharmacokinetic and Pharmacodynamic Evaluation

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Abstract

Objective:
Exenatide, a GLP-1 receptor agonist administered twice daily (BID) via subcutaneous (SC) injection, improves glycemic control, often with associated weight reduction. This double-blind, placebo controlled, 3-period, 3-treatment study evaluated the pharmacokinetics and pharmacodynamics of exenatide transdermal patch (TDP), placebo TDP, and exenatide SC (10 mcg BID). Meals were given 3, 7, and 13 hours after TDP application and the patch was removed after 24 hours. SC exenatide was administered before the breakfast and dinner meals. Blood samples were collected for plasma exenatide and glucose concentrations throughout the study.

Result:
With exenatide TDP, mean peak concentrations of 301 pg/mL were achieved at 19 hours and minimal efficacious concentrations (>50 pg/mL) were maintained for 21 hours. Significant reduction in postprandial glucose (PPG) was observed mainly after lunch and dinner when the exenatide plasma concentrations were at therapeutic concentrations. Glucose AUC(0-24h) was reduced by 31.6% for exenatide TDP compared to placebo. Exenatide TDP was generally well-tolerated with no serious adverse events (AEs) or hypoglycemic events. The most frequent AEs with exenatide TDP were nausea, headache, and vomiting.

Conclusion:
This data showed that exenatide administered by the transdermal route resulted in sustained therapeutic plasma exenatide concentrations and postprandial glucose lowering in patients with type 2 diabetes.

Introduction

- Exenatide, a GLP-1 receptor agonist administered twice daily (BID) via subcutaneous (SC) injection, has been demonstrated to improve glycemic control, often with associated weight reduction.[1]
- A once-daily transdermal exenatide patch is designed to provide sustained exenatide concentrations in patients with type 2 diabetes.
- The exenatide patch utilizes the microporation technology developed by Altea Therapeutics (PassPort® System) that enables transdermal delivery by creating aqueous microchannels through the stratum corneum into the viable epidermis.
- The Exenatide PassPort® System is a drug-device combination product designed to be used by patients with type 2 diabetes (see Fig 1).

Objective

This double-blind, placebo controlled, 3-period, 3-treatment study evaluated the pharmacokinetics/ pharmacodynamics (PK-PD) and safety of the exenatide transdermal patch (TDP) in subjects with type 2 diabetes.

Fig. 1 Exenatide PassPort® Transdermal Delivery System

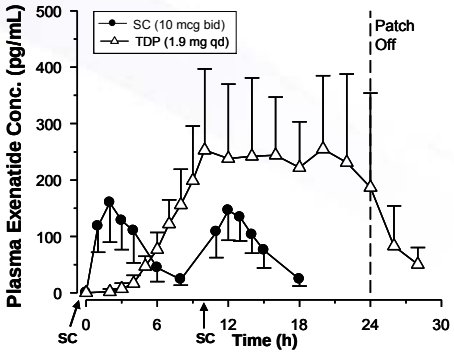

Fig. 2 Transdermal exenatide (mean +SD) vs. SC exenatide (mean –SD) clinical PK

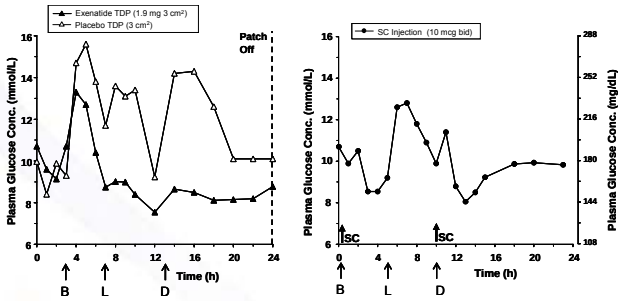

Fig. 3 Transdermal exenatide clinical pharmacodynamics (mean plasma glucose concentration). Meals marked for breakfast (B), lunch (L), dinner (D) and SC injections marked (SC).

Methods

- This Phase 1 study was a PK-PD study involving three treatments: an active exenatide patch, a placebo patch, and subcutaneous injection (SC) in a 3-way crossover study
- Subjects were randomly assigned to one of three treatment sequences (Table 1).
- Eleven patients with type 2 diabetes were enrolled and 9 subjects completed the study (Table 2).
- On separate days, subjects received a single dose of exenatide TDP (1.9 mg exenatide, 3 cm^2, 120 microchannels/cm^2), placebo TDP (3 cm^2, 120 microchannels/cm^2) or exenatide SC (10 mcg BID Byetta®).
- The investigator and subject were blinded to exenatide/placebo TDP content. The placebo TDP had the same excipient composition as the exenatide TDP and did not contain exenatide. The placebo TDP was used as a control to assess skin responses to the patch independent of exenatide exposure.
- Standardized breakfast, lunch and dinner meals were provided. For TDP, meals were given after application (3, 7, 13 h) and the patch was removed after 24 h. For SC, meals were given at 0, 5, 10 h and injections were administered just prior to breakfast and dinner. The washout prior to subsequent treatments was 24 h after patch removal and 14 h after the last SC injection.
- The skin response to the patch was evaluated by visual scoring (modified Draize scale) and transepidermal water loss (TEWL) measurements.
- Blood samples were collected for determination of plasma exenatide and glucose concentrations throughout the study. Exenatide concentrations were determined by a proprietary Enzyme-Linked Immunosorbent Assay (ELISA) (LLOQ 10 pg/mL). Plasma glucose was determined by assay on a Roche Modular Analyzer (hexokinase enzymatic method).
- Pharmacokinetic parameter estimates for exenatide and glucose concentrations were calculated by standard noncompartmental methods of analysis using WinNonlin Enterprise 5.0.1

Table 1 Treatment Sequences

Sequence	N	Day 1	Day 2 or 3	Day 4 or 5
1	3	Exenatide TDP	Placebo TDP	SC
2	3	Placebo TDP	SC	Exenatide TDP
3	3	SC	Exenatide TDP	Placebo TDP

Table 2 Subject Demographics

DEMOGRAPHICS	
N	9 patients with T2DM
Gender/Race	7 male 2 female 5 Caucasian 4 African-American
	Mean ± SD (range)
BMI	33.2 ± 3.8 kg/m^2 (26.2 - 37.6)
Age	49 ±14 years (28 - 64)
HbA1c	8.2 ± 1.0% (6.9 - 9.4)
FPG	157.4 ± 66.5 mg/dL
Duration of T2DM	6 ± 3 years

Results & Discussion

- After a single dose exenatide patch application, plasma exenatide concentrations increased gradually for 10 hours reaching a Cmax of 301 pg/mL. On average, plasma concentrations were sustained at approximately 250 pg/mL until the patch was removed at 24 hours (Fig 2).
- Plasma exenatide concentrations were maintained above 50 pg/mL for 21 hours (median) with a range of 14-25 h (Fig 2). A The minimum effective plasma exenatide concentration required for a glucose lowering effect is 50 pg/mL.[2]
- The pharmacokinetic-pharmacodynamic relationship followed a direct response relationship with changes in plasma glucose concentrations relating to changes in exenatide concentrations (See Figs 2 & 3). As expected, for the placebo patch, there were postprandial glucose excursions after the standardized breakfast, lunch, and dinner meals were given. For the SC injection, the administration of AM and PM doses of 10 µg SC prior to mealtime resulted in a suppression of the postprandial glucose profile associated with breakfast and dinner. In comparison, the exenatide patch caused substantial postprandial glucose reductions after lunch and dinner when the exenatide concentrations reached therapeutic concentrations but only had a slight reduction of plasma glucose after breakfast.
- Glucose concentrations AUC(0-24h) were reduced by 31.6% for exenatide TDP and 25.6% for SC compared to placebo.
- The relative bioavailability of the exenatide patch compared to the 10 mcg SC injection treatment was approximately 3% using a patch formulation that was not optimized for bioavailability.

Table 3 Transdermal Exenatide & SC Clinical PK

Pharmacokinetic parameter	SC (am dose)	Exenatide TDP
Dose (µg)	10	1920
N*	8	8
T_{lag} (h)	NA	3.0 (1.0 - 4.0)
C_{max} (pg/mL)	153 (48)	301 (67)
T_{max} (h)	2.0 (1.9 – 2.9)	18.9 (9.9 - 23.9)
C_{last} (pg/mL)	15.9 (34)	24.4 (79)
T_{last} (h)	8.0 (5.9 – 10.0)	29.0 (25.8 – 35.8)
AUC_{0-last} (pg•h/mL)	606 (53)	4040 (59)
Time > =50 pg/mL (h)	3.0 (1.0 – 5.0)	21.0 (14.0 – 25.0)
Bioavailability	NA	3.0%

Notes: Values for exenatide concentration parameters presented as geometric mean (CV%)
Values presented for time parameters are median (range)
*8 of 9 completed subjects analyzed; one subject had no exenatide concentrations for SC or patch treatments.

- Single transdermal doses of exenatide were safe and generally well tolerated by subjects with type 2 diabetes when administered for 24 hours in this study. The most frequently reported drug-related adverse events were nausea, headache and vomiting with. exenatide TDP demonstrating a higher incidence than SC injection due to the higher plasma exenatide concentrations achieved. In some subjects, there was mild transient erythema at the application site seen after patch removal.
- The skin response as measured on a modified Draize scale and skin barrier function as measured by TEWL were similar between the sites treated with placebo and exenatide TDP indicating that the mild erythema was primarily due to the process of creating micropores in the stratum corneum.

Table 4 Adverse Events Summary

	Frequency of Adverse Events Number of Adverse Events [Number of Subjects with Adverse Events]		
MedDRA preferred term	TDP Placebo (N=9)	TDP Exenatide (N=11)	SC Exenatide BID (N=10)
Nausea	1 [1]	9 [7]	5 [4]
Headache	1 [1]	7 [6]	2 [2]
Vomiting	0 [0]	8 [5]	1 [1]
Application site pruritis	2 [1]	1 [1]	0 [0]
Dizziness	0 [0]	1 [1]	2 [1]
Abdominal pain	0 [0]	2 [2]	0 [0]
Abominal pain (upper)	0 [0]	2 [2]	0 [0]
Eructation	0 [0]	2 [2]	0 [0]
Application site pain	1 [1]	0 [0]	0 [0]
Application site reaction	1 [1]	0 [0]	0 [0]
Overall Total	6 [4]	32 [10]	10 [4]

Abbreviations: BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects studied; SC = subcutaneous; TDP = Transdermal Patch

Conclusion

This study showed that exenatide can be administered by the transdermal route resulting in sustained therapeutic plasma exenatide concentrations and postprandial glucose lowering in patients with type 2 diabetes.

References

1. Byetta® label; http://pi.lilly.com/us/byetta-pi.pdf
2. Fineman, M, et al., *Clinical Pharmacokinetics*. 2011; 50(1):65-74.

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