Dose–Response Relationship of an Oral Insulin Spray in Six Patients with Type 1 Diabetes: A Single-Center, Randomized, Single-Blind, 5-Way Crossover Study

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ABSTRACT

Objective: This study evaluated the pharmacokinetic and pharmacodynamic properties and dose–response effects of an oral insulin spray formulation compared with those of subcutaneously injected regular insulin and placebo in patients with type 1 diabetes mellitus.

Methods: This was a single-center, randomized, single-blind, open-label, 5-way crossover study in which patients with type 1 diabetes received 5, 10, and 20 puffs of the oral insulin spray; regular insulin 0.1 U/kg SC; and placebo spray. The pharmacokinetic parameters of interest were the maximum serum insulin concentration (Ins-C_{max}); the incremental insulin AUC from 0 to 120 minutes (Ins-$AUC_{0–120}$), from 0 to 240 minutes, and from 0 to 360 minutes; and the time to maximum serum insulin concentration (Ins-T_{max}). The pharmacodynamic parameters of interest were the maximum glucose infusion rate (GIR_{max}); the incremental glucose AUC from 0 to 120 minutes (GIR-$AUC_{0–120}$), from 0 to 240 minutes, and from 0 to 360 minutes; the time to maximum GIR (GIR-T_{max}); the time to early half-maximal GIR (early T50%); and the time to late half-maximal GIR (late T50%). Pharmacokinetic and pharmacodynamic parameters were assessed using the euglycemic clamp technique.

Results: The study enrolled 6 white men with type 1 diabetes (mean [SD] age, 37.5 [16.2] years, mean weight, 82.7 [17.0] kg). Ins-T_{max} was shorter for 5, 10, and 20 puffs of oral insulin spray than for SC insulin (26.7 [13.7], 29.2 [7.4], 23.3 [5.2], and 142.5 [73.2] min, respectively; $P < 0.05$). There was no effect of dose on Ins-T_{max}. The Ins-$AUC_{0–120}$ for 5, 10, and 20 puffs of oral insulin spray (304.8 [277.9], 689.2 [353.0], and 1808.8 [1252.6] μU/mL per min, respectively; $P < 0.05$) and the corresponding Ins-C_{max} (12.9 [8.7], 26.7 [14.5], and 47.6 [40.1] μU/mL; $P < 0.05$) suggested a dose–response relationship. Five, 10, and 20 puffs of oral insulin spray had an earlier onset of action than SC insulin (early T50%: 23.3 [15.1], 28.3 [12.3], 31.2 [111.8], and 87.0 [39.6] min, respectively; $P < 0.05$), an earlier maximal effect (GIR-T_{max}: 40.0 [23.7], 45.8 [22.7], 44.2 [5.8], and 145.0 [43.7] min; $P < 0.05$), and a shorter duration of action (late T50%: 56.5 [31.0], 70.2 [12.9], 75.5 [6.0], and 290.8 [84.0] min; $P < 0.05$). Dose-dependent increases in maximal metabolic effect were observed with 5, 10, and 20 puffs: the GIR_{max} was 0.9 (0.5), 2.0 (1.3), and 3.9 (2.5) mg/kg per minute, respectively ($P < 0.05$), and the GIR–$AUC_{0–120}$ was 39.6 (34.9), 76.8 (67.4), and 189.1 (163.0) mg/kg per minute ($P < 0.05$).

Conclusions: In this study in patients with type 1 diabetes, oral insulin spray had a faster onset and shorter duration of action than subcutaneously injected regular insulin. A dose–response relationship was noted in the metabolic effect and absorption of oral insulin spray. (*Clin Ther.* 2005;27:1562–1570) Copyright © 2005 Excerpta Medica, Inc.

Key words: oral insulin spray, type 1 diabetes, dose–response relationship, pharmacokinetics.

INTRODUCTION

Clinical trials have shown that tight glycemic control can reduce the risk of developing the long-term complications of diabetes mellitus.[1,2] However, some individuals with diabetes may consider the necessary regimens burdensome and may find adherence diffi-

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cult to maintain. For this reason, efforts have been directed toward finding noninjectable routes of insulin administration.[3]

A novel oral spray system* delivers an insulin formulation† containing human recombinant insulin, a surfactant, a solubilizer, a micelle-creating agent, emulsifying agents, and hydrofluoroalkane 134a. All excipients in the formulation are on the US Food and Drug Administration's list of excipients generally recognized as safe. The delivery device is a pressurized metered dose inhaler similar to an asthma inhaler and is used to administer small- and large-molecule drugs to the oropharyngeal mucosa. It consists of an actuator with a dust cap, a metering valve, and an aluminum canister. It produces an aerosol of uniform-sized particles, with 85% of particles having a mean size of ≥10 μm and the remainder having a mean size of <10 μm. The mixed micelles result from the combination of absorption enhancers and stabilizers that encapsulate and protect the insulin molecules. The system introduces the aerosol into the oropharyngeal cavity at a high velocity (100 mph); the impelled micelles traverse the superficial oropharyngeal mucosal layers, and, with the aid of the absorption enhancers, insulin molecules are rapidly absorbed into the bloodstream.[4,5]

To demonstrate clinical viability, this insulin delivery system would have to be dose-titratable in a fashion similar to SC injections. Therefore, the present study investigated the pharmacokinetic and pharmacodynamic properties of different doses of the oral insulin spray compared with subcutaneously injected regular insulin and placebo spray in patients with type 1 diabetes. SC regular human insulin was chosen as the comparator because the oral insulin spray is an aerosolized aqueous regular human insulin solution.

PATIENTS AND METHODS

This was a single-center, randomized, single-blind, open-label, 5-way crossover study. Patients with type 1 diabetes in good clinical health were recruited from the Diabetes Clinic of Hadassah Hebrew University Hospital, Jerusalem, Israel, after receiving detailed information about the purpose of the study, its procedures, and the potential risks. Written informed consent was obtained from all patients before participation in the study. The study was approved by the local ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki, including all amendments through October 2000 (Edinburgh, Scotland),[6] and consistent with good clinical practice guidelines.[7]

Exclusion criteria were any current or previous significant medical condition or treatment, including oral lesions and/or disease involving the oral cavity; glycosylated hemoglobin (HbA_{1c}) >11%; >1 episode of severe unexplained hypoglycemia with seizures or coma in the past year; a history of repeated ketoacidosis; participation in another study within the previous 90 days; and any significant abnormality on electrocardiography (ECG) or routine laboratory blood screening.

Screening included physical examination (weight, height, vital signs) and clinical and laboratory tests within 14 days before study entry. Blood pressure was measured with the patient in the seated position using an automated sphygmomanometer (M4-1, Omron Corporation, Kyoto, Japan) on the upper part of the dominant arm; heart rate was measured in beats per minute by both ECG and the palpation method at the level of the radial artery; and respiratory rate was measured in breaths per minute. ECG was performed using the GE Marquette MAC 5000 resting ECG system (GE Healthcare, Chalfont St. Giles, United Kingdom). Laboratory tests included hematology (hemoglobin, red blood cell count, total white blood cell count, platelets), biochemistry (HbA_{1c}, electrolytes, creatinine, total protein, bilirubin, alanine transaminase, aspartate transaminase, γ-glutamyltransferase, alkaline phosphatase), and urinalysis (dipstick analysis for protein, blood, glucose, and ketones).

Patients were instructed to consume an isocaloric weight-maintenance diet (~25–30 kcal/kg per day), adjusted to the level of physical activity (caloric distribution: 55% carbohydrates, 30% lipids, 15% proteins[8]) and to avoid strenuous physical exercise, alcohol, or concomitant medications throughout the study period.

The study treatments consisted of 4 doses of oral spray (5, 10, and 20 puffs of insulin spray and 10 puffs of placebo spray) and 1 dose of human regular insulin 0.1 U/kg SC. Subjects were hospitalized on the evening before each day of dosing and received an overnight IV infusion of insulin and 20% glucose solution

*Trademark: Generex RapidMist™ (Generex Biotechnology Corporation, Toronto, Canada).
†Trademark: Oral-lyn™ (Generex).