The U.S. "New Patient" and "Transfer" Studies

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The large-scale clinical trials of human insulin (recombinant DNA) in the United States consisted of a "New Patient" study and a "Transfer"study. The "New Patient" study involved 101 patients (38% type I) who have never received insulin and who were treated with human insulin and followed for 6 mo using NPH insulin alone or in combination with Neutral Regular Insulin (NRI). Shortly after treatment, serum glucose and total glycohemoglobin concentration fell. No patients developed insulin lipoatrophy or insulin allergy. Two patients developed insulin hypertrophy; in one, it was transient. Intradermal tests to varying dilutions of human insulin did not change over 6 mo. In addition, there was no evidence of development of antibodies to *Escherichia coli* polypeptide. Two-hundred-and-forty-three patients, 91% of whom had type I diabetes, were transferred in a controlled double-blind study from mixed beef-pork or purified pork insulin (PPI) either to human insulin or back to their previous insulin treatment and followed for 3 mo. While insulin dosage did not change, there was a slight increase in fasting serum glucose and a statistically significant increase in fasting ketonuria. There was no change in the frequency of the complications of insulin treatment. These limited data are consistent with the conclusion that NPH human insulin is slightly shorter acting than its animal insulin counterparts. Overall, human insulin is a safe, effective insulin. DIABETES CARE 5 (SUPPL. 2): 135–139, 1982.

Shortly after the completion of the initial clinical pharmacology studies in normal subjects,[1–3] two large-scale studies in diabetic patients were begun in the U.S. In one, patients who had never received insulin were treated with human insulin (recombinant DNA). In the other, patients who had been treated with animal insulins were transferred to human insulin. This report will summarize the results of these two studies.

NEW PATIENT STUDY

One-hundred-and-one patients who had never received insulin were treated with human insulin in six centers specializing in the treatment of diabetes in the U.S. (Table 1). The design and other details of the "New Patient" protocol are listed in Table 2. The data presented here are based on 6-mo experience with human insulin. Blood glucose was measured at home by patients using a Dextrometer. Patients were instructed to check their blood sugars fasting on Sunday and Tuesday mornings, and 1 h after breakfast on Sundays and 1 h after the evening meal on Tuesdays. The results were recorded and brought to the clinic at each visit. The study nurse then calculated the mean and standard deviations for the fasting and 1-h postmeal sugars and these were entered into the case report forms. Sera for glucose were also run at the Lilly Clinic using the method of Trinder.[4] Total glycohemoglobins were measured using the method of Simon and Eissler.[5] Antibodies to *E. coli* polypeptide were measured using the methods of Baker et al.[6] Finally, serum insulin antibody titers were measured in the laboratory of Dr. S. E. Fineberg,[7] whose assay procedures are described elsewhere in this journal.

Intradermal testing was performed before and 6 mo after treatment with human insulin using a double-blind "test kit" consisting of human insulin 0.02, 0.2, 2.0 and 20.0 U/ml and administered in 0.05-ml volumes. The positive control

TABLE 1
Investigators for "New Patient" protocol

Theodore G. Duncan, M.D.	Philadelphia, PA
Donnell D. Etzwiler, M.D.	Minneapolis, MN
Richard A. Guthrie, M.D.	Wichita, KS
Arthur Krosnick, M.D.	Trenton, NJ
Robert L. Nielsen, M.D.	Seattle, WA
Frederick W. Whitehouse, M.D.	Detroit, MI

was histamine phosphate, 0.05 mg/ml, and the negative control was Neutral Regular Insulin Diluting Fluid. For each variable in the "New Patient" study 6-mo data were compared with baseline data by means of a one sample *t*-test.

RESULTS

In Table 3 are presented the serum glucose responses before and 6 mo after treatment with human insulin in 93 patients, including 35 with type I diabetes and 58 with type II diabetes. Fifty percent of patients were over 50 yr of age and 73% over the age of 30. It will be noted that significant reductions in serum glucose were observed following treatment with human insulin. Also, glycohemoglobin concentrations decreased significantly in both groups of patients. In Table 4 are presented a comparison of self-glucose monitoring results and the serum glucose concentrations recorded at the time of the bimonthly visit. If the self-glucose results is increased by 12% to "convert" it from a whole blood to a serum result, excellent correlation between the two values is evident.

No patients developed insulin allergy or atrophy. Two patients developed insulin hypertrophy, one responded promptly to reinstruction on the necessity of rotating insulin injection sites, and the other continued to have insulin hypertrophy. There were no changes in intradermal tests. Moreover, there was no evidence of development of antibodies to *E. coli* polypeptide. Finally, as reported elsewhere,[8] the rate and degree of formation of antibodies to human insulin is comparble to that observed in a group of matched control patients who had received only purified pork insulin (PPI).

TABLE 2
"New Patient" study design

Open label study of 101 patients who had not previously received insulin were treated with NPH or NPH and Regular human insulin for 6 mo
- Type 1—38 patients
- Type 2—61 patients
- Other—2 patients

Visits: 0, 1, 2, 4, and 6 mo . . . 24 mo

Observations:
- Usual clinical parameters including serum glucose and total glycohemoglobin
- Evidence of complications of insulin therapy
- Serum insulin antibody titers (S. E. Fineberg, M.D.)
- Serum titers to *E. coli* polypeptide
- Human C-peptide (A. H. Rubenstein, M.D.)
- Intradermal testing (0 and 6 mo)

TABLE 3
"New Patient" study

	Admission (before insulin)	6 mo
Type I diabetic (N = 35)		
FBS	301	163
1-h ppbs*	426	246
Glycohemoglobin	14.2%	10.2%
Dose (U/kg)		0.52
Type II diabetic (N = 58)		
FBS	301	170
1-h ppbs*	378	237
Glycohemoglobin	14.3%	10.4%
Dose (U/kg)		0.44

*Postprandial serum glucose after Sustacal, 1 ml for each calorie in usual breakfast (up to 240 ml); no insulin was given before the meal.

TRANSFER STUDY

Two-hundred-and-forty-three patients in eight centers (Table 5) specializing in the care of diabetic patients enrolled in the "Transfer" protocol (Tables 6 and 7). Fifty-seven percent of the patients were under the age of 31 yr. Patients had been treated either with mixed beef-pork or PPI for at least 6 mo and were followed for 1 mo on that insulin and then "transferred" on a double-blind basis either to remain on the mixed beef-pork or PPI they had been taking or to human insulin. Since human insulin was available only as NPH and Regular U-40, the control insulins were provided only in these forms. Forty patients who were taking animal Lente Insulins were switched to NPH study insulins. The data presented here are for 3-mo follow-up only. (Elsewhere in this journal, Fineberg et al. present the serum insulin antibody responses of this group of patients after 6 mo of treatment with the study insulin.)

For each variable except ketonuria 3-mo data were compared with baseline data by means of a one sample *t* test within each treatment group. Additionally, the treatment groups were compared with respect to mean changes from baseline using a two-sample t test. For ketonuria the treatment groups were compared with respect to change from baseline incidence by means of a Chi square test. (Ketostix, Ames Co., Elkhart, Indiana, was used to assess ketonuria.) (No distinction was made between various semiquantitative estimates of ketonuria reported by the investigators. For instance, a report of "moderate" ketonuria was given the same weight in the analysis as a "trace" or "large" reading.)

RESULTS

The metabolic responses to PPI, mixed beef-pork, and human insulin are presented in Tables 8 and 9. Several points are of interest. First, the metabolic control for all treatment groups is suboptimal. Second, switching to study insulins, be they the same species the patient had been on or to human

TABLE 4
"New Patient" study office visit serum glucose versus self glucose results

	4 mo		6 mo	
	Fasting	1 h postprand.	Fasting	1 h postprand.
Type I				
Mean office results	158	259	163	246
Mean SG results	142	180	136	178
	(159)*		(152)*	
Type II				
Mean office results	171	244	169	237
Mean SG results	144	195	148	185
	(161)*		(166)*	
Composite				
Mean office results	166	250	167	241
Mean SG results	143	188	144	182
	(159)*		(161)*	

*Home glucose result × 1.12 to convert whole blood result to "serum" glucose.

TABLE 5
Investigators for "Transfer" study

Dewitt E. DeLawter, M.D.	Chevy Chase, MD
James I. Malone, M.D.	Tampa, FL
James M. Moss, M.D.	Alexandria, VA
Philip Raskin, M.D.	Dallas, TX
Julio V. Santiago, M.D.	St. Louis, MO
Luther B. Travis, M.D.	Galveston, TX
Louis Vignati, M.D.	Boston, MA
Charles M. Clark, Jr., M.D.*	Indianapolis, IN
Jaime A. Davidson, M.D.*	Dallas, TX

*Because of their later participation, data from these investigators are not a part of this report.

TABLE 7
"Transfer" study design (continued)

Parameters:
Usual clinical observation in diabetes practice including
Fasting and postprandial serum glucose
Self glucose monitoring
Glycohemoglobin
In addition:
Intradermal skin tests
Serum insulin antibody titers (S. E. Fineberg, M.D.)
Fasting and stimulated human C-peptide
Serum antibody titers to *E. coli* polypeptides

insulin, resulted in some increase in blood glucose. Third, there was a statistically significant increase in the frequency of ketonuria when patients were switched from mixed beef-pork or PPI to human insulin.

In Table 10 is presented the course of the complications of insulin therapy. Here, minor changes in the frequency of complications occur both in the control groups and in patients switched to human insulin. However, no significant changes are noted. We ascribe this to the short duration of treatment (3 mo) on the study insulin. Finally, there was no evidence of antibody formation to *E. coli* polypeptides.

COMMENTS

Both the "New Patient" and "Transfer" studies indicate that human insulin is a safe and effective form of insulin treatment. Metabolic control was clearly better in the "New Patient" than in the "Transfer" study. There are two possible reasons for this. First, the "New Patient" study group con-

TABLE 6
"Transfer" study design. Two hundred and forty-three patients on animal insulin followed for 1 mo on their current insulin and then "switched" in a double-blind fashion to human insulin or to their usual animal insulin

Purified pork (PPI) (N = 107)			Mixed beef-pork (MBP) (N = 136)		
	To human insulin	To PPI		To human insulin	To MBP
Type I	51	47	Type I	59	68
Type II	4	5	Type II	7	2

Monthly visits for 4 mo and then every 2 mo for 2 yr.

TABLE 8
Metabolic control in human insulin transfer studies

Mixed Beef-Pork (N = 136)	Baseline	3 mo
To MBP		
Dose (U/kg)	0.75 ± 0.3	0.75 ± 0.3
OSG*		
Fasting	265 ± 117	260 ± 111
1 h postprandial	354 ± 122	359 ± 105
HGM†		
Fasting	155 ± 167	170 ± 133
1 h postprandial	220 ± 163	199 ± 141
%Patients with ketonuria	40%	41%
Glycohemoglobin	13.3 ± 3.1%	13.1 ± 3.0%
To human insulin		
Dose (U/kg)	0.74 ± 0.3	0.76 ± 0.3
OSG		
Fasting	223 ± 120	257 ± 131
1 h postprandial	309 ± 100	335 ± 140
HGM		
Fasting	155 ± 199	170 ± 180
1 h postprandial	228 ± 192	213 ± 140
%Patients with ketonuria	27%	55%‡
Glycohemoglobin	12.8 ± 2.7%	12.4 ± 3.0%

*Office serum glucose.
†Home glucose monitoring.
‡Statistically significant.

TABLE 9
Metabolic control in human insulin transfer studies (continued)

Purified pork (PPI) (N = 107)	Baseline	3 mo
To PPI		
Dose (U/kg)	0.66 ± 0.3	0.67 ± 0.3
OSG*		
Fasting	181 ± 93	204 ± 86
1 h postprandial	332 ± 104	345 ± 102
HGM†		
Fasting	152 ± 163	154 ± 129
1 h postprandial	247 ± 164	229 ± 124
%Patients with ketonuria	35%	40%
Glycohemoglobin	12.4% ± 2.4	12.0% ± 1.9
To human insulin		
Dose (U/kg)	0.62 ± 0.3	0.67 ± 0.3
OSG		
Fasting	207 ± 104	257 ± 102
1 h postprandial	318 ± 114	379 ± 103
HGM		
Fasting	142 ± 152	181 ± 182
1 h postprandial	218 ± 155	244 ± 140
%Patients with ketonuria	49%	73%‡
Glycohemoglobin	12.3% ± 2.5	12.6% ± 2.4

*Office serum glucose.
†Home glucose monitoring.
‡Statistically significant.

TABLE 10
The course of complications of insulin therapy

Local insulin allergy	Insulin lipoatrophy	Insulin lipohypertrophy
MBP to MBP	MBP to MBP	MBP to MBP
0/70 → 0/57	6/70 → 2/57	19/70 → 16/57
MBP to human insulin	MBP to human insulin	MBP to human insulin
0/66 → 0/60	5/66 → 4/61	16/56 → 15/60
PPI to PPI	PPI to PPI	PPI to PPI
2/52 → 0/47	6/52 → 4/47	12/52 → 13/47
PPI to human insulin	PPI to human insulin	PPI to human insulin
2/55 → 2/48	9/55 → 8/50	7/55 → 6/48

tained a higher number of type II patients, i.e., older individuals with significant endogenous insulin secretory reserve. Conversely, 91% of the patients in the "Transfer" study were classified as type I and were younger, many being adolescents. Finally, the "New Patient" study, being an open label trial of a novel form of insulin, may have inspired the investigators and their patients to achieve better metabolic control. We are now conducting a double-blind controlled study with "new patients", which will include a higher proportion of type I diabetics.

The decrease in metabolic control in patients switched to human insulin is probably related to the fact that the human insulin, particularly NPH, is shorter acting than its animal counterparts. This possibility is supported by Clark et al.[9,10] and our own clinical pharmacologic studies.[3] If the clinical pharmacologic studies have failed to disclose striking or consistent statistically significant differences between human insulin and PPI, why are the two insulins different clinically? We hypothesize that small differences in the chain of events between injection and interaction between insulin antibodies may be cumulative. Thus, in comparison with animal insulins, human insulin is slightly better absorbed and less tightly bound both by the protamine in NPH insulin and serum insulin antibodies, leading to the clinical differences reported.

The failure to demonstrate a change of intradermala tests in the "New Patient" study and the absence of evidence of antibodies to *E. coli* polypeptide are consistent with the conclusion that bacterial proteins that might arise from the fermentation process do not survive the purification procedures used in the manufacture of human insulin.

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