Comparative Evaluation of Efficacy and Safety of Human Biosynthetic Insulin and Human Semisynthetic Insulin

S. K. Date*, A. Kapur, Seshiah***, N. Rais+, S. Jindal++, K. M. Prasanna Kumar+++,C. S. Yajnik^, and H. B. Chandalia^^**

ABSTRACT

Semisynthetic Human Insulin (SHI) has been available in India for approximately two years and is well accepted. Biosynthetic Human Insulin (BHI) (genetically engineered human insulin of Sacchromyces Cervisase origin) is likely to be shortly introduced. An open multicentric clinical trial to compare the efficacy and safety of BHI with SHI was conducted over a twenty week period in ninety insulin requiring diabetics receiving mixture of short acting and intermediate acting insulin twice.

There was neither a statistically significant change in insulin dose nor a change in the parameters of control, during the period of study, indicating that the two human insulin's been practically indistinguishable clinically. Both insulins were well tolerated with no significant adverse event recorded. The results of the trial provide adequate evidence to conclude that BHI is as effective and safe as SHI and change over can be made dose to dose, without any problems.

INTRODUCTION

Insulin identical to the one produced by human pancreas become commercially available for the firs time in 1982, exactly sixty years after insulin was first used for treating diabetes.

Human insulin differs from animal insulin its amino acid sequence. These differences between insulin of porcine origin are minor as compared to that of bovine origin. More the difference in amino acids, greater is the immunogenicity of the preparation. With the availability of human insulin, problems related to immunogenicity have been considerably reduced. A decade after the commercial availability of human insulin, it has become the most widely used insulin worldwide. It is estimated that more than 75% of insulin usage worldwide is of the human variety.

The initial method of producing human insulin involved conversion of pork insulin into human insulin by replacing the B-30 alanine with threonine at the same position as present in human insulin by a transpeptidation reaction. This is referred to as human semisynthetic insulin. However, human insulin is now also manufactured using the fermentation technology involving genetically engineered E. coli bacteria or the ordinary Baker's yeast Saccharomyces cerevisiae. This later method of insulin production goes a long way in reducing dependence on availability of animal pancreas for preparing human insulin.

Semisynthetic human insulin (SHI) has been availability in India since 1988 and has been increasingly used. We undertook he present study to assess the efficacy and safety of biosynthetic human insulin BHI, genetic engineered human insulin manufactured by Novo Nordisk A/S using the Saccharomyces cerevisiae method) with SHI, already available in India.

MATERIALS AND METHODS

An open multicentric comparative clinical trial was conducted in 90 insulin requiring diabetics, already receiving SHI regularly for at least the preceding eight weeks prior to inclusion in the

---

* General Manager, Medical Division, Sarabhai Chemicals, Baroda.
** Medical Advisor, Novo Nordisk A/S, Bombay Liaison Office, Bombay.
*** Professor and Head, Department of Diabetology, Madras Medical College and Govt. General Hospital, Madras.
+ Consultant Diabetologist, Chowpatty Medical Centre, Bombay.
++ Lecturer, Dept. of Medicine, Gandhi Medical Centre, Bombay.
+++ Associate Professor, Dept. of Endocrinology, MS Ramaiah Medical Teaching Hospital, Bangalore.
^ Wellcome Diabetes Study, KEM Hospital, Pune.
^^ Hon. Professor of Medicine and Diabetes, Grant Medical College, Bombay and Endocrinologist, Jaslok Hospital and Research Centre.

trial. Patients with acute metabolic complication, presence of associated diseases, brittle diabetics and those requiring insulin only temporarily, such as gestational diabetics were excluded from this study. All patients underwent two blood glucose estimations, (fasting and two hours post meal); glycosylated haemoglobin (HbA_{1C}) and three uring sugar estimations (one each before each meal) before changeover to BHI.

Blood sugar estimations were done to assess glycaemic control while urine sugar estimations helped physicians adjust dosage of particular insulin (short or intermediate acting) at a particular time (morning or evening).

Patients were then switched over to BHI on a dose to dose basis. At the end of week 1, the two-point blood glucose and urine sugar estimations were repeated. At the end of four, eight and twelve weeks (end of the trial), all investigations were repeated. In addition, all patients underwent routine blood counts and urine analysis before and at the end of the study. Patients were questioned for adverse effects at each follow-up visit.

RESULTS

Ninety patients completed the study. Forty were females and fifty males. The age range was 15 to 67 years with a mean of 38.75 years. 71% of the patients had insulin dependent diabetes mellitus (IDDM) while the rest were a patient of non-insulin dependent diabetes mellitus requiring insulin. The average duration of disease was 6.65 years. Nine patients were suffering from neuropathy and one from retinopathy. None of the patients had diabetic retinopathy.

The mean daily insulin requirement at different centres ranged from 13.8 to 18.2 for human actrapid and 19.52 to 46.90 for human monotard. The mean value for the entire patient population was human actrapid 16.46 ± 6.33 u/day and human monotard 29.24 ± 12.57 u/day. The mean glcosylated haemoglobin value for the entire patient population was 8.6±1.99% with a range of 5.94 to 10% at different centres.

The mean fasting and post-prandial blood sugar values were 138 ± 45.07 mg/dl and 208 ± 77.21 mg/dl respectively.

At the end of first week following crossover to BHI, there was a slight increase in mean fasting glucose value (149 Vs 138 mg/dl) although this changes was not significant. Post-prandial values reduced from 207.66 mg/dl to 198.25 mg/dl but the change was not significant.

The doses of the two insulin types were adjusted if required and treatment with BHI continued for twelve weeks. The results of the entire of the study are summarised in Table I.

TABLE I

Insulin requirements, blood glucose and glycosylated haemoglobin values on SHI (Day 0) and at 1, 4, 8 and 12 weeks after crossover to BHI (n=90)

		Week0	Week1	Week 4	Week8	Week12
Insulin requirements units/day (Mean ± SD)	A	16.46 ±6.33	--	17.13 ±6.70	19.38 ±7.44	17 ±7.65
	M	29.24 ± 12.57	--	29.85 ±12.79	32.15 ±13.58	31.24 ±14.67
Blood Glucose	F	138.17 ±45.07	148.77 ±54.43	131.58 ±51.79	138.15 ±48.12	138 ±37.9
	PP	207.66 ±77.21	198.25 ±52.46	181.43 ±51.79	187.28 ±78.88	183 ±50.25
Glycosylated Haemoglobin % (Mean ± SD)		8.6 ±1.99	--	9.5 ±1.08	9 ±1.19	8.5 ±1.67

A=Actrapid M=Monotard F=Fasting PP=Post prandial

Insulin Doses

Insulin requirements on SHI (actrapid and monotard) before crossover were 16.46 ± 6.33 and 29.24 ± 12.37 respectively. The requirements for BHI actrapid rose slightly to 19 ± 7.44 at the end of eight weeks but was almost same at the end of twelve weeks (17 ± 7.65) as before the crossover. The dose of BHI monotard rose slightly from 29.24 ± 12.57 to 31 ± 14.67 at the end of twelve weeks. However, there was no statistically significant difference between requirements of either actrapid or monotard at the beginning and end of the trail. This indicates that the two insulins are equally effective.

Metabolic Control

The mean fasting blood glucose levels rose from 138 ± 45.07 mg/dl on Day 0 to 149 ± 54.43 mg/dl at the end of first week after changeover to BHI. However, the fasting blood glucose values again settled down to 132 ± 40.99 mg/dl at the end of week four and remained at a similar level right

throughout the study. The rise at one-week level was not statistically significant.

The mean post-prandial blood glucose value on SHI before crossover was 208+77.21 mg/dl. This value came down to 183 + 50.25 mg/dl, however the difference was not statistically significant and probably reflect better dose adjustments and increased care as a result of closer follow-up.

The mean glycosylated haemoglobin value showed no statistically significant difference between week zero and week twelve, thereby indicating stable control over the period of observation.

The urine sugar estimations were done primarily to help the physician to adjust the dosage of insulin. There was less number of patients showing positive urine sugar at the end of 12 weeks than those at the beginning (day 0). This difference, again, was not statistically significant.

Thus all the indices that BHI is practically indistinguishable from SHI and both insulins provide an equally good metabolic control. No adverse effects were reported except for repeated hypoglycaemia in one patient who was later diagnosed to have primary hypothyroidism, which is a known predisposing factor to hypoglycaemia.

DISCUSSION

The advent of newer insulin's (highly. purified porcine, monocomponent porcine and monocomponent human) have practically eliminated the main adverse effects of insulin injection, that is, insulin allergy and lipodystrophy, (1, 2, 3). In fact, this insulin's can reverse the lipoatrophy caused by the use of conventional bovine insulins. This may be due to the fact that these insulin's, e specially the monocomponent human insulin are the least antigenic, (4, 5, 6). Further, it is very significant to note that the relative immunogenicity of human has been less clearly distinguishable with SHI than with BHI, in patients transferred from purified porcine to human insulin. Studies upto date suggest a lower immunogenicity with BHI as compared to SGI, (7).

Insulin, being an endogenous substance, is also free from other adverse effects. In the present study also, none of the patients had any adverse either on SHI or BHI. In only one case out of ninety, significant hypoglycaemic episodes were noted. The patient was subsequently diagnosed to have primary hypothyroidism, which is known to predispose to hypoglycaemia.

This multicentric clinical trial was undertaken to assess the efficacy and safety of BHI (not yet available in our country) and to compare it with SHI, which is already being used in India. The trial results have provided adequate evidence to conclude that BHI is as effective as SHI for the treatment of insulin requiring diabetes mellitus patients. Also, both the insulins are equally well tolerated. In a similar but less extensive crossover trial, which compared the efficacy of three months treatment with short plus intermediate acting preparations of purified porcine SHI and BHI in ten type I diabetics. There was no significant difference between the insulin with respect to mean daily blood glucose concentrations or daily insulin requirements, (8). The two insulins are thus practically indistinguishable from each other clinically. Two other recently published studies (9, 10) have also made similar conclusions that SHI and BHI are similar as regards their pharmacokinetics and clinical efficacy.

REFERENCES

1. Ferland L, Ehrlich R. M. Single-peak Insulin in the Treatment of Insulin-induced Fat Atrophy J. Paediatr. 1975; 86: 741-43.
2. Jones G. R. Statham B., Owens D. R. Jones M. K. and Haves T. M., Lipoatrophy and monocomponent Porcine Insulin. Br. Med. J. 1981; 202:292.
3. Tenscher A. treatment of Insulin Lipoatrophy with Monocomponent Lente Insulin's. Diabetologia 1974; 9: 492-98.
4. Virgile F., Frigate F., Magnanini P. G., Coronel G. A. and lavicoli M. Reduction in insulin Antibodies 42 months. After Transfer from Porcine to Human Monocomponent Insulin's. Diabetes Research, 1988; 9: 19-20.
5. Schernthaner G., Borkenstein M., Fink M., Mayr W. R., Menzel J. and Schober E. Immunogenicity of human Insulin (Novo) or Pork Monocomponent Insulin in HLA-DR-Typed Insulin Dependent Diabetic Individuals. Diabetes Care 1983; 6(1): 43-48.
6. Brogden R. N. and Heel R. C., "Human Insulin – A Review of its Biological Activity, Pharmacokinetics and Therapeutic Use", Drugs 1987; 34: 350-371.
7. Lunetta M. et al. Biological Activity of Semisynthetic and Biosynthetic Human Insulin I Type I Diabetic Patients: A Comparative Study. IRCS Medical Science 1985; 13: 279.
8. Davidson J. A. et al. Transfer of Patients with Diabetes from Semisynthetic Human Insulin to Human Insulin prepared by Recombinant DNA Technology using baker's yeast: A double-blind, randomisedstudy. Clinical therapeutics 1992; 13(5): 557-68.
9. Raskin P. et al. The Use of human Insulin derived from baker's yeast by recombinant DNA technology. Clinical therapeutic 1992; 13(5): 569-78.