

Review

ANIMAL INSULINS - CURRENT STATUS

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ABSTRACT

There is no significant difference in the metabolic control with animal or human insulin. At present there is no clinical data comparing the diabetes related mortality and complications, with animal or human insulin. The earlier animal insulins were more immunogenic as compared to human insulin, but the present day highly purified monocomponent insulins are less antigenic and the difference in the antigenicity as compared to human insulin has not proved to be of clinical importance. The receptor binding affinity of animal insulin at the major sites of action as well as the post receptor events is similar to human insulin. The complications like insulin lipodystrophy, lipoatrophy, insulin allergy and insulin resistance seen with the older impure animal insulins is uncommon with the highly purified animal insulins and synthetic insulins. Hypoglycemic unawareness is seen more with the human insulin as compared to the animal insulin. The animal insulins are more cost effective in the long-term management of the insulin requiring diabetics, especially in a developing country like ours.

KEY WORDS: Human insulin; Bovine insulin; Porcine Insulin; Immunogenicity; Hypoglycemia.

Insulin has been available for therapeutic purposes for over 80 years since Banting and Best discovered it in 1921. Until the 1980s only animal insulins (bovine insulins and porcine insulins) were available for treatment of diabetic patients. Human insulin produced either by chemical synthesis or by recombinant DNA technique was introduced in the early 1980s without scientific proof of advantage over existing purified animal insulin preparations. At the time of introduction of human insulin, marketing strategies suggested that the lower immunogenicity of human insulin and the anticipated decline in antibody titres would offer a clinical advantage for insulin treated diabetics. Seventy percent of the trials then were funded by the major insulin manufacturers. The overall picture does not indicate substantial differences in metabolic control and hypoglycemic events between insulin species. Physicians have long-term experience with the safety and efficacy of

animal insulins for about 80 years whereas the same is limited to 15-17 years with human insulins. The long experience with natural insulins has been satisfying both for the patients as well as their physicians, especially so after the availability of the monocomponent insulins.

METABOLIC EFFECTS

The metabolic control with animal insulins and human insulins are comparable in most studies. A systematic review conducted by Richter. B et al (1) evaluated 18 randomized controlled clinical trials that consisted of 11 crossover and 7 parallel group studies. Despite heterogeneous designs, participants and locations, most of the parallel and all the crossover trials did not suggest any important differences between insulin species in terms of glycemic control as measured by glycated hemoglobin and fasting plasma glucose. Only one study by Lam HC et al (2) showed a significant decrease in HbA_{1c} of 1.9% after porcine insulin administration. Another trial by Fletcher JA et al (3) reported increase of fasting plasma glucose of 1.1 µmol/L after human insulin administration and a decrease of 1.6 µmol/L after porcine insulin administration. No significant difference in dosage has been noted between the insulin species. There is no comparable data regarding diabetes related mortality, complications of diabetic nephropathy and diabetic retinopathy or quality of life in patients treated with animal and human insulins.

IMMUNOGENICITY

Porcine insulin structurally differs from human insulin by one amino acid (alanine replaces threonine at B30) whereas bovine insulin differs from human insulin by three amino acids (A8 alanine, A10 valine and B30 alanine) (4). Bovine insulins are generally considered to be more immunogenic than porcine and human insulins (5). The purity of an insulin preparation influences the amount of insulin antibodies found in patients with diabetes. Highly purified monocomponent porcine or bovine insulin induces fewer antibodies than the several times crystallized insulin of the same formulation (6-8).

Standard animal insulins available today are much purer than the conventional insulins of the past. Current animal insulins have proinsulin contents of less than 50 ppm in contrast to the older insulins with proinsulin like substances in the range of 30000 ppm. Beef or pork insulins labeled highly purified (purified by chromatographic methods) have less than 10 ppm proinsulin content and monocomponent insulins usually <1 ppm. Significant insulin antibody titres may be found in patients on highly purified insulin if they were on conventional insulins in the past. The biological effects of pork and synthetic human insulins are identical (9) although the human hormone is less antigenic. However, this difference has not proved to be of clinical importance (10). Most studies did not detect a significant decline in antibodies after switch from bovine to human insulin. There is no solid evidence that the presence of circulating insulin antibodies is associated with better glucose control, development of complications, inhibition of endogenous insulin secretion or preservation of residual β – cell function. It can no longer be said that human insulin produces less antibodies, as there is no evidence to support this. In a small pilot study conducted in our institution, 66 patients with type 1 diabetes mellitus were screened for anti-insulin antibodies. Majority of the patients were on animal insulins for a duration ranging from 1-10 years. About 87.8% were found to be negative for significant amounts of anti insulin antibodies (Table 1).

Table 1: Immunogenicity of Insulins - Anti Insulin Antibody (AIA)

Patients	Positive (AIA)	Negative (AIA)	Totalnumber
Normal- (N)	1	28	29
Type 1 DM- (N)	8	58	66

The clinical significance of immunogenicity is in terms of complications like insulin lipodystrophy and lipoatrophy, insulin allergy and insulin resistance. Insulin lipodystrophy and lipoatrophy may occur at insulin injection sites (11). This was seen with the older impure animal insulins and is uncommon with the highly purified animal insulins and synthetic insulins.

Primarily IgE antibodies mediate allergic reactions to insulin, although IgG may participate. These are rare with the newer insulins. Allergy may develop with initiation of insulin therapy usually within the first month, but severe reactions occur in patients who resume therapy after an insulin free period. Patients

with allergic reactions to animal insulins may be shifted to human insulin.

Insulin resistance in which antibodies (IgG) are directed against insulin occurs in only about 0.01% of insulin treated subjects even though essentially all patients have detectable levels of insulin antibodies after three months of therapy. Auto-antibodies against insulin can cause either insulin resistant hyperglycemia or if they release bound insulin inappropriately, may result in hypoglycemia. The level of circulating antibodies has declined with the purified monocomponent insulins. The binding affinity of insulin to insulin receptors at the three major sites of action namely muscle, adipocyte and hepatocyte as well as the post receptor events in terms of autophosphorylation of insulin receptor substrate have been found to be similar with bovine, porcine and recombinant synthetic insulin.

STORAGE AND STABILITY

All insulin preparations are temperature sensitive hence it is crucial that proper storage is maintained. Insulin vials should be stored preferably in the refrigerator at a temperature of 2-8 degree Celsius. Freezing should be avoided as it damages the crystal structure of complexed preparations. Dissolved insulin will precipitate on freezing and will slowly go back into solution after thawing. However, when refrigeration is not feasible it can be kept in a dark cool place in the house or in earthenware pots away from sunlight and heat for about 4-6 weeks, with no significant loss in biologic activity. At 25 degree Celsius, 2% loss of potency will take 6 months to occur and only at higher temperatures (40 degree Celsius) a 2% loss can occur every week. There is no difference in the storage requirement among the various insulin preparations.

DERMATOLOGICAL PROBLEMS

The incidence of insulin lipodystrophy or lipoatrophy has almost disappeared with the advent of the highly purified animal insulins and human insulin. Atrophy or hypertrophy may occur at injection sites. Lipoatrophy tends to develop during the first year of therapy and regress thereafter. It was prevalent in children and women and may involve an immune reaction to some contaminant of the older insulins because it improves with purified animal insulins or human insulin. Lipoatrophy correlates with high circulating insulin antibody levels and immune complexes containing insulin can be demonstrated at the site of skin problems. It improves when purified,

particularly porcine or human insulin is injected to the sites. Hypertrophic masses can develop and absorption of insulin from such areas is unpredictable and may cause erratic or poor control. There is no evidence that the antigenicity of insulin contributes to injection site hypertrophy. This is thought to reflect the anabolic properties of insulin.

Insulin allergic reactions mainly mediated by IgE may be in the form of local allergy or systemic allergy. Local reactions are characterized by erythema, pruritis and induration at the injection site, whereas systemic allergy is manifested by generalized urticaria, angioneurotic edema or frank anaphylaxis. Local insulin reactions respond to antihistaminics and if animal insulins are used, a switch to biosynthetic human insulin should be made. Systemic reactions are now rare with the purified animal insulins, but may require desensitization when it occurs.

HYPOGLYCEMIA

No important differences in the risk of hypoglycemia have been noted between the animal and human insulin preparations in majority of the studies. Two crossover studies (12-16) described hunger and sweating significantly more frequent as initial warning symptoms during porcine insulin therapy. No study noted a significant difference in severe hypoglycemic events, the total number of hypoglycemic episodes, the number of events per patient, hypoglycemic coma, frequency or time of occurrence and unexplained or nocturnal hypoglycemic episodes. Mean events per day ranged from 0.1 to 0.37 for human insulin and 0.22 to 0.37 for porcine insulin. Mean events per patient ranged from 3.1 to 5.3 hypoglycemic events for human insulin and 3.1 to 8.8 for porcine insulin. There has been intense debate about the effect of insulin species on the warning symptoms of hypoglycemia. Whether there is any effect of species per se on the symptom complex of hypoglycemia still remains uncertain.

ECONOMICS AND AVAILABILITY

During the 1980s, at the time of introduction of human insulin, it was suggested that their greater use would reduce the cost of these insulins. Many clinicians switched over to human insulin with a hope that their patients would get better and economical insulins. This was not based on any scientific proof of advantage over existing purified animal insulin, especially porcine insulin. From 1985 to date the cost of human insulins has escalated from Rs 200/- vial in 1987 to about Rs 250/- per 400 unit vial today,

despite the increase in usage from less than 3% to nearly 60%. The cost of bovine insulin is about Rs 70/- and that of porcine Rs 135/- per 400 unit vial. The comparison between the current prices in India of the various insulins is tabulated in Table 2. Despite 20 years of technology the cost of synthetically produced insulin continues to mount, threatening the existence of those who depend on it for treatment, in developing countries.

Table 2: Economics of Insulin in India*

Insulin Species	Strengths		Price Per Unit-Rs
	40 IU/ml	100 IU/ml	
Bovine	Rs.73		0.18
Porcine	Rs.144		0.36
Human	Rs.220-244	Rs.515-560	0.54-0.58

Unlike in the west where 90% of population is covered by health insurance, hardly 1.5% of Indian population is covered by insurance and 8-10% of the population is covered by ESI, CGHS and public/private sector medical benefits. These people are mostly residing in towns and cities. Majority of the Indian patients have to fund for themselves. With the data that shows the comparable efficacy of animal and human insulins health care decision makers now have the power to negotiate prices more effectively with insulin manufacturers.

In recent years major insulin producing companies ceased to manufacture animal insulins. There is a real threat of shortage of animal insulins especially in developing countries. Many hypothetical conditions of availability of animal insulin in future and animal insulin crystals invoking diseases (Bovine Spongiform Encephalitis) are not stumbling blocks for animal insulin usage. Manufacture of animal insulins needs sacrificing the animals in large numbers (1500 pigs and 18500 cows- 800 pounds of pancreas yield one pound of insulin to serve one year supply to 750 patients). It was anticipated that animal sources will dwindle and availability will be a problem in the future. The problem of shortage of animal insulins in the US was raised even 20 years ago. We have not faced any shortage of animal insulin in our country till date. But the concern is the increase in the number of new patients year after year.

SUMMARY

In the industrialized world 85- 95% of all insulins used are human insulins. Human insulin usage has also been spurred due to religious beliefs and porcine/

bovine insulins are considered taboo by certain religions. The lack of evidence of any significant superiority of human insulin over animal insulins, in terms of glycemic control or adverse events and the fact that the research done has not addressed key issues like mortality, diabetic complications like nephropathy and retinopathy, changes the whole outlook for patients, doctors and especially for government health departments. In developing countries like India where there is no universal healthcare plan, the use of human insulin must rest largely on economical grounds. It can no longer be said that human insulins are better than the highly purified monocomponent animal insulins available today. Doctors and health care professionals can now provide their patients with insulin treatment choices based on evidence, not assumption. Developing countries can now ensure that affordable animal insulins remain available. We can be assured that the animal insulins we provide are comparable both in terms of safety and efficacy to human insulin.

Editor's Note: Due to recent changes in pricing of insulins, the references to price of insulins are no longer applicable. Human insulin in vials costs about Rs 150/-, bovine insulin is about Rs 70/- and price of porcine insulin is Rs 135/- per 400 unit vial.

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