Family Practice

Insulin and Insulin Antibody

What a Family Physician should Know ?

Sanjeevi C. B.* Seshiah V.**

SUMMARY

Antibodies develop to injected insulin frequently. The development of anti-insulin antibodies is maximum to conventional bovine insulin compared to the porcine variety. The immunogenicity of the insulin is not only due to the species from which the insulin is prepared but also the impurities that are present in the preparation like proinsulin and other islet ceil hormones. Hence the purified insulins produce lesser amount of antibodies and among the purified insulins, the least is produced by human insulin.

The production of these antibodies depends on the insulin preparation, the route of administration, age and sex and the genetic status of the individuals. These antibodies produce various complications. They include allergy, lipoatrophy, insulin resistance, alteration of metabolic control, hypoglycemia, reduction in the duration of remission period and fetal hypoglycemia when given during the gestational period. These can be overcome by the use of purified insulins.

* *Research Fellow, Department of Immunology, Tuberculosis Research Centre, Chetput, Madras 600 031.*

** *Professor and Head, Department of Diabetology, Madras Medical College Government General Hospital, Madras 600 003.*

Insulin is commonly prescribed by the family physicians for uncontrolled diabetes mellitus. In patients who have insulin–dependent diabetes mellitus (IDDM), exogenous insulin administration is mandatory. In another category called non-insulin dependent diabetes mellitus (NIDDM) insulin administration is recommended when there is severe hyperglycemia or complicated diabetes. In gestational diabetes mellitus (GDM), insulin injections are prescribed to maintain normoglycemia.

In all these situations, insulin antibodies are produced in response to the administered insulin in patients. These insulin antibodies are responsible for various complications, which can be avoided when care is shown in choosing the right insulin preparation[1]. In the following article, the factors responsible for the production of insulin (Table I), the complications they may produce (Table II) and the means by which they can be overcome, are discussed.

Table I. Factors responsible for the formation of anti-insulin antibodies

- Insulin Preparation
  - (i) Acidity of insulin
  - (ii) Adjuvants in insulin
  - (iii) Source of Insulin
- Route of administration
- Age and sex of the patient
- Genetic susceptibility

Table II. Complications due to insulin antibody

- Insulin allergy
- Insulin resistance
- Lipoatrophy
- Hypoglycemia
- Shortening of remission period
- Fetal hyperinsulinemia and neonatal hypoglycemia

INSULIN ANTIBODIES

Insulin antibodies develop several weeks after starting of Insulin irrespective of whether it is beef, pork or even human in origin. The antibodies develop earlier to bovine insulin as compared to porcine insulin[2]. The antibodies produced are of the IgG class. Insulin antibodies may bind to insulin and form immune complexes along with their attendant complications.

pH of Insulin : The initial form of insulin that is administered, determines the subsequent responsiveness to insulin. An acidic form of crystalline porcine insulin produces a detectable antibody response compared to the neutral form. If the neutral form of insulin is given first, followed by the acidic form of insulin, the level of antibodies produced is subsequently much less.

Adjuvants in Insulin : Zinc, which is present in the long–acting preparation of insulin, is another determinant to insulin antibody production. Protamine in Isophane or NPH insulin is a substance that is often responsible for the production of insulin antibody. It is derived from fish sperm and produces the highest antibody levels in addition to allergy, and topical adverse reactions at the injection site. It also stimulates complement[3].

Source of Insulin : Discussing the origin of insulin, bovine insulin is more immunogenic than porcine insulin. Even purified bovine insulin is more immunogenic than the purified porcine insulin. Comparing human to porcine, purified human insulin is less immunogenic. Therefore the inference that follows is that purified insulins are better and purified human insulin is even better. The purified insulin, which may be pure at the time of preparation, if not maintained under ideal conditions, develops the potential to produce antibody when injected, due to the aggregation of the insulin molecules. This factor could also be responsible for the formation of insulin antibodies.

Patients who develop insulin antibodies, require more and more insulin for the control of diabetes and subsequently develop insulin resistance. These patients benefit immensely when switched over to the purified insulins. Their insulin requirement falls and the antibody level decreases.

Intravenous Vs Subcutaneous Route

The degree of antibody formation depends on the route of administration. A state of adaptation or tolerance is produced and negligible insulin antibodies are formed when insulin is administered by continuous intravenous infusion. Breaks in insulin administration by subcutaneous route are responsible for development of heightened antibody response. This leads to the development of insulin resistance. Administration of purified insulins in situations like surgery and pregnancy would overcome this problem seen commonly with impure insulins, which are otherwise called 'dirty insulins'.

Miscellaneous

The antibody production to injected insulin also depends on the genetic susceptibility of the individual. Patients who are HLA DR 7 postive show higher levels of insulin antibody when compared to those with HLA B8[4] who are unresponsive even to immunogenic bovine insulin.

Women tend to produce more antibody after six months of treatment with beef isophane insulin. No such sex difference has been seen with beef lente insulin with advancing age. Further a decline in the antibody production is observed[5].

COMPLICATIONS DUE TO INSULIN ANTIBODY

Allergy : Allergy to insulin is rare, but when it does occur it can produce life-threatening complications. The patient would give a prior history of treatment with a bovine insulin and in testing with bovine insulin would show wheal and flare reaction. Desensitisation is often successful. In most instances, insulin allergy occurs because of the zinc component of the insulin preparation[6].

Insulin Resistance : Insulin resistance per se is rare. Patients with insulin resistance show high level of insulin antibodies. Reduction in the insulin antibody level reduces insulin requirements. Such a reduction is brought about by switching from conventional to purified insulins. The antibody–mediated insulin resistance usually occurs during first year of treatment. Nearly one–third of the patients with insulin resistance also show insulin allergy. IgE is raised in insulin al-

lergy but IgG is elevated in Insulin resistance. Desensitisation may aggravate antibody-mediated insulin resistance but the use of sulphated insulin would overcome this resistance.

Lipoatrophy : Occurring at the site of insulin injection, lipoatrophy has an incidence of approximately 25% in patients treated with the conventional bovine insulin. Lipoatrophy is a local form of immune complex disease in which the insulin and the contaminating protein along with antibody and complement, produce local inflammation and destruction of the subcutaneous tissue. It seems to occur more in females than males and these patients show elevated levels of anti-insulin antibody. Patients taking purified insulin do not develop lipoatrophy.

Miscellaneous : Unexplained hypoglycemia sometimes occurs in patients taking conventional bovine insulin, due to dissociation of insulin from the insulin-anti insulin antibody complex. The resulting increase in the free insulin level causes this hypoglycemia. The dissociation of insulin from the insulin-anti insulin antibody complex occurs during carbohydrate restriction of increased utilisation[7].

Freshly detected diabetics in whom insulin is started, often go into a "honeymoon" period. During this period the insulin requirement falls and the patient maintains euglycemia with the available endogenously secreted insulin. This is also referred to as the remission period. If the initial insulin administration is conventional bovine insulin, the patients develop anti-insulin antibodies. Those who develop anti-insulin antibody come out of the remission period earlier and present with severe disease.

Insulin that is injected normally does not cross the placental barrier. It is only when insulin is bound to insulin antibody, the insulin - antibody complex crosses the placental barrier. Diabetic mothers who are to be given conventional bovine insulin, may develop insulin antibodies which form a complex and cross the placental barrier. These complexes stimulate the fetal pancreas. Insulin antibody belongs to IgG class, which can cross the placenta on its own and stimulate the fetal pancreas. Thus both insulin and proinsulin are released from the fetal pancreas. Increased carbohydrate utilization (available from the maternal circulation) leads to the development of fetal macrosomia. But soon after the delivery of the macrosomic fetus, the non-availability of adequate carbohydrates which were available from the maternal source, in the presence of now excess insulin; produces neonatal hypoglycemia.

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Doctors will have more lives to answer for in the next world.
than even we Generals

– Napoleon Bonaparte