Feature Article

NEW INSULINS AND INSULIN DELIVERY SYSTEMS

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This article summarises the high-lights of the review lectures and data presented and discussed in the course on 'New insulins and insulin delivery systems' held at Taj Place, New Delhi July 23-25th, 1983. The faculty included Dr. Joseph Shipp, Regent's Distinguished Professor, University of Nebraska Medical Centre, U.S.A.; Dr. Robert Mecklenburg, Endocrinologist, The Mason Clinic, U.S.A.; Dr. M.M.S. Ahuja, Professor and Head, Department of Endocrine and Metabolic diseases, All India Institute of Medical Sciences; Dr. Dinesh Kumar, Associate Professor of Endocrine and Metabolic diseases, University of Southern, California, Los Angeles; Dr. M. Vishwanathan, Directcor, Diabetes Research Centre, Madras and Dr. Lily John, Professor and Head, Department of Medicine III, Christian Medical College and Hospital, Vellore. Course was coordinated by Dr. H.B. Chandalia Honorary Associate Professor of Medicine and Diabetes, Grant Medical College and J.J. Hospital, Bombay; Honorary Physician, Endocrine and Metabolic Diseases, Jaslok Hospital and Research Centre, Bombay.

Dr. Chandalia introducing the theme of course pointed out that in spite of restricted need as well as restricted availability of new insulins and insulin delivery systems, it is important to learn more about these new modalities of treatment. A patient sees a physician with the hope that the physician will advise him the best form of treatment within his reach. This unwritten contract makes it mandatory for all of us to utilise all available knowledge and mobilise all available resources in treating our patients. This principle justifies the organisation of a course of this type even in a developing country.

New Insulins

Dr. J. Shipp pointed out that diabetes was being treated inadequately and badly until recently. The advent of new insulins, new monitoring devices and new insulin delivery systems have made it possible for the first time to control a type 1 diabetic adequately. Dr. M.M.S. Ahuja described the conventional insulins and the drawbacks with their use, especially the problems of allergy, immunological resistance and lipodystrophy. He pointed out that we were not yet certain whether insulin-antibody complex was responsible for microangiopathy. After a prolonged discussion it was concluded that the available evidence was insufficient to incriminate insulin-antibody immune-complexes in the etiology of microangiopathy. Dr. Ahuja presented his data on monocomponent insulins, bringing out the fact that antibody titers were low in patients treated with these insulins as compared to those with the conventional insulins.

Dr. Chandalia described the types of new insulins. The new insulins are purified and contain minimal amounts of impurities, while conventional insulins contain fairly large

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amount of proinsulin, glucagon, pancreatic polypeptide and somatostatin. Monocomponent insulins contain less than 10 parts per million proinsulin. Species source of insulin is also important. Porcine insulin evokes much attenuated antibody response as compared to bovine insulin. Human insulin, derived from two different sources is now in clinical use. However, porcine and human insulin behave similarly regarding their pharmacokinetics and hypoglycemic potency. Immunogenicity of human insulin, as measured by insulin specific IgG antibodies may be less than that of porcine insulin. From a clinical standpoint, other important difference is more rapid absorption of human regular insulin following a subcutaneous injection as compared to porcine insulin. Advantages of new insulins include (1) better stability because of their neutral pH (2) very low incidence of allergy. However, Dr. Chandalia described 5 patients of insulin allergy due to monocomponent insulins. Of these patients, 4 had local skin allergy and. 1 had anaphylaxis. He also described a patient of allergy to human actrapid insulin (3) virtua.l absence of lipoatrophy with monocomponent insulin. Dr. Chandalia found lipoatrophy in only one patient out of a tot.al of 73 patients treated with monocomponent insulin (4) low immunogenicity. It was recommended that these insulins should be used in patients having allergy or lipoatrophy to conventional insulins. They are preferred for intermittent use, e.g. in gestational diabetes or during transient insulin therapy for surgery in a diabetic, as they are less likely to cause allergy during subsequent use. It is debatable whether every insulin dependent or insulin requiring diabetic should be put on these insulins. Dr. Chandalia and Dr. Dinesh Kumar felt that they would do so while Dr. Shipp felt that these insulins should only be used in special circumstances.

Dr. Vishwanathan described his experience of monocomponent (MC) insulins in 300 patients. These insulins were used mainly for insulin resistance (insulin requirements greater than 80 units/d), insulin allergy, lipoatrophy, chronic vascular complications and acute infections with good clinical response. The dosage required were low and antibody titre started falling after one week of their use. Problem of allergy was resolved in 25 patients but 5 patients were also found to be allergic to MC insulins.

Dr. Dinesh Kumar outlined his approach to patients with insulin allergy. He described the methods of allergy testing and desensitisation. He emphasized that a small dose of insulin should be continued to maintain the state of desensitisation even if the patient does not need insulin for metabolic control. He brought out the fact that contaminating proteins in conventional insulins enhance antibody response to insulin and may render it antigenic if it would ordinarily be not so. Immune response to insulin may be genetically determined, as certain D-related HLA are more frequently associated with it.

Dr. Lily John described her experience with MC insulins. She brought out the problems of cost and availability.

Insulin Delivery Systems

Dr. Ahuja described the basis of openloop insulin delivery systems. He elaborated on the normal physiology of insulin secretion, emphasising the importance of continuous basal supply of insulin at night and hepatic extraction of insulin. He described how the insulin pumps can mimic the post-prandial and continuous basal secretion seen in non-diabetics.

Dr. Dinesh Kumar elaborated on the types of insulin-pumps and the history of their development. Dr. Mecklenburg described the extensive experience of his group at Mason Clinic in use of insulin pumps in over 100 patients. He described the process of selection and education of patients and continuous medical supervision required for this form of therapy. He emphasised the need for self blood glucose monitoring and availability of alternative stand-by pump from the Clinic in case of pump failure. He pointed out the psychological problems associated with the use of pump. The metabolic control achieved with the use of pump was good, resulting in normalisation of glycohemoglobin in about half of the patients. However, on prolonged follow-up glycohemoglobin remained normal throughout the period of study in only 15 per cent of patients.

Dr. Shipp pointed out the complications of pump therapy. The main problems are skin infections, hypoglycemia and pump failure. In the event of failure, patient may go into acute ketoacidosis. Dr. Mecklenburg presented analysis of Mason Clinic data, yet unpublished, which compared the patients on pump with controls regarding incidence of infection, ketoacidosis and hypoglycemia. These data revealed that incidence of infection was 1 episode per 31 patient-months. Ketoacidosis was more frequent in pump users (1 per 78 patient-months in pump patients versus 1 per 196 patient-months in controls). Hypoglycemia was less frequent in pump-users. An analysis of pump-death was presented by Dr. Mecklenburg, pointing out the safety of most pumps.

A varieties of pumps were demonstrated by Dr. Mecklenburg and Dr. Shipp. Day to day problems of blocking of pump tubings with insulin aggregation, fibril formation and air bubbles were discussed.

The Indian faculty presented its limited experience with insulin pumps and the problems of developing countries. Dr. Chandalia described his experience with Mayfuser pump of Japanese make in 3 patients of acute, sensori-motor peripheral neuropathy and 3 patients of macular edema. Acidic insulin used in India diminishes chances of insulin aggregation. Dr. Vishwanathan described restoration of insulins sensitivity following a. brief period of pump therapy. Dr. Ahuja described his experience with a Mill-Hill infuser.

Close monitoring of blood glucose is essential component of insulin pump therapy. Dr. Shipp elaborated on the accuracy and limitations of self blood glucose monitoring methods. He pointed out that most expensive item in the cost of diabetes-care at present is the cost of monitoring control of diabetes. Dr. Chandalia emphasized the value of glycosylated hemoglobin in judging control of diabetes. He compared the column method and chemical method used in the estimation of glycosylated hemoglobin and brought out the overall superiority of the chemical method used by him. In a set of 800 estimations he found the interpretation of control of diabetes different in about one-half of the patients on the basis of glycosylated hemoglobin estimation as compared to blood glucose estimation.

Dr. Shipp discussed the glucose-controlled insulin infusion system (GCIIS, closed loop insulin delivery system). He described the algorithms of this system and its use in research and clinical practice. This equipment can be used to control diabetes rapidly and in determining insulin requirements of a patient. It is also useful in controlling diabetics undergoing major surgery. Dr. Mecklenburg described the new developments likely in the area of implantable open-loop or closed-loop insulin infusion pumps.