Lente Insulin in Diabetic Children

Robert A. Lussky, M.D., Alvah L. Newcomb, M.D.,†*
and Howard S. Traisman, M.D.,‡ Evanston, Illinois

Lente insulin has been used in the diabetes outpatient clinics of the Children's Memorial Hospital and Evanston Hospital for the past eighteen months. This paper is the first report of our experiences with this new type of insulin.

Since 1922, when insulin was first discovered, many modifications have been tested, and several have been made available for clinical use. No single preparation has been entirely satisfactory, although various combinations have been used with better results. Recently a new modification, Lente insulin, has become available. Developed in the Novo Laboratories in Denmark, it was first described by Hallas-Møller in 1951.[1] Since then a number of reports have indicated that this insulin has a definite place in the treatment of diabetes mellitus.[2, 3, 4, 5, 6]

The production of Lente insulin is based on the recent discovery that insulin together with a small quantity of zinc, the combination precipitated in an amorphous or crystalline state, has a protracted effect. The need for various modifying agents such as protamine, globin, histone and surfen, which are foreign proteins, is not necessary. By using an acetate buffer, instead of the commonly employed phosphate buffer which combines with zinc, and by carefully regulating the *p*H during precipitation, combinations of zinc and insulin can be produced in two different physical forms. The amorphous form, designated Semilente, shows only a slight prolonged action, approximately twelve hours. The crystalline form, designated Ultralente, has a very low solubility and shows a range of activity of more than 30 hours. The zinc content of both preparations is the same as in protamine zinc insulin, 2 mg. per thousand units. The *p*H of the preparation is 7.2. A mixture of these two forms consisting of 70 per cent of the Ultralente and 30 per cent of the Semilente has been designated Lente insulin and has a range of activity of about twenty-four hours. This mixture, which we used in our study, was furnished by the Eli Lilly Company.

The preliminary report by Hallas-Møller[1] indicated that satisfactory control of blood sugar could be obtained in a large number of difficult cases of diabetes mellitus with a single daily injection of an appropriate mixture of Semilente and Ultralente insulins. Peck and Kirtley[2] concluded that the ratio of 30 per cent Semilente to 70 per cent Ultralente was generally most useful; its action was similar to NPH insulin and in occasional cases somewhat longer in duration. Ferguson[3] compared Lente insulin with multiple daily injections of soluble insulin in fifteen diabetic children and found that the control of blood sugar was at least as good with Lente insulin, and in some cases better. He felt that the majority of diabetic children could probably be satisfactorily controlled with the insulin-zinc suspensions. Gurling[4] studied 45 diabetic children, 30 of whom were patients of long standing. Of these 30 patients, 11 showed improvement with the new insulin while the other 19 patients remained unimproved in the control of their diabetes. The other 15 patients were recently diagnosed cases, and all were satisfactorily controlled. Both authors[3, 4] had to vary the percentage of Semilente and Ultralente insulin in the mixtures they used for adequate control of their patients.

The indications for the use of Lente insulin include difficult control with other insulin preparations, requirement of multiple injections, and allergy to other types of insulin.

METHOD OF STUDY

Fifty-four children were studied in private practice and in the diabetes outpatient clinics and hospitals whence

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*Clinical Assistant in Pediatrics, Northwestern University Medical School; Attending Physician, Evanston Hospital, Evanston, Illinois, and Children's Memorial Hospital, Chicago.

†Assistant Professor of Pediatrics, Northwestern University Medical School; Attending Physician, Evanston Hospital, Evanston, Illinois, and Children's Memorial Hospital, Chicago.

‡Instructor in Pediatrics, Northwestern University Medical School; Attending Physician, Evanston Hospital, Evanston, Illinois, and Children's Memorial Hospital, Chicago.

Address requests for reprints to Dr. Howard S. Traisman, 6354 N. Broadway, Chicago 40, Ill.

this paper originates. Fifteen were previously untreated diabetics who were managed with Lente insulin immediately following the treatment of their initial acidosis with crystalline zinc insulin. The other thirty-nine children had diabetes of long duration and showed variable degrees of control prior to their transfer to Lente insulin. None of the children was hospitalized specifically for this study. Only those with complications requiring hospitalization were subjected to laboratory studies other than the simple urine tests for glucose and acetone.

A few of the children received Lente insulin while hospitalized, but the majority received it as a routine procedure in the clinic. The initial dosage was one unit of Lente insulin for each unit of the previous insulin used. In the first few cases, Lente was used alone, but it soon became apparent that crystalline insulin would have to be added in approximately the same amount as was prescribed with NPH insulin. Variations in insulin dosage of a few units were frequently made when indicated but were not felt to be significant. The insulin was given in one daily injection before breakfast. When crystalline insulin was added to the Lente insulin, it was mixed in the same syringe by the patient. The dose of crystalline insulin was small, usually one-fourth of the total, but in a few instances one-half of the total daily insulin was prescribed. In one case it was necessary to mix the insulins in the bottle.

All patients received a weighed diet of approximately 3 to 4 gm. of protein per kilogram of body weight, with a protein to fat to carbohydrate ratio of approximately 1:1:2. The total caloric value was appropriate for their ages and ideal weights. The division of calories among the three main meals was approximately equal and varied only slightly in the individual patients when it seemed that extra food at a particular meal controlled the hypoglycemic tendencies following that meal. The weighed diets were maintained at home and in the hospital with slight variations in the amount of the mid-afternoon and bedtime feedings. A few of the patients also received mid-morning feedings.

The patients were unrestricted in their activity. They were required to test their urine three to five times daily, and to record in a notebook in appropriate colors the presence or absence of glycosuria. In the hospital the patients' urine was checked four times daily, frequent fasting blood sugars were determined, and twenty-four-hour urinary glucose was determined quantitatively. The activity of the hospital patients was unrestricted within the ward but was generally less than at home.

The estimation of clinical control was based on the patient's well-being, freedom from symptoms, and a normal gain in weight. If acetone appeared in the urine, or glycosuria appeared in more than half of the daily urine specimens, or mild reactions occurred, diabetes was considered to be unsatisfactorily controlled and readjustment of the insulin dosage or diet was made. Under the conditions of the study, it was impossible to set up more rigid criteria of satisfactory control. The parents were questioned about the general condition of the child, and their observations were recorded in the patient's chart. This study is based upon these observations. Laboratory studies, other than the simple urine tests for sugar and acetone, were used primarily as an aid to achieving good clinical control.

RESULTS

The ages of the children varied from 15 months to 15 years, the duration of the diabetes from 2 weeks to 8½ years. In nine children NPH insulin was reinstituted for the following indications: Eight children were poorly controlled with Lente insulin. Of this group one father felt that his son's general condition was better with NPH insulin after a one-month trial with Lente insulin. This boy observed no dietary restrictions at home and varied his insulin from one-half to twice the prescribed dosage. Blood glucose determinations while the patient was in the hospital showed much better control with Lente insulin.

The ninth child who was returned to NPH insulin seemed to be doing well with Lente insulin. His weight gain was good and he had less glycosuria. However, after a three-month period his liver became enlarged. The liver function tests were normal except for hypercholesterolemia. One month later, with no decrease in hepatomegaly, NPH insulin was prescribed. There was a recession in liver size after three months.

BRIEF CASE REPORTS

1. J. Z., a girl of five years, entered the Children's Memorial Hospital with diabetic acidosis which responded well to therapy with crystalline insulin and parenteral fluids. She was well controlled in the hospital with Lente insulin and crystalline insulin. However, because of the parents' inability to comprehend the mixing of Lente and crystalline insulin, it is now mixed in the proper proportions in one bottle, as needed. She is gaining weight, and her glycosuria is well controlled.

2. L. S., a Puerto Rican girl of five years, had received an unknown amount and type of insulin prior to her first admission to Children's Memorial Hospital. She weighed 12 kg. and had had symptoms of diabetes for about five months. Her history was obtained through an interpreter and was incomplete. Her mother and maternal grandmother are diabetic. Nineteen units of Lente insulin and 10 units of crystalline insulin were prescribed. Blood glucose determinations at two-hour intervals between 8:30 a.m. and midnight were between 50 and 125 mg. per 100 cc. from noon until midnight, but the mid-morning spe-

cimen was over 400 mg. per 100 cc. This extremely high value was thought to be due to an insufficient amount of crystalline insulin. On the following day, additional crystalline insulin was used with better blood glucose control in the morning. She gained 6 kg. in the next five months.

3. J. H., a boy of nine years, had been managed for four years with a mixture of NPH and crystalline insulin. He was changed to 34 units of Lente insulin without added crystalline insulin seven months ago, and since then his general well-being and control have been better. This child was one of the two patients we were able to manage with Lente insulin alone.

Of the 15 previously untreated patients, 14 have been managed with a mixture of Lente insulin and crystalline insulin following the treatment of their initial acidosis with crystalline insulin. The other one, an 11-year-old girl, had been satisfactorily controlled on 32 units of Lente insulin alone. She has gained 4 kg. Control of all the new diabetics has been very satisfactory in spite of difficult home situations in two instances.

DISCUSSION

Our observations of 54 juvenile diabetic patients over a period of 18 months has shown that Lente insulin appears to be an effective and reliable intermediate-acting insulin preparation for the treatment of diabetes mellitus in children. Its time and mode of action are very similar to those of NPH insulin, but in some cases somewhat longer in duration. When a patient has been well controlled on NPH insulin, the transition to Lente insulin on a unit for unit basis is usually smooth.

In most patients, we found it necessary to add some crystalline zinc insulin to the Lente insulin to achieve adequate control. The two insulins were then mixed in the same syringe. The difference in *p*H of the two preparations seemed to cause no noticeable alteration in the time action of the Lente insulin other than what would be expected by the addition of crystalline insulin. Mixtures with approximately 40 per cent Semi-lente insulin and 60 per cent Ultralente insulin may more nearly approximate the needs of most diabetic children.

The specific advantages of this new insulin preparation as compared to NPH insulin are the absence of a foreign protein and a slightly longer duration of action. The stinging sensation noted in about 20 per cent of our patients is a minor disadvantage. Another disadvantage of the Lente insulin is the occurrence of more frequent early morning reactions which may be overcome by careful prescription of the bedtime feeding or reduction of the dose of Lente insulin.

Indications

We have prescribed Lente insulin for all new diabetic patients, for all whose matutinal glycosuria has not been satisfactory, and for all poorly controlled "brittle" diabetics.

Unusual Reactions

Patients who had repeated severe hypoglycemic reactions are likely to have similar episodes with the new insulins and are particularly to be cautioned concerning the probable timing of hypoglycemic episodes. Severe hypoglycemic episodes have been observed under a variety of circumstances, including change from daylight saving time to standard time, later breakfast on Sunday after an active week end, and change to Lente insulin. For example, a 13-year-old girl who was poorly controlled on various mixtures of 120 units of insulin, had 2 severe reactions with Lente insulin until her new insulin requirement was found to be 80 units. Another girl developed hives which disappeared when NPH insulin was prescribed. Infants and children up to five years of age have been less well controlled and have appeared to have more frequent insulin reactions with Lente insulin.

SUMMARY

Fifty-four diabetic children were studied in hospitals and out-patient clinics and in private practice. With a weighed diet and unrestricted activity, their level of control was estimated on subjective and objective evidence. Of the 39 previously diagnosed and treated juvenile diabetics, 24 were improved with Lente insulin, 6 showed no change, and 9 were returned to their former type of insulin. The 15 newly discovered diabetic patients were satisfactorily controlled with Lente insulin.

The change to the new insulin was usually uncomplicated, and alteration of dosage was insignificant. Hepatomegaly developed in one patient and urticaria in another, but both conditions receded when NPH insulin was reinstituted.

Lente insulin is an effective and reliable intermediate-acting insulin preparation for the treatment of juvenile diabetes mellitus. Its time and mode of action are very similar to those of NPH insulin but in some cases somewhat longer in duration. When a patient has been well controlled with NPH insulin, the transition to Lente insulin on a unit for unit basis is usually smooth. In most patients it is necessary to add some crystalline zinc insulin to the Lente insulin to achieve adequate control.

SUMMARIO IN INTERLINGUA

Insulina Lente in Diabeticos Juvenil

Esseva studiate 54 diabeticos juvenil in hospitales, clinicas a patientes visitante, e le practica private. Con dietas a peso determinate e sin restriction del activitate, lor grados de controlo del morbo esseva estimate super

le base de datos subjective e objective. Le gruppo includeva 39 diabeticos juvenil qui habeva essite diagnosticate e tractate ante le tempore del presente studio. Inter illes, 24 esseva meliorate per insulina Lente, 6 monstrava nulle alteration, e 9 esseva retornate a lor previe typo de insulina. Le 15 novemente discoperite casos, etiam includite in le serie total, attingeva satisfacente grados de controlo del morbo per medio de administrationes de insulina Lente.

Le transition al nove typo de insulina causava generalmente nulle complication. Le alteration del dosage non esseva significative. Hepatomegalia se disveloppava in un patiente e urticaria in un altere, sed ambe iste conditiones dispareva quando insulina NPH-50 esseva reinstituite.

In le tractamento de patientes juvenil de diabete mellite, insulina Lente es un efficace preparato a action intermediari. Su tempore e su modo de action es similissime a illos de insulina NPH-50, sed in certe casos insulina Lente ha un durantia plus extense. In le caso de patientes qui ha attingite bon grados de controlo per medio de insulina NPH-50, le transition a insulina Lente in dosages identic es generalmente libere de complicationes. In le majoritate del casos il es necessari adder al insulina Lente un pauco de crystallin insulina a zinc pro obtener adequate grados de controlo.

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Vitamin B_{12} Deficiency in Vegetarians

Children appear to be more adversely affected by the (vegetarian) diet than adults, and Wokes *et al.* suggest that the absence of symptoms in the group of American vegans studied by Hardinge and Stare may be because the British group contained more young people "who are probably more susceptible to vitamin B_{12} deficiency." That a vitamin B_{12} deficiency was involved was suggested by the serum of vitamin B_{12} levels. These ranged from 45 to 193 micromicrograms per milliliter (average 111 micromicrograms per milliliter) as compared with the average normal range of 200 to 300 micromicrograms per milliliter, and in more than half the vegans the average concentration was less than 120 micromicrograms per milliliter. Further, the deficiency symptoms in vegans could be alleviated by administration of vitamin B_{12}, and one of the investigators (J. Badenoch) has described [*Proc. Roy. Soc. Med.* 47:426 (1954)] the case of a vegan boy, age 15, who developed a severe vitamin B_{12} deficiency with subacute combined degeneration of the cord which "responded dramatically" to treatment with vitamin B_{12} alone. Some support for these findings of vitamin B_{12} deficiency in vegans is provided by a Dutch study [W. F. Donath, I. A. Fischer, H. C. van der Meulen-van Eysbergen, and J. F. de Wijn, *Voeding* 14:153 (1953)] of 59 adult vegans, 12 per cent of whom developed oral symptoms, and 6 per cent paresthesia. Wokes and co-workers believe that the lower incidence of symptoms "was probably because 72 per cent of the Dutch vegans . . . had been on the vegan diet for less than two years, as compared with an average of five to six years for British vegans."

It is perhaps not surprising to find symptoms of vitamin B_{12} deficiency occurring in people who have been subsisting for years on the vegan diet which, of course, contains no animal protein.

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