Insulin Treatment of Juvenile Diabetes

Observations on the Combined Use of Intermediate and Regular Insulins

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For many years the management of diabetes mellitus at the Pediatric Clinic of the State University of Iowa has had as its objective to attain and maintain physiologic control. To accomplish this end we have found the administration of insulin on a percentage distribution basis practicable.

Under the standard conditions of quantitative diet and exercise in the hospital, we obtained normoglycemic diurnal curves when four doses of regular insulin were distributed as 35, 22, 28, and 15 per cent of the total daily dosage, the injections being given one-half hour before meals and once during the night. This pattern of distribution, in keeping with the generally acceptable three-meal plan of the child, has guided us when modifying our regimen as new types of insulin have become available. We found it impossible to attain our objective using protamine-zinc insulin. In 1944, when globin insulin with zinc was made available, we started to use it in a regimen which we had developed in our clinic. In this plan, one dose of globin insulin with zinc given one hour before the evening meal replaced the evening and night doses of regular insulin.[1] In 1953, when NPH insulin was made available, we studied its use in place of globin insulin and observed no significant differences in the diurnal blood sugar curves for groups of well regulated diabetic children.[2]

The purpose of this study is to present the development of a satisfactory two-injection regimen employing mixtures of an intermediate insulin and regular insulin as the morning injection and an intermediate insulin as the evening injection. The intermediate insulins employed are NPH and globin insulin with zinc.

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METHOD OF STUDY

Subjects used for the development of the new regimens were limited to diabetic children living under controlled conditions in the hospital. The nursing staff cooperated in an effort to attain accuracy in dosage of insulin, site and depth of injection, standardization of exercise, collection of urine specimens and recording of any variable factors which arose during the period of study. Competent dietitians were responsible for the calculation of diets and the weighing and preparation of food. All urine voided was analyzed by laboratory technicians, who also determined blood sugar values one or two days each week at the following hours: 7, 9, and 11 a.m., 4 and 10 p.m., and 2 and 6 a.m. All subjects used were emotionally adjusted and free from infections. Each child underwent a prolonged observation period during which the insulin requirement became constant for the standard condition imposed by the therapeutic regimen. All subjects remained free both from glycosuria and from clinically significant insulin reactions and maintained approximately normal diurnal blood sugar fluctuations.

Data for study of the regimen during hospitalization and under home conditions of the diabetic children have been compiled over a three-year period.

Our standard diet distribution during the control period was used for patients receiving regular insulin one-half hour before the morning and noon meals and globin insulin with zinc one hour before the evening meal. This diet distribution consists of 6/18 of the caloric intake at breakfast, 6/18 at noon, and 5/18 at supper, with an evening supplement of 1/18.

The type of diet distribution used by the experimental groups has been one in which the total diet for the day was also divided into 18 portions, with 4/18 being given at breakfast (7:15 a.m.), followed by a mid-morning snack approximately two to two and one-half hours after breakfast (9:30 a.m.) consisting of 2/18 of the total caloric intake for the day; the noon meal was 5/18 of the daily allowance, followed by a mid-afternoon snack at 3 p.m. of 1/18; supper at 4:45 p.m. was 5/18, and an evening snack at 9 p.m., 1/18. This

diet distribution was adjusted to meet the varying needs of patients under home management.

IN-PATIENTS

A total of 16 patients was observed during hospitalization. As an initial program, separate injections of an intermediate insulin and regular insulin were given in the morning, the third injection of the day being an intermediate insulin administered in the evening.

Various proportions of the regular and intermediate insulins were studied beginning with a percentage distribution of the twenty-four-hour insulin requirement of 30 per cent NPH or globin and 30 per cent regular insulin in the morning, and the remaining 40 per cent as NPH or globin in the evening. We shall designate this distribution for convenience as the 30-30-40 distribution, the intermediate insulin being the first and last named in the series. We progressed through the percentage distributions 35-25-40, 40-25-35, and 45-20-35 until the most satisfactory distribution of 50-15-35 was reached. It will be noted that the percentage of intermediate insulin in the morning injections was gradually increased, whereas the percentage of regular insulin was gradually decreased. The percentage of the total daily quantity of insulin given as an intermediate insulin in the evening was progressively decreased.

To ascertain the effect of the varying proportions of regular and intermediate insulin on the diurnal blood sugar values, each type of distribution was analyzed and compared with the range of diurnal blood sugar values obtained in six nondiabetic children and also the mean and range of values observed in 55 hospitalized diabetic children in excellent control. Figure 1 is based on 12 diurnal blood sugar curves of two patients using the 30-30-40 insulin distribution. It was observed that there was an initial fall in the blood sugar level to the lowest levels at 9 a.m., followed by a rise to peak levels at 4 p.m., with subsequent gradual decline in blood sugar levels until the 2 a.m. specimen, and then a slight increase in the 6 a.m. specimen.

Figure 2 is based on three diurnal blood sugar curves of two patients using the 35-25-40 distribution of insulin. The lowest levels occurred in the 11 a.m. specimens, and the high levels again were observed at 4 p.m. The peak was followed by a steady decline in blood sugar levels until the 2 a.m. specimen, and then a rise during the 6 a.m. tests.

Figure 3 shows the average of two diurnals of a patient receiving insulin distributed in the 40-25-35 plan. The lowest blood sugar values of any distribution test were noted in this plan. Low levels were observed at

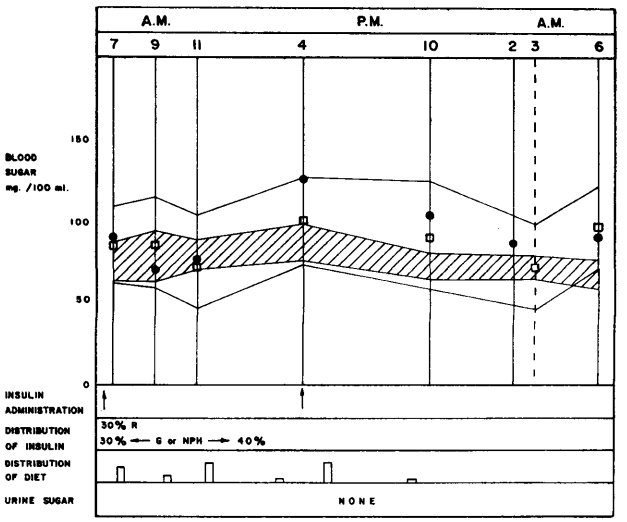

FIG. 1. The cross-hatched area represents the range of 12 diurnal blood sugar values observed in 6 nondiabetic children. The open squares and the area between the two black lines represent the mean and mean plus and minus one standard deviation, respectively, of 176 diurnal blood sugar values observed in 55 hospitalized diabetic children in excellent control. The solid dots represent the mean of 12 diurnal blood sugar values of 2 patients receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 30-30-40.

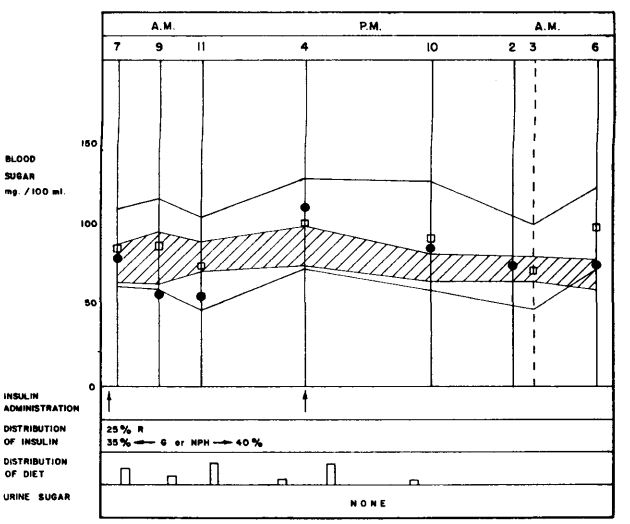

FIG. 2. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of three diurnal blood sugar values of two patients receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 35-25-40.

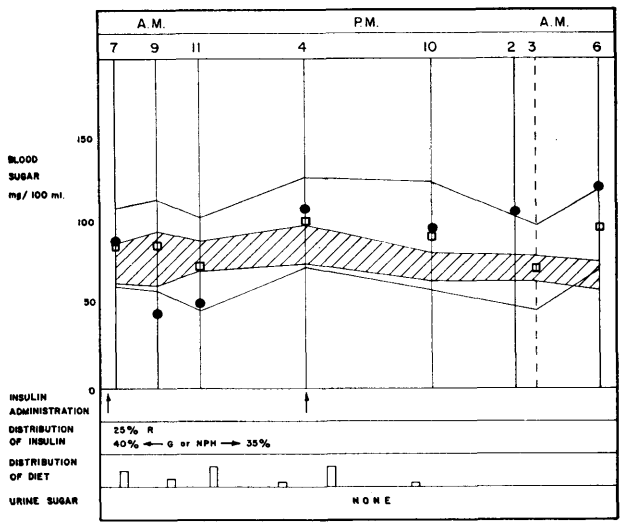

FIG. 3. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of two diurnal blood sugar values of one patient receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 40-25-35.

9 a.m., with a peak at 4 p.m., followed by a decline until 10 p.m., and then a rise at 2 and 6 a.m.

Figure 4, based on three diurnal blood sugar curves of one patient using the 45-20-35 distribution, shows the highest peak levels, which were reached at 4 and 10 p.m.,

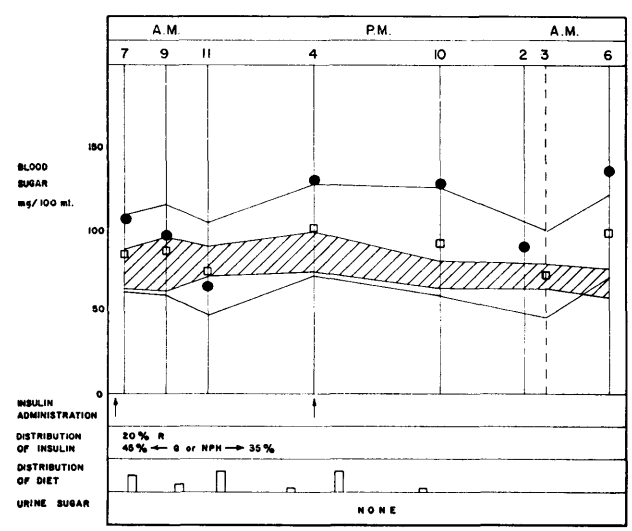

FIG. 4. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of three diurnal blood sugar values of one patient receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 45-20-35.

following an initial drop to the lowest level at 11 a.m. Again there was a decline from peak level until the 2 a.m. tests, with subsequent rise in the 6 a.m. specimens.

Figure 5 shows the mean of 18 diurnal blood sugar values of four patients receiving insulin distributed according to the 50-15-35 plan. This distribution resulted in the most consistent average blood sugar level, with a gradual decline from 7 to 11 a.m., followed by increasing values until the peak was reached at 10 p.m., with a slight decrease at 2 a.m. and a minimal rise at 6 a.m.

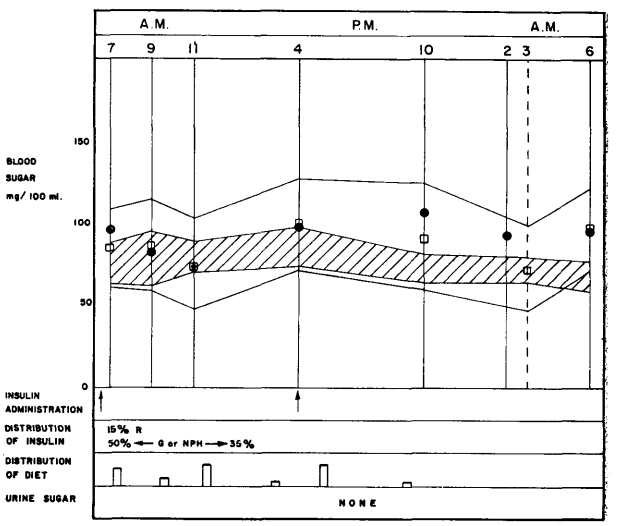

FIG. 5. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of 18 diurnal blood sugar values of four patients receiving separate injections of regular and an intermediate insulin in the morning and an injection of an intermediate insulin in the evening. The percentage distribution of the insulin is 50-15-35.

The next step was an attempt to use a two-injection program: a mixture of intermediate and regular insulin administered as a single injection before breakfast, and an injection of intermediate insulin in the evening. On the basis of our studies with separate injections, the 50-15-35 distribution was selected and a trial was made of a mixture of NPH and regular insulin as the morning injection and NPH for the evening. Figure 6 depicts the mean of nine diurnal blood sugar curves of three patients using this plan. The diurnal blood sugar values are not as smooth as those obtained by separate injections, which may indicate a certain amount of interaction between NPH and regular insulin when mixed. The blood sugar values, however, indicate adequate control, remaining within one standard deviation of the mean values of diabetic children in ideal control.

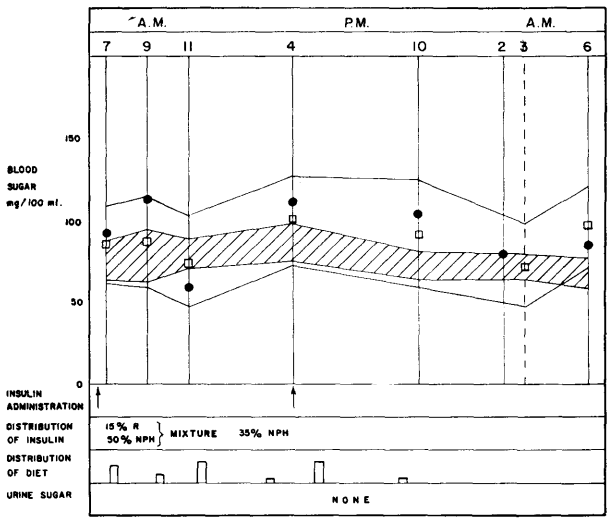

FIG. 6. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of nine diurnal blood sugar values of three patients receiving a mixture of NPH and regular insulin in the morning and an injection of NPH insulin in the evening. The percentage distribution of the insulin is 50-15-35.

Trials of a program using a mixture of globin and regular insulin as the morning injection and globin for the evening were made. On the basis of the separate injection plans and the apparent loose combination between globin and insulin in which the relative proportions of the two ingredients may vary over a wide range, the percentage distribution 45-20-35 was selected. Figure 7 shows the mean of seven diurnal blood sugar curves of three patients using the mixture program with the 45-20-35 percentage distribution. The blood sugar values using this distribution indicated an even and adequate control.

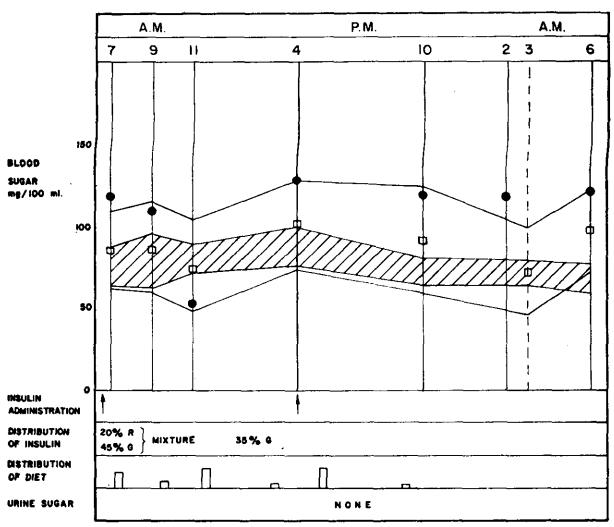

FIG. 7. The cross-hatched area, the area between the black lines, and the open squares represent the same as in figure 1. The solid dots represent the mean of seven diurnal blood sugar values of three patients receiving a mixture of globin insulin with zinc and regular in the morning and an injection of globin insulin in the evening. The percentage distribution of the insulin is 45-20-35.

OUT-PATIENTS

After we had demonstrated to our satisfaction that diabetic children could be well controlled as in-patients with a mixture of regular and intermediate insulin, we began studies on this program on an out-patient basis in an attempt to determine whether or not it would prove to be a practical method of home regulation of juvenile diabetics. Only a few trials of the globin and regular mixture have been made under home conditions.

Of the 80 patients who have received the NPH mixture on an out-patient basis, 39 have records which are deemed reliable and complete enough for research studies. Table 1 is a summary of some of our findings in this group of patients.

The 39 children selected for this study have been arranged according to their degree of control during the experimental period (regimen of NPH and regular insulin mixture). Each subject has been observed for an equal length of time during the control period and during the study of NPH and regular mixture; and, in all but a few cases, the two periods have been contiguous, representing a total of 2616 patient weeks for the entire study, or 1308 patient weeks of observation of the regimen of NPH and regular insulin mixture.

It was noted that there was no dramatic change in the level of diabetic control in most cases when a patient was changed from the control regimen to the program of NPH and regular insulin mixture. In some instances diabetic control improved, while in others it was less satisfactory.

The number of insulin reactions also was not appreciably affected by a change in regimen but, as should be expected, reactions were more frequent in those patients in suboptimal diabetic control. Six patients in the study had ten or more insulin reactions during one or the other of the observation periods. Electroencephalographic studies were available in five of these cases with normal findings in three, borderline in one, and abnormal in one.

DISCUSSION

When the NPH and regular insulin mixture is used for control of a juvenile diabetic in the home, it has been our policy to ascertain first the degree of proficiency with which the parents are able to manage the problem using the standard regimen; that is, regular insulin before the morning and noon meals and globin or NPH

TABLE 1

No.	Sex	Chronologic age years and months: At onset of diabetes mellitus	When disease completely controlled	At beginning of study	Length of each observation period (weeks)	Observation Periods: Control: Range of insulin dosage (units)	Degree of control	Reactions: Mild	Moderate	Severe	Experimental: Range of insulin dosage (units)	Level of control	Reactions: Mild	Moderate	Severe
1	F	5-4	5-6	6-0	20	7-15	Good	0	0	0	15-20	Good	3	0	0
2	F	5-0	5-1	7-3	52	17-24	Good	0	1	0	24-32	Good	4	0	0
3	M	10-6	10-7	10-9	12	10-42	Fair	0	0	0	24-35	Good	0	0	0
4	M	11-1	11-2	11-2	36	25-33	Good	1	0	0	31-51	Good	1	0	0
5	F	1-5	1-7	11-4	28	49-53	Fair-poor	0	0	0	51-54	Good	0	0	0
6	M	6-2	6-4	12-5	52	48-66	Good	4	1	0	66-73	Good	6	0	0
7	M	12-2	12-3	12-10	52	45-57	Good	0	0	0	57-90	Good	0	0	0
8	F	2-5	2-7	13-5	16	80-104	Good	0	0	0	64-104	Good	0	0	0
9	M	10-4	10-5	13-6	24	60-84	Good	0	0	0	71-85	Good	0	0	0
10	M	13-11	14-1	14-1	32	54-64	Good	0	0	0	54-88	Good	0	0	0
11	F	8-11	9-0	14-2	12	70-101	Good	0	0	0	72-51	Good	0	0	0
12	M	7-8	7-10	14-5	32	69-120	Good	0	0	0	116-128	Good	0	0	0
13	M	14-2	14-4	14-7	52	9-14	Good	0	0	0	13-14	Good	1	0	0
14	F	9-6	9-7	14-10	32	38-42	Good	0	0	0	38-39	Good	0	0	0
15	M	13-10	14-0	14-10	40	48-73	Good	0	0	0	51-75	Good	0	0	0
16	M	15-1	15-3	15-7	8	30-31	Good	1	0	0	38-40	Good	3	0	0
17	F	16-0	16-3	16-8	52	48-60	Good	2	0	0	52-57	Good	2	0	0
18	M	14-10	15-0	18-1	24	35-38	Good	0	0	0	35-38	Good	0	0	0
19	M	2-10	2-11	3-9	52	10-13	Fair	2	0	0	11-12	Fair	0	0	0
20	M	5-2	5-3	5-3	36	8-14	Good	0	0	0	10-18	Fair	1	0	0
21	F	4-5	4-6	5-1	12	9-13	Fair	1	0	0	9-18	Fair	0	0	0
22	F	4-6	4-8	6-5	16	21-25	Fair-poor	5	1	0	23-26	Fair	2	2	0
23	M	3-10	4-0	7-7	52	17-25	Fair	10	0	0	30-40	Fair	15	4	0
24	M	0-9	0-11	11-9	40	30-42	Good	2	0	0	55-84	Fair	4	0	0
25	M	2-3	2-5	13-11	28	61-72	Fair	4	0	0	68-108	Fair	10	1	0
26	F	3-1	3-4	17-6	36	51-77	Fair	22	1	0	51	Fair	0	0	0
27	F	6-2	6-4	17-7	12	76-80	Fair-poor	0	0	0	80-81	Fair	0	0	0
28	F	10-3	10-7	18-2	48	49-57	Fair	4	2	0	54-60	Fair	1	0	1
29	F	3-0	3-5	4-10	8	23-32	Fair-poor	4	0	0	28-39	Fair-poor	1	0	0
30	M	4-9	5-1	5-3	48	11-27	Fair-poor	0	0	0	30-34	Fair-poor	0	0	0
31	F	4-6	4-10	5-4	64	10-30	Fair-poor	4	3	0	28-40	Fair-poor	10	0	1
32	F	4-8	5-0	7-6	28	39-49	Fair-poor	20	0	0	32-48	Fair-poor	10	0	0
33	F	5-5	5-6	10-0	24	25-42	Fair-poor	4	0	0	42-51	Fair-poor	0	0	0
34	M	8-8	8-10	10-1	44	41-47	Fair	0	0	0	42-53	Fair-poor	1	0	0
35	M	8-1	8-2	12-10	12	36-38	Fair-poor	0	0	0	36-39	Fair-poor	1	0	0
36	M	5-7	5-9	13-0	24	49-60	Fair	0	0	0	51-60	Fair-poor	0	0	0
37	F	7-4	7-5	14-1	8	68-75	Fair-poor	15	0	0	58-92	Fair-poor	19	0	0
38	M	11-2	11-3	16-6	16	90-95	Fair-poor	0	0	0	88-97	Fair-poor	1	0	0
39	F	1-6	1-8	17-9	32	56-68	Fair-poor	0	0	0	49-60	Fair-poor	0	0	0

*Basic diet prescribed permits fluctuations in caloric intake to compensate for variations in physical activity.

Basic diet*	
Control period	Experimental period
No change	Increased 200 cal.
No change	Increased 200 cal.
No change	No change
Increased 200 cal.	Increased 200 cal. more
No change	Increased 200 cal.
No change	Increased 400 cal.
No change	Increased 400 cal.
No change	Decreased 200 cal.
No change	No change
Decreased 200 cal.	Increased 300 cal.
No change	No change
No change	No change
No change	No change
No change	Decreased 200 cal.
No change	No change
No change	Increased 300 cal.
Decreased 200 cal.	No change
No change	Increased 200 cal.
No change	Increased 200 cal.
Increased 400 cal.	Increased 200 cal. more
No change	Increased 200 cal.
No change	No change
Increased 400 cal.	Increased 200 cal. more
Increased 200 cal.	No change
Increased 300 cal.	Increased 400 cal. more
Decreased 400 cal.	No change
No change	No change
Decreased 200 cal.	No change
No change	No change
Increased 200 cal.	Increased 400 cal. more
Increased 200 cal.	Decreased 200 cal.
No change	No change
No change	No change
No change	No change
No change	No change
No change	No change
No change	Decreased 200 cal.
No change	Increased 150 cal.
No change	Increased 200 cal.

before the evening meal as described in previous papers.[1, 2] This policy serves a dual purpose. First, it is thought that parents unable to control a child satisfactorily by using this program will, in general, not be able to maintain adequate control with a modified regimen. Second, it is desirable that the parents be familiar with the method of control using regular insulin, so that in the event of intercurrent infection or danger of wide and sudden fluctuations in insulin requirements, they will be able to use a program utilizing insulin with a shorter duration of action to maintain better control when the insulin dosage is changing rapidly.

During hospitalization, we have been able without exception thus far to maintain good diabetic control in patients by using the NPH or globin and regular insulin mixture. On an out-patient basis, however, a small percentage of patients have been changed back to two doses of regular and one of intermediate insulin, the most common reason given being inability to control the glycosuria as well when using the new program.

Other difficulties reported by a few patients relate to the problem of the mid-morning and mid-afternoon snacks. In some instances the proper type of food is not readily available so that a lunch basket must be carried to school. This problem is most evident in children of grade school age; in the older age groups the mid-morning and mid-afternoon supplements fit very conveniently into the recess periods when other children also are eating snacks.

Another factor entering into the picture in some patients who have reverted to the previous regimen is that of great confidence in the standard program, such that it is difficult for the parents to comprehend how any other program could be as satisfactory. At the first hint of difficulty they return to the program with which they are most familiar and in which their confidence lies.

On the other hand, the vast majority of patients after changing to the program of NPH and regular insulin mixture are extremely enthusiastic. Greatly appreciated is the elimination of the noon insulin injection. Others express gratitude for being able to participate in the snacks with a clear conscience, enhancing their feeling of normality and boosting their morale. It was observed, however, that in some instances patients overstepped their new-found freedom.

It has been our experience that in some patients who had been extremely difficult to control using other programs, good control has followed institution of the new regimen.

At the present time a total of 81 patients have used the NPH-regular mixture with six reversions to the older program.

Studies in progress at this time indicate that satisfactory control may also be maintained using a two-injection schedule consisting of a globin-regular mixture in the morning and an injection of globin insulin in the evening. The dietary distribution is the same as that used in the NPH-regular mixture program.

SUMMARY

A program of juvenile diabetic management using a mixture of NPH and regular insulin as the morning injection and NPH for the evening injection is presented. Also discussed are the studies leading to the selection of a satisfactory ratio for the mixture and the type of dietary distribution. Studies of similar regimens using a mixture of globin and regular insulin as the morning injection and globin insulin for the evening injection resulted in satisfactory control of hospitalized patients. Further studies with globin and regular insulin mixture are in progress.

Follow-up statistics on those patients using the new program at home are tabulated.

It is now possible to maintain satisfactory regulation of juvenile diabetes in approximately 90 per cent of cases, using a two-injection program, a mixture of NPH or globin and regular insulin in the morning and globin or NPH insulin in the evening.

SUMMARIO IN INTERLINGUA

Insulina in le Tractamento de Diabeticos Juvenil: Observationes Super le Uso Combinate de Insulinas Intermediari e Regular

Es presentate un programma therapeutic pro diabeticos juvenil, usante un mixtura de insulina NPH e insulina regular como injection matinal e insulina NPH como injection vespertin. Es etiam discutite le studios que establiva un satisfacente proportion del insulinas in le mixtura e un recommendabile typo de distribution dietari. Studios con un simile programma usante un mixtura de insulina globinic e insulina regular como injection matinal e insulina globinic como injection vespertin resultava in satisfacente controlo de patientes hospitalisate. Studios additional con insulinas globinic e regular es in execution.

Es presentate tabulationes statistic post-hospitalari pro le patientes qui usa le nove programma a lor domicilios.

Il es nunc possibile mantener un satisfacente regulation in circa 90 pro cento del casos de diabete juvenil, usante un programma a duo injectiones: un mixtura de insulina NPH o insulina globinic con insulina regular in le matino e insulina NPH o insulina globinic al vespere.

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