Evaluation of an Eight-hour Therapeutic Regimen in Uncontrolled Diabetes

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SUMMARY

A treatment regimen based on the emergency program of Woodyatt has proved very satisfactory as a guide for house officers to the management of diabetes during acute complications. This report of the detailed results of treatment with the eight-hour regimen has been prompted by the absence of previous documentation of the efficacy of any of the similar methods in common use. In eighteen of twenty episodes in nineteen cases of uncontrolled diabetes, good control (by specified criteria) was established within an average time of two days. Hypoglycemic episodes were identified during eleven of the 530 treatment cycles. DIABETES *16*:341-45, May, 1967.

The proper therapy for the control of diabetes during acute complications involves the administration of unmodified insulin and carbohydrate at frequent intervals.[1] The therapeutic regimens in common use differ in detail, however, and may not be equally effective. Attempts to evaluate variations in the details of therapy in profound ketoacidosis and coma have been reported.[2,3] In these circumstances the success of therapy is judged by survival rates. The treatment of diabetic patients with less severe ketoacidosis, or with conditions which interfere with their usual diet, conforms to the same principles, but as life is not threatened different criteria of efficacy apply. Here the results are to be judged by the safety, rapidity and convenience with which metabolic compensation can be effected. The literature is strangely silent on this point. We could find no formal evaluation of the efficacy of any of the various regimens that have been described for the treatment of diabetes seriously out of control but not to the extent of producing vomiting or stupor. There is thus no published basis for evaluating the possible advantages of variations in applicable therapeutic technics.

We have used a regimen of eight-hour cycles in the treatment of uncontrolled diabetes in patients who are able to tolerate oral feedings, and have found it to be effective and practical within the setting of a large public hospital. This report is presented in the belief that documentation of the results of even "tried and true" methods of treatment is desirable, and in the hope that demonstration of the usefulness of the eight-hour regimen will encourage its adoption elsewhere.

METHODS AND PATIENTS

The eight-hour regimen is distinguished by the following features: (1) eight-hour periodicity, (2) formula feedings, and (3) staggered administration of insulin and feedings.

A fixed sequence of procedures was repeated in every eight-hour cycle. At the beginning of each cycle, semiquantitative measurements of glycosuria and ketonuria were made on urine collected over the last hour or so of the previous cycle. This was followed by the administration of Regular Insulin. One hour later a standard portion of the diet was consumed, with a supplement four hours later. This schedule is diagrammed in figure 1.

Insulin dosage

The initial insulin dosage was estimated by taking into account the degree of glycosuria, ketonemia and ketonuria, the previous insulin requirement, and the presence or absence of complicating conditions. Each subsequent dose was adjusted according to the effect of the dose given eight hours previously. This approach, common to all orthodox therapeutic regimens, differs radically from a common and often undesirable practice of prescribing an arbitrary number of units of insulin per "plus" of the tests for glycosuria and ketonuria.

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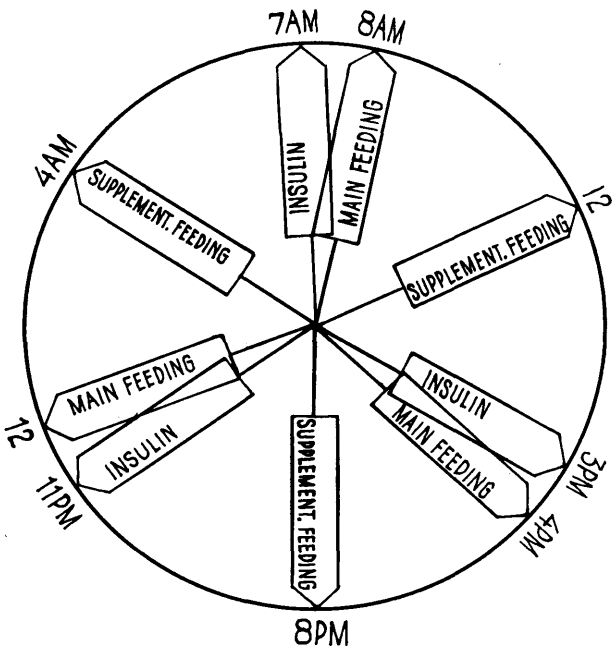

FIG. 1. Diagram of the eight-hour regimen.

Diet

Each day a diet formula was prepared by dissolving 300 gm. of a commercial milk powder* in 720 ml. of skimmed milk. One third of this, together with four soda crackers, was provided at each main meal. The supplemental feeding consisted of 350 ml. of fruit juice or 150 ml. of chocolate or plain milk together with another four crackers. The caloric value of the diet can be manipulated up or down (from 1880 to 2350 calories per day) by substituting varying portions of whole milk for the skimmed milk in the main feedings. The carbohydrate and fat content can be varied by adjusting the proportions of fruit juice or skimmed or whole milk.

The basic formula (using skimmed milk) provides the following food values daily: carbohydrate: 300 gm.; protein: 80 gm.; and fat: 40 gm. Each day's supply was divided into three aliquots and was refrigerated until administered to the patient.

Miscellaneous Aspects of Management

Blood was obtained for glucose determination just before the morning and afternoon main meals. Plasma glucose concentration was measured using a standard glucose oxidase method (Boehringer kits). This information was not utilized in estimating insulin requirements, but provided a retrospective view of the response to therapy. In addition the total twenty-four-hour urinary glucose was estimated using a crudely quantitative test ("Clinitest"). Clinically recognized hypoglycemia was treated with glucagon (1 mg. IM) after obtaining a blood sample for subsequent glucose determination.

Criteria of Degree of Control

To simplify evaluation of the efficacy of therapy, criteria were adopted for assessment of diabetic control (table 1). To qualify for good or fair control, each of the relevant criteria had to be satisfied continuously for twenty-four hours.

TABLE 1
Criteria for assessment of control*

Degree of control	Glycosuria†	Ketonuria†	Urinary glucose per 24 hrs.	Hypoglycemic episode(s)
"Good"	0 to trace (¼%)	0	<5 gm.	None
"Fair"	1+ to 2+ (½% to ¾%)	Tr. to 1+	5-15 gm.	None
"Poor"	3+ to 4+ (1% to 2% or >)	2+ to 4+	>15 gm.	Evident‡

*To qualify for degree indicated, criteria must be fulfilled for twenty-four hours.
†Urine checked eight-hourly with Clinitest and Acetest tablets, and results expressed on the conventional 0-4+ scale.
‡Blood glucose below 50 mg. per 100 ml. with symptoms, or below 40 mg. per 100 ml. if no symptoms present.

Patients

The efficacy of the eight-hour regimen was evaluated in twenty episodes of uncontrolled diabetes (i.e., poor control, by the above criteria) in nineteen patients. The patients were selected at random from the general medical wards according to the indications given by Colwell[1] for the "six-hour emergency program." Their clinical features are presented in table 2. Five patients were newly discovered diabetics. In nine patients diabetes had appeared before the age of eighteen. The patients had spent an average of seven days (range one to twenty-two days) in the hospital before commencement of the eight-hour regimen, so that poor control had persisted despite prior therapy.

Under usual clinical circumstances transition to conventional long-term management could probably be effected after forty-eight hours of good control on the eight-hour regimen although in this study the regimen was maintained for an average period of eight days, thus providing data in a total of 530 eight-hour cycles. Trans-

*"Meritene" (D. M. Doyle Co., Minneapolis) was used in this study.

TABLE 2

Clinical features of patients

Case number	Age and sex	Usual daily medication	Blood glucose (mg./100 ml.) and urinalysis at start of 8-hour regimen		Indications for 8-hour regimen	Days required for good control
1	49F	45 U NPH	—	4+/3+	Pharyngitis, urinary infection, persistent glycosuria and ketonuria despite NPH and Regular Insulin during previous seven days in hospital.	2 1/3
2	37F	0.5 gm. tolbut.	252	4+/3+	Ketoacidosis (CO_2 17 mEq./L.).	2
3	18F	70 U NPH	—	4+/1+	Periodontal abscess, heavy glycosuria and ketonuria during two previous days in hospital.	2 1/3
4	18F	80 U NPH	220	4+/3+	Ketoacidosis (CO_2 14 mEq./L.). Brittle diabetes.	Only fair control
5	18F	New diabetic	216	3+/2+	Continuous glycosuria and ketonuria despite NPH and Regular Insulin during four previous days in hospital.	1 2/3
6	24M	55 U NPH	—	4+/0	Continual heavy glycosuria despite NPH and Regular Insulin during previous thirteen days in hospital.	1/3
2nd episode			302	2+/0	Heavy glycosuria during previous week in hospital.	1 2/3
7	61M	New diabetic	338	4+/0	Hyperglycemia and mild acidosis (CO_2 22 mEq./L.).	2
8	21F	55 U Lente	264	4+/0	Very brittle, out of control.	5
9	42M	20 U NPH	290	4+/1+	Diabetes chronically out of control; hypoglycemic coma previous day.	2 2/3
10	41M	New diabetic	192	Tr./0	Alcoholic. Diabetes not stabilized during previous two weeks in hospital.	1 1/3
11	18F	65 U NPH	322	4+/2+	Ketoacidosis with drowsiness.	1 1/3
12	46M	40 U NPH	264	4+/1+	Persistent mild acidosis (CO_2 23 mEq./L.) despite two previous days in hospital.	Only fair control
13	36M	New diabetic	571	4+/0	Diabetes not stabilized by NPH and Regular Insulin during previous three weeks in hospital.	1/3
14	39F	25 U NPH	361	4+/2+	Ketoacidosis (CO_2 17 mEq./L.).	3
15	51F	New diabetic	465	2+/1+	Intermittent severe hyperglycemia and continuous glycosuria during previous week in hospital.	2
16	18M	80 U NPH	351	4+/0	Brittle diabetes, not controlled during previous five weeks in hospital.	1 2/3
17	40M	25 U NPH	519	4+/2+	Bleeding peptic ulcer, diabetes out of control during previous four days in hospital.	1 2/3
18	57M	65 U NPH	267	3+/0	Huge draining carbuncle; wide fluctuations in blood sugar on NPH and Regular Insulin during previous three weeks in hospital.	3
19	18F	160 U NPH	330	4+/2+	Periodontal abscess, gross obesity, insulin insensitivity.	2

ition to long-term management was achieved by substituting Lente or NPH insulin for the unmodified insulin, starting at 7 a.m. with a dose two thirds as large as the total insulin requirement of the preceding twenty-four hours. A further dose of depot insulin was administered in the late afternoon if necessary. Generally the feeding schedule of the eight-hour regimen was maintained for a day or two after conversion to depot insulin.

RESULTS

Good control was established in eighteen of the twenty episodes. The average time to the beginning of the first twenty-four hours of continuous good control was slightly less than two days. The longest time required was five days. In one patient (case 4, table 2) with brittle diabetes, only fair control was achieved. Another (case 12) chose to leave the hospital on the fifth day of the regimen, although his diabetes was not yet under good control.

Blood glucose values are graphed in figure 2, which shows the progressive trend toward improvement. Values between 50 and 180 mg. per 100 ml. were arbitrarily classed as "satisfactory," and values up to 250 mg. per 100 ml. as "acceptable." Of the thirty-three blood sugar determinations made in the forty-eight hours preceding the start of the eight-hour regimen

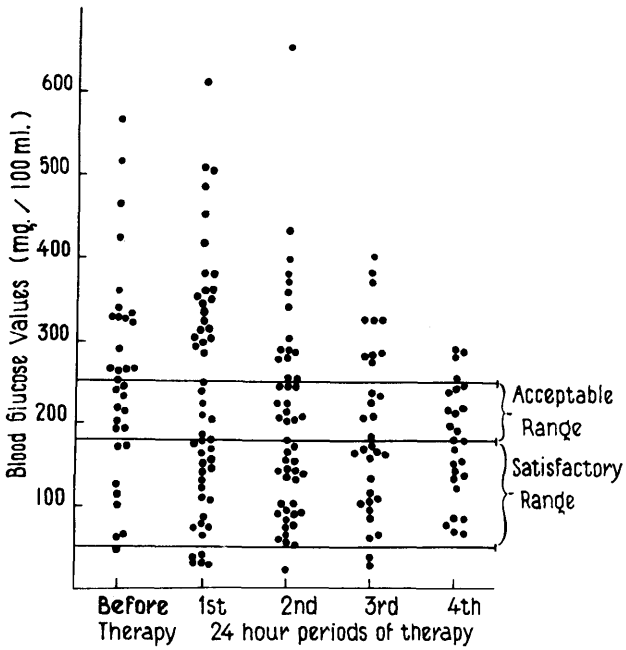

FIG. 2. Blood glucose concentrations during the forty-eight hours preceding, and during successive twenty-four-hour intervals after, the start of the eight-hour regimen. The "Before Therapy" values represent morning fasting blood sugars or readings obtained on admission to hospital.

only seven (21 per cent) were satisfactory. By the second day of therapy 48 per cent were within this range, but this percentage did not increase in the blood sugars obtained in the third and fourth days. The percentage of blood sugar values within the acceptable range increased progressively from 45 per cent in the forty-eight hours before the start of the eight-hour regimen to 85 per cent during the fourth day of treatment.

Hypoglycemia, as defined in the footnote to table 1, was noted in eleven (2 per cent) of the 530 eight-hour cycles of this study. Three of the eleven episodes were asymptomatic, having been detected in routine blood glucose determinations. Most symptomatic episodes were characterized by a "shaky" sensation; one patient experienced diplopia (blood glucose 28 mg. per 100 ml.) and one appeared confused on two occasions (blood glucose 38 and 40 mg. per 100 ml. respectively). In no case was unconsciousness seen. Two of the episodes occurred between the time of the insulin injection and the main meal—one of these occurred less than thirty minutes after the administration of insulin, and the other just as the patient was starting the meal. The lowest blood glucose encountered was 28 mg. per 100 ml.

Insulin requirements decreased progressively in most patients as the eight-hour program progressed. In one patient (case 19) insulin was discontinued after progressive reduction of the dosage as indicated by continuing freedom from glycosuria. She was a very fat girl of eighteen whose diabetes could be well controlled by diet alone despite the fact that she had been taking 160 U. of insulin daily at the time she was admitted with ketoacidosis.

DISCUSSION

The eight-hour regimen was designed to improve on the convenience of similar regimens, such as the six-hour emergency management, without sacrifice of safety or effectiveness.

Until information is available on the time course of insulin activity under various circumstances, the timing of insulin doses must remain empirical. The half-time in serum of injected insulin is variable, depending on the activity of circulating insulin-antibody and possible other as yet unidentified factors.[4] Antagonism to insulin has been observed in sera of patients with ketoacidosis,[5,6] suggesting that the time course of insulin activity may be altered in this condition. We made no attempt to estimate the course of insulin action in our patients and secured no data to indicate the extent of overlapping of effect from one period to the next. Our observations provide only the information that the administration of insulin at eight-hourly intervals appeared to be adequate for establishing good control within a reasonable period of time.

The effectiveness of the method reported here can be gauged by the fact that the diabetes was brought under good control within an average period of two days, in all but two of twenty trials. This seems a satisfactorily brief period, considering that all patients were in poor control for twenty-four hours or more preceding institution of the eight-hour regimen, and that in many of the patients less intensive therapy had proved unsuccessful.

Molnar and his associates[7] have observed, as we did, that fluctuations in blood glucose may continue despite "good clinical control" in these circumstances. In our patients meticulous control of the blood sugar was not a direct objective of therapy. We feel justified, therefore, in classifying as "acceptable" blood glucose concentrations (in samples obtained three hours after the supplementary feeding) between 50 and 250 mg. per 100 ml. The increase in the number of values within this range from 45 per cent on the first day of the eight-hour regimen to 68 per cent on the second and 85 per cent

during the fourth day reinforces belief in the efficacy of this type of therapy.

The risk of hypoglycemia is probably the most important factor in assessing the safety of frequent insulin administration programs. The following features of the eight-hour regimen were designed specifically to minimize this risk:

(1) Insulin is given one hour before each feeding. Little danger of hypoglycemia is to be anticipated for the first hour following administration of insulin. By delaying the meal for that hour, postprandial glucose supplies should more completely overlap the period of insulin action than if meals and insulin injections were to coincide. (One hour may not be the optimal interval for avoiding hypoglycemia and ensuring overlap of the insulin effect and the effect of the meal, but was simply chosen for convenience and probable safety. The possible advantages of a different schedule were not explored.)

(2) Supplemental feedings midway between main feedings are designed to minimize the possibility of hypoglycemia at a time when the hyperglycemia from the main feeding has waned.

(3) The use of feedings containing all three basic food elements should prolong the stabilizing effect of feedings on blood sugar, with more gradual fluctuations than would be caused by pure carbohydrate feedings.

The eleven hypoglycemic episodes, almost all of them symptomatically mild, identified in the course of 530 therapeutic cycles would not seem to constitute an excessive incidence. As blood glucose concentrations were measured at the time in each eight-hour period when hypoglycemia would be most probable, it is unlikely that many hypoglycemic episodes were overlooked. In order to reduce the risk of hypoglycemia, every feeding must be consumed entirely. If for any reason the patient cannot cooperate, the therapeutic regimen must be modified appropriately.

The management of a patient with uncontrolled diabetes entails a considerable expenditure of time and energy on the part of the medical staff. Eight-hour scheduling provides the responsible physician a relatively long respite between doses as compared to regimens of shorter periodicity. Over a period of days, and especially nights, this benefit is substantial. The use of formula meals likewise has been welcomed by dietitians and nurses because of its convenience in standardizing food intake from cycle to cycle.

In summary, the eight-hour regimen conforms to accepted principles but differs in detail from methods previously described. Its salutary features as well as its defects are probably very similar to those of other methods which embody the same therapeutic approach. It may have certain added advantages, or disadvantages, but this cannot be verified for lack of previous reports. Our experience has been satisfactory and we believe it can be recommended for quick control of diabetes in patients able to tolerate liquid feedings, or for maintaining control in patients temporarily unable to tolerate solid food.

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