"LENTE" INSULIN (INSULIN ZINC SUSPENSION): FURTHER STUDIES

BY

WILFRID OAKLEY, M.D., F.R.C.P.

Physician, King's College Hospital

A preliminary trial of "lente" insulin was reported by Lawrence and Oakley (1953). The present paper gives the results of further experience with this insulin in the treatment of diabetics, both in the ward and in out-patients, in the Diabetic Department of King's College Hospital.

The researches of Hallas-Møller, Petersen, and Schlichtkrull (1952) in the Novo Laboratories in Copenhagen, and the characteristics of their three new long-acting insulin preparations, "semilente," "lente," and "ultralente"—insulin zinc suspension (amorphous), insulin zinc suspension, and insulin zinc suspension (crystalline)—were briefly described in the account of the preliminary trial. The first clinical studies of these new zinc insulin preparations with prolonged action were carried out by Hallas-Møller, Jersild, Petersen, and Schlichtkrull.

The results now presented are those obtained with lente, the intermediate form; for reasons given later, we have concentrated at King's on the therapeutic trial of this preparation. The trial has been carried out on two series of cases: (1) in-patients, old and new cases; and (2) out-patients, old and new cases.

In-patients

In all, 29 patients have now been studied, of which 21 were treated and 8 untreated diabetics.

(a) Old Cases

The results obtained in the first 11 cases were described by Lawrence and Oakley (1953). In that paper the conditions necessary for the therapeutic trial of any insulin preparation were laid down.

In the cases described the patient was first stabilized on two injections of soluble, a single mixed injection of soluble and P.Z.I., or a single dose of P.Z.I. or globin insulin, and then changed over to a single dose of lente, equal in size to the total previous dose. The urine was examined for

sugar and ketone bodies at 7 a.m., 8 a.m., 11 a.m., noon, 6 p.m., and 9 p.m., and blood-sugar estimations were carried out at 8 a.m. (fasting), noon, 6 p.m., and 9 p.m. These results are summarized in Table I.

In the remaining 10 cases no attempt was made to compare by means of serial blood sugars the degree of control obtainable by the use of lente with that with the older insulins. The total dose of soluble insulin, P.Z.I., or mixture was converted into lente and an attempt then made to control the diabetes by adjusting the dose of lente. Six of these patients received comparable doses of different batches of lente with a view to determining the extent of batch-to-batch variation.

Good control was obtained in five cases, in two the result was fair, in two poor, and in one lente completely failed to control the hyperglycaemia; it is perhaps significant that the only satisfactory method of stabilizing this patient was by means of two relatively large doses of soluble insulin.

In these cases the results are not quite so good. One reason for this is that in the six who received different batches of lente it was essential not to vary the dose even if it proved inadequate at any time during the experiment; temporary shortage of lente insulin at this time also made good stabilization difficult, and, had more been available, almost one case classified as fair would almost certainly have been good.

(b) New Cases

Eight cases of severe untreated diabetes have received lente insulin in hospital; in seven of them no previous insulin therapy was given. Details of this series are shown in Table II.

Heavy glycosuria and hyperglycaemia exceeding 250 mg. per 100 ml. was present in every case, and in all but one there was also severe ketosis. The glycosuria after treatment is expressed qualitatively, the figure representing the mean result of six tests a day over the last four days of treatment. Control was regarded as good if the blood sugar before breakfast was 150 mg. or less, before the midday meal 180 mg. or less, and there was no evening relapse. As judged by these standards the control in six cases was good, in one fair, and in one poor. In the two latter cases 60 units of lente failed to produce good control; in one this was in part due to the fact that the patient was one of those used to compare the action of different batches of lente insulin, and the dose had therefore to be kept at a constant level until there was insufficient time left to study the effect of larger doses, but even allowing for this the response was not good.

In two of these cases five blood-sugar estimations were carried out during the twenty-four hours in order to follow the action of lente (Fig. 1). The course of the fasting and noon blood sugars, glycosuria, ketosis, and dosage of lente insulin is shown in two of the new cases whose control

TABLE I.—Comparison Between Lente Insulin and Other Insulin Preparations

Case No.	Insulin	Blood Sugar in mg./100 ml.				Result
		8 a.m.	Noon	6 p.m.	9 p.m.	
1	40 S.I.+28 S.I.	190	135	190	305	Better
	68 lente	180	100	200	75	
2	40 S.I.+36 S.I.	—	190	—	—	Good
	76 lente	110	210	115	170	
3	28 S.I.+20 P.Z.I.	210	238	100	110	Better
	48 lente	120	140	140	95	
4	28 S.I.+20 P.Z.I.	125	150	150	190	Same
	48 lente	135	110	215	220	
5	44 S.I.+16 P.Z.I.	165	260	140	118	Worse
	60 lente	200	375	260	255	
6	20 S.I.+16 P.Z.I.	168	238	95	190	Better
	36 lente	105	100	155	155	
7	24 S.I.+20 P.Z.I.	110	155	130	195	"
	44 lente	130	105	110	94	
8	24 S.I.+16 P.Z.I.	155	210	170	—	"
	40 lente	140	180	135	—	
9	28 globin	155	245	165	—	Same
	28 lente	165	205	170	250	
10	52 P.Z.I.	190	178	195	250	Better
	52 lente	95	140	175	180	
11	52 P.Z.I.	95	205	240	250	"
	52 lente	70	210	180	180	
	52 "	75	188	140	210

FIG. 1.—Blood-sugar estimations in two new cases treated in hospital with lente insulin.

was classified as good. Glycosuria is expressed in the same way as in Table II (Figs. 2 and 3). In both instances there is seen to be a gradual fall in the level of the blood sugar, disappearance of ketosis, and a reduction in glycosuria; there were no hypoglycaemic reactions. The ketosis persisted for three days in one case and four days in the other, which is a little longer than is usual when two injections of soluble insulin are used at the onset of insulin therapy. All cases classified as good showed a satisfactory gain in weight.

Out-patients

A small series of 14 out-patients have been treated with lente; ten of these were new untreated diabetics and four relatively mild long-standing cases.

The out-patient treatment of new cases of moderately severe and severe diabetes has proved remarkably easy and successful. The results obtained in 6 out of the 10 cases are shown in Table III, and are all regarded as good. In the remaining four cases two were as good as those shown, one was fair, and one looks as if it will be good, but has not yet been on treatment long enough to warrant classification.

The four long-standing cases were all on a single morning dose of P.Z.I., which controlled the blood sugar in the

fasting state but not during the day. In three cases lente improved the control in this respect, and in one the results were unreliable owing to complete disregard of diet.

Batch Variability

It must be realized at the outset that in moderately severe and severe diabetes there is likely to be a day-to-day variation in the course of the disease, and exact similarity of results between different batches of any insulin cannot be expected. It should also be remembered that, from the point of view of this investigation, the degree of control is not of great importance, provided that conditions remain constant and there is no ketosis.

The results of this investigation are shown in Table IV and are regarded as indicating a reasonably close similarity between the hypoglycaemic action of the different batches of lente insulin tried.

Local and Hypoglycaemic Reactions

There have been no significant local reactions to lente insulin in our series of cases. In one patient a change to lente completely relieved persistent painful reactions to P.Z.I.

TABLE II.—*New Cases treated in Hospital with Lente Insulin*

Case No.	Sex and Age	Before Treatment		After Treatment		Units of Lente			Time in Days	Control
		Glycosuria	Ketosis	Glycosuria 4-day Mean	Ketosis	Initial	Max.	Final		
1	M 40	++++	+++	Tr.	0	40	60	48	18	Good
2	F 20	++++	+++	Tr. to +	0	32	60	36	20	"
3	M 57	+++	+++	S. Tr. to Tr.	0	24	42	36	14	"
4	M 55	++++	Fe++++	+ to ++	0	24	60	60	11	Poor
5	M 25	++++	Fe Tr.	+	0	40	80	60	14	Good
6	F 39	+++	Fe+	++	0	60	60	60	21	Fair
7	F 9	++++	+++	Tr. to +	0	20	32	32	19	Good
8	F 7	++++	Fe+++	+	0	20	28	28	9	"

TABLE III.—*New Cases treated as Out-patients with Lente Insulin*

Case	Sex and Age	Day	Lente Dose	Glycosuria		Ketosis		Noon B.S.	Weight st. lb. oz.	Diet Carbo-hydrate	Hypo-glycaemia
				a.m.	p.m.	a.m.	p.m.				
G. P.	M 30	1	30	+++	+++	+++	+++	360	10-12-8	160 g.	Nil
		3	40	++++	++++	+++	+++	238	11-1-12	160	"
		8	50	++++	++++	0	0	220	11-5-8	160	"
		14	40	Tr.	S. Tr.	0	0	140	11-8-14	160	Noon
		22	40	0	Tr.	0	0	85	11-11-8	160	10 a.m.
		29	40	0	0	0	0	88	11-13-10	160	10.15 a.m.
A. W.	F 54	1	30	++++	++++	Fe S.Tr.	Fe S. Tr.	330	7-9-14	160 g.	Nil
		8	30	0	0	0	0	120	8-2-12	180	"
		15	30	0	0	0	0	85	8-3-2	180	"
		22	30	0	0	0	0	175	8-6-4	180	"
H. V.	F 74	1	—	+++	+++	0	0	500	8-0-0	100	Nil
		28	30	+++	+++	0	S. Tr.	430	7-12-13	160	"
		35	30	0	+	0	0	245	8-4-8	160	"
		42	30	+++	+++	0	0	150	8-6-0	160	"
C. T.	F 45	1	—	+++	+++	0	0	350	11-2-8	120	Nil
		21	20	+++	+++	+	0	—	10-13-10	160	"
		29	30	++++	++++	S. Tr.	0	233	11-5-12	160	"
		36	40	+++	+++	Tr.	Tr.	193	11-6-0	160	"
		43	40	+	Tr.	0	0	175	11-9-9	160	"
		50	40	S. Tr.	S. Tr.	0	0	110	11-12-10	160	"
		57	40	V. S. Tr.	—	0	—	73	11-12-9	160	"
		64	30	0	0	0	0	110	12-2-12	160	"
C. P.	M 11	1	20	++++	++++	Fe Tr.	+++	480	6-2-4	180	Nil
		6	30	++++	++	0	0	260	6-5-0	200	"
		13	24	+	+++	0	0	90	6-8-0	200	"
		20	24	0	0	0	0	62	6-9-11	200	"
L. S.	F 56	1	20	++++	++++	0	0	360	10-7-13	160	Nil
		6	30	+++	+++	+	Tr.	313	10-4-0	160	"
		13	40	+++	+++	0	0	303	10-3-0	160	"
		20	40	0	+++	0	0	223	10-5-12	160	"
		27	40	V. S. Tr.	S. Tr.	0	0	218	10-8-0	160	"
		34	40	0	S. Tr.	0	0	190	10-7-8	160	"

FIG. 2.—Fasting and noon blood sugars, glycosuria, ketosis, and dosage of lente insulin in a male patient aged 40. New case; control good.

FIG. 3.—Fasting and noon blood sugars, glycosuria, ketosis, and dosage of lente insulin in a female patient aged 20. New case; control good.

There have been remarkably few hypoglycaemic reactions either in the in-patients or in the out-patients. Such reactions as have occurred have been quite typical and relatively mild, except in one or two instances in which the dose given has been clearly too large and had to be greatly reduced.

Reactions have been observed at 10 a.m., three hours after injection, and at noon in the same patient, but not on the same day. The commonest times at which patients on lente insulin before breakfast are liable to have hypoglycaemic reactions appear to be during the morning or afternoon. Nocturnal reactions are uncommon in our experience, and hypoglycaemia rarely occurs in the early hours of the morning.

Conclusion

The reason why we have concentrated on lente insulin is that we think it is the most generally useful of the three preparations and the one which, if any, should be put on the market in the near future. We feel that further knowledge is required to determine whether or not ultralente has, for practical purposes, the same action as P.Z.I. and semilente the same action as globin insulin; if this is shown to be the case then it would seem reasonable to suggest that, if and when these two insulins of the lente series are put on the market, P.Z.I. and globin insulin should be simul-

taneously withdrawn so as to lessen the confusion which would inevitably result from having seven insulin preparations available to doctors and patients at one and the same time.

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THE NEW INSULINS—LENTE, ULTRALENTE, AND SEMILENTE

BY

IAN MURRAY, M.D., F.R.C.P.Ed., F.R.F.P.S.

AND

ROBERT B. WILSON, M.B., B.Sc., M.R.C.P.

From the Department of Metabolic Diseases, Victoria Infirmary, Glasgow

TABLE IV.—Comparison Between the Hypoglycaemic Action of Different Batches of Lente Insulin.

Batch No.	Lente Units	Fasting B./S.	Noon B./S.	Batch No.	Lente Units	Fasting B./S.	Noon B./S.
12	40	160	150	12	68	354	313
13	40	150	160	13	68	210	283
14	40	160	162	14	68	309	250
15	40	115	154	15	68	270	240
16	40	130	140	16	68	296	255
			150				
12	60	198	220	12	60	250	250
13	60	180	230	13	60	233	268
14	60	190	—	14	60	250	260
14	68	176	200	14	60	260	260
		176	—	15	80	180	260
15	68	45	136	16	80	135	—
16	68	77	166			140	250
		96	—			50	50
			—			100	115
			—			120	110

Much interest has been aroused in the new insulin preparations of the Novo Therapeutisk Laboratories in Copenhagen (Hallas-Møller *et al.*, 1952a, 1952b; Lawrence and Oakley, 1953; Nabarro and Stowers, 1953). Through the courtesy of Dr. Hallas-Møller supplies of these insulins were made available to us in October, 1952, and since then we have investigated the effects in 28 patients. We have endeavoured to compare the action of these new insulins with that of insulins in current use, and to consider, in the event of their proving to be superior, whether such superiority was sufficient to warrant their introduction for general usage.

Initially, study was made on in-patients in hospital suffering from diabetes of considerable severity but well controlled with various combinations of soluble insulin and protamine zinc insulin, in order to compare the action of these with that of Novo insulins—"semilente," "lente," and "ultralente." Later we tried the new insulins on some patients in whom control was difficult, in the hope that these might give better results.