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Effect of Oral Hypoglycaemic Drugs on Glucose Tolerance and Insulin Secretion in Borderline Diabetic Patients*

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Summary. A double blind controlled clinical trial was undertaken to test the effectiveness of oral hypoglycaemic drugs in improving blood glucose and plasma insulin levels of borderline diabetic patients. Between 1969 and 1971, 120 men aged 25 to 55 with borderline impairment of glucose tolerance according to standard criteria at 2 successive oral glucose tolerance tests entered the study. They were randomized into 4 groups according to treatment: dimethylbiguanide + glibenclamide (n = 29), placebo B + glibenclamide (n = 28), placebo S + dimethylbiguanide (n = 30), placebo B + S (n = 33). In each group drugs were taken twice a day before breakfast and lunch at a total dosage of 1.7 g/day dimethylbiguanide and/or 4 mg/day glibenclamide. Treatment was stopped after 2 years. Patients returned 2 months after entry into the trial, then every 4 months for 2 years. Treatment was continued up to each oral glucose tolerance test except before the last test (drugs stopped 15 days before). 29 patients weighed 20% or more over their ideal body weight and 23 between 10% and 20%. After a dietary survey, these men were subjected to a total colorie restricted diet according to their excess weight. Results indicate that during the 2 years of treatment, no significant lasting effect of the biguanide on blood glucose and plasma insulin levels was detectable. During the oral glucose tolerance test at 14 months in the groups receiving sulphonylurea a significant decrease of blood glucose levels was observed at 0, 180 and 240 min. Glibenclamide had no effect on weight reduction while biguanide administration was accompanied by a significant weight reduction.

Key words: Randomized clinical trial, borderline diabetes, oral hypoglycaemic drugs, glucose tolerance, insulin secretion, dimethylbiguanide, sulphonylurea.

Prospective studies in man [1–3] and animals [4–6] support the concept that optimal control of blood glucose level delays the development of microvascular lesions in overt diabetes. Lowering blood glucose levels in borderline diabetic patients, then, appears a logical aim of treatment in order to achieve early prevention of degenerative vascular changes. We have therefore investigated the effectiveness of oral hypoglycaemic drugs on the glucose and insulin responses to an oral glucose load in patients with borderline impairment of glucose tolerance [7], in a controlled clinical trial.

Material and Methods

Oral Glucose Tolerance Test

Because of the variability in carbohydrate tolerance at successive examinations [8–12], a two step procedure was employed to test eligibility of patients:

1. At the first test venous blood glucose concentration fasting was measured, (BG_0) and 2 h (BG_2) after a 75 g oral glucose load, by a glucose – oxidase method [13]. The subjects were classified according to the European Diabetes Epidemiology Study Group (EDESG) criteria [14–15]: when BG_0 was lower than 100 mg/100 ml and BG_2 lower than 120 mg/100 ml the subject was considered normal, when BG_0 was equal to 130 mg/100 ml or more and BG_2 equal to 150 mg/100 ml or more, the subject was considered diabetic. All remaining subjects were classified borderline and submitted to the second test.

2. The second test was performed 8 to 15 days later under standard conditions [16] with, in particular, dietary preparation

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Table 1. Distribution of 120 eligible subjects according to 6 different criteria [20] applied to the 5 h OGTT results

	The subjects are recognized as:					
	Normal		Diabetic		Borderline	
	No of patients	%	No of patients	%	No of patients	%
According to the criteria of:						
Fajans, Conn [35]	40	33	80	67	–	–
Wilkerson [18]	100	83	20	17	–	–
BDA [19]	31	26	89	74	–	–
UGDP [31]	36	30	84	70	–	–
WHO [36]	27	23	64	53	29	24
EGSED [14–15]	0	–	13[a]	11	107	89
All criteria	0	–	8	7	112[b]	93

[a] These subjects were classified as borderline at the first test by the EDESG criteria

[b] Patients who were not recognized as normal or diabetic by all criteria were classified as borderline

including 250 g of carbohydrates for the three days before the test. Blood glucose levels were determined fasting and at 15, 30, 60, 120, 180, 240 and 300 min after an oral glucose load. Two limits l_1 and l_2 were defined for the blood glucose levels measured at zero, 30, 60 and 120 min post glucose load (BG_o, BG_{30}, BG_{60}, BG_{120}). Below the lower limit l_1, blood glucose values were considered normal; on the upper limit l_2 or above, blood glucose values were considered diabetic. The chosen values were for l_1 respectively 100, 160, 160 and 120 mg/100 ml and for l_2 respectively 130, 220, 220 and 150 mg/100 ml, as recommended by the EDESG [14].

According to these criteria, the subjects were classified as follows: all subjects with normal responses at the four times were excluded as well as the subjects with both BG_o and BG_{120} diabetic responses. Among the remainder, eligible subjects were either those with BG_{120} equal to or greater than 120 mg/100 ml or else those with BG_o, BG_{30} and BG_{60} all equal to or greater than their respective limits l_1.

These criteria were established prior to the beginning of the trial according to the experience of 7 diabetologists *in order to exclude any subject for whom they judged there was no possible choice between treatment and placebo* [17].

Patients

One hundred and twenty patients were recruited from among the male population spontaneously asking medical advice in a screening centre for Diabetes at the Hotel Dieu Hospital in Paris, between March 1969 and October 1971. They were 25 to 55 years old, free from any other apparent clinical disease, and taking no drugs. 29 (25%) of them were 20% or more over their ideal body weight and 23 (19%) between 10% and 20%. Thirty four patients (24 during the first year, 10 during the second year of the study) were lost to follow-up; they came equally from the four different treatment groups and exhibited similar baseline characteristics to the follow-up patients. Their removal from the trial did not introduce any bias into the study.

To judge the inclusion criteria previously defined the 120 subjects selected for the trial were classified according to 6 different international criteria regarding their 5 h OGTT results (Table 1). In the study sample, 83% were normal according to the Wilkerson point system [18] whereas only 26% were normal according to the British Diabetic Association criteria [19]. None of the subjects would be recognized as normal by all criteria, while 7% of them would be universally recognized as diabetic. These results show the discrepancy between the different criteria as emphasized in another study [20].

Allocation to Treatment

Based upon sequence of entry to the study, patients in each group were assigned a trial number. This determined the treatment they received, but the trial number gave no indication of the treatment. Randomization with equal numbers of patients in each treatment group was carried out.

Treatment

Four treatment groups were studied:

1. Sulphonylurea-treated group (S group) who received 2 mg of Glibenclamide and a biguanide placebo before breakfast and before lunch.
2. The biguanide-treated group (B) received 0.85 g of dimethylbiguanide and a sulphonylurea placebo before breakfast and before lunch.
3. Combined therapy group (B + S) who received both drugs in the above doses.
4. The placebo group (P) who received a sulphonylurea placebo and a biguanide placebo.

Tablets were taken every day for the 2 years of the trial. None of the patients under study exhibited symptoms of intolerance requiring a change of therapy. Fourteen patients, equally distributed in the four groups, admitted to having stopped their drug intake for 1 month or less.

All patients were regularly questioned on their dietary habits. Overweight patients were prescribed calorie restriction in order to approach their ideal body weight [21]. The diet was aimed at restricting firstly, alcohol consumption, then sweets and pastries, then extra fats, such as butter and oil, and finally bread if necessary. In all cases, the balance between the different nutrients was respected.

Data Collection

Every four months, clinical and biochemical examinations were performed. In practice, none of the patients exhibited any pathological symptom during the survey. Oral glucose tolerance tests were performed 2, 14 and 26 months after the baseline test (i. e. 2nd test for eligibility) as defined above. At 2 and 14 months, the patients received their tablets before the oral glucose tolerance test. Then the treatments were stopped 15 days before the 26 months test. Besides blood glucose measurements, plasma insulin levels were estimated by radioimmunoassay [22].

Statistical Analysis

The study was designed for two way analysis of variance [23]. Thus, the inclusion of the four possible combinations of treatments into the study allowed us to test if:

1. the effect of biguanides was the same whether sulphonylureas were given at the same time or not,
2. the effect of sulphonylureas was the same whether biguanides were given at the same time or not (test of interaction).

Absence of significant interaction allowed the biguanide effect to be tested by the comparison of both group B with group P, and of group B + S with group S: and, similarly, to test the effect of the

Table 2. Baseline characteristics in the 4 groups of treatment: placebo (P), biguanide (B), sulphonylurea (S) and combined therapy (B + S). The values represent mean ± SEM and the range is in parenthesis

Group	n	Age (a)	Weight (kg)	Overweight (%)
P	33	45±1	79±2	14±2
		(25–54)	(65–118)	(−5–47)
B	30	44±1	74±2	8±2
		(26–53)	(63–91)	(0–43)
S	28	43±2	75±2	9±3
		(25–54)	(56–99)	(−11–50)
B+S	29	44±1	78±3	14±3
		(29–54)	(54–106)	(−13–85)

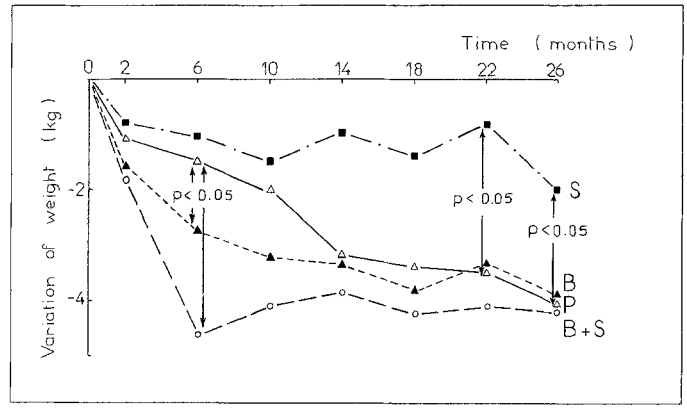

Fig. 1. Changes in weight from baseline in the 4 groups: placebo (P), biguanide (B), sulphonylurea (S) and combined therapy (B + S)

Table 3. Baseline blood glucose and plasma insulin values in the 4 groups of treatment: placebo (P), biguanide (B), sulphonylurea (S) and combined therapy (B + S). The values represent mean ± SEM and the range is in parenthesis

Group	n	Time (min) after glucose load							
		0	15	30	60	120	180	240	300
a) Blood glucose (mg/100 ml)									
P	33	103±2	130±3	172±4	199±5	136±6	85±5	76±2	79±2
		(79–121)	(101–176)	(117–228)	(150–282)	(67–210)	(58–168)	(55–103)	(65–98)
B	30	108±2	134±4	170±5	190±7	133±5	82±5	77±2	82±2
		(90–126)	(102–176)	(122–228)	(106–263)	(79–197)	(49–160)	(56–101)	(62–100)
S	28	101±2	121±4	156±5	184±7	143±6	82±4	73±2	79±2
		(84–134)	(90–159)	(120–222)	(112–250)	(69–224)	(56–153)	(52–105)	(56–102)
B+S	29	104±2	129±3	167±5	198±6	133±6	83±5	76±3	79±2
		(76–124)	(96–175)	(112–244)	(121–300)	(60–214)	(49–133)	(50–124)	(51–98)
b) Plasma insulin (μU/ml)									
P	31	16±2	35±4	56±6	85±10	75±13	26±4	15±1	12±1
		(2–40)	(13–72)	(19–136)	(20–340)	(10–380)	(4–116)	(4–33)	(5–25)
B	29	14±1	45±4	64±7	99±8	71±7	28±5	15±2	13±1
		(6–30)	(10–86)	(10–144)	(16–200)	(16–130)	(5–133)	(3–33)	(3–34)
S	28	16±2	30±4	48±7	74±8	73±7	27±5	14±2	12±1
		(4–66)	(10–112)	(14–136)	(20–156)	(28–150)	(6–134)	(3–40)	(2–25)
B+S	28	16±2	35±3	51±5	87±13	95±5	33±5	18±2	14±1
		(2–42)	(2–73)	(21–117)	(17–200)	(23–400)	(11–116)	(2–58)	(2–26)

sulphonylureas by comparison of group S with group P and of group B + S with group B.

Finally, classical analysis of variance provided a test for the effect of biguanide and sulphonylurea which involved all the patients under study in each comparison. This achieved a more efficient method of analysis than the usual comparisons of means between groups.

Results

Baseline Characteristics

Comparison of the four groups was performed for each baseline characteristic (clinical table 2; biochemical table 3). No significant difference between the 4 groups was observed; this indicates the effectiveness of the randomisation.

Body Weight

Mean changes in weight are shown for the 4 groups in figure 1. Weight reduction was observed in each group, placebo group included. All these reductions were significantly different from zero by Student's t-test. Moreover, the comparisons with the placebo group showed at 6 months a greater weight loss in the 2 groups receiving biguanide. The weight loss was smaller in the S group than in the P group, differences reaching a significant level at 22 and 26 months.

Results of the two way analysis of variance are shown in Table 4. At 6 months and afterwards body weight was significantly lower in the B and B + S groups than in the P and S groups. No significant

Table 4. Effect of biguanide (B) and sulphonylurea (S) on body weight (kg). Group "with B" includes B and B + S – group "without B" includes P and S. Group "with S" includes S and B + S – group "without S" includes P and B. Values represent mean ± SEM; NS = Differences not significant. Number of subjects is indicated in parenthesis

Group	Time of examinations (in months from baseline)						
	2	6	10	14	18	22	26
with B	74 ± 1 (47)	72 ± 1 (50)	71 ± 1 (47)	71 ± 1 (47)	72 ± 1 (44)	71 ± 1 (44)	70 ± 1 (45)
without B	76 ± 1 (42)	76 ± 1 (46)	76 ± 1 (44)	74 ± 1 (47)	74 ± 1 (39)	75 ± 1 (42)	74 ± 1 (40)
significance	NS	$p<0.05$	$p<0.05$	$p<0.05$	NS	$p<0.05$	$p<0.05$
with S	75 ± 1 (41)	74 ± 1 (48)	73 ± 1 (46)	73 ± 1 (44)	73 ± 1 (39)	72 ± 1 (43)	73 ± 1 (43)
without S	75 ± 1 (48)	74 ± 1 (48)	73 ± 1 (45)	72 ± 1 (50)	73 ± 1 (44)	73 ± 1 (43)	72 ± 1 (42)
significance	NS	NS	NS	NS	NS	NS	NS

Table 5. Blood glucose values (mg/100 ml) at the successive 5 h OGTT in the 4 treatment groups: placebo (P), biguanide (B), sulphonylurea (S) and combined therapy (B + S). Values represent mean ± SEM

Group	n	Time (min) after glucose							
		0	15	30	60	120	180	240	300
a) at 2 months from baseline									
P	31	97 ± 2	119 ± 3	155 ± 5	174 ± 6	113 ± 5	73 ± 3	74 ± 2	77 ± 2
B	30	96 ± 2	119 ± 3	155 ± 4	173 ± 6	128 ± 6	77 ± 4	71 ± 2	78 ± 2
S	27	94 ± 2	116 ± 4	157 ± 6	176 ± 8	128 ± 6	73 ± 3	68 ± 3	72 ± 2
B+S	28	93 ± 3	118 ± 4	153 ± 6	171 ± 7	118 ± 6	72 ± 4	69 ± 2	76 ± 2
b) at 14 months from baseline									
P	26	97 ± 2	129 ± 5	160 ± 6	178 ± 7	123 ± 7	79 ± 5	73 ± 2	75 ± 2
B	24	92 ± 3	117 ± 5	153 ± 6	167 ± 7	119 ± 6	71 ± 4	71 ± 2	77 ± 2
S	22	92 ± 3	119 ± 5	152 ± 5	165 ± 8	123 ± 6	66 ± 3	66 ± 3	72 ± 3
B+S	24	87 ± 3	117 ± 5	147 ± 6	154 ± 8	107 ± 4	66 ± 3	65 ± 2	73 ± 2
c) at 26 months from baseline									
P	19	95 ± 2	125 ± 5	166 ± 6	188 ± 9	113 ± 5	72 ± 4	73 ± 3	78 ± 2
B	23	95 ± 2	128 ± 5	167 ± 7	177 ± 6	115 ± 5	73 ± 4	72 ± 2	79 ± 2
S	22	90 ± 2	114 ± 4	148 ± 6	164 ± 8	113 ± 6	71 ± 5	70 ± 2	74 ± 3
B+S	22	93 ± 3	127 ± 4	167 ± 5	176 ± 9	115 ± 4	70 ± 4	69 ± 3	78 ± 2

difference, however, was observed between the S and B + S groups when compared to B and P groups.

Blood Glucose

Mean values of blood glucose levels at the successive 5 h OGTT are indicated in Tables 5 and 6. No significant effect of dimethylbiguanide could be detected at any time in the course of the trial. In the groups receiving glibenclamide (S and B + S), blood glucose mean values were generally lower at the 14 months examination than in the groups without S (P and B). The 5% level of significance was reached for observed differences at fasting, 180 and 240 min after glucose. But at the 2 and 26 months examinations, there was no significant difference.

Plasma Insulin

Tables 7 and 8 show the failure of glibenclamide and dimethylbiguanide to modify plasma insulin level under the test conditions.

Insulin Glucose Relationships

They were evaluated by the slope of insulin on glucose regression line calculated for each individual OGTT [12]. Sulphonylurea and biguanide had no apparent effect on these relationships (Table 9).

Table 6. Effect of biguanide (B) and sulphonylurea (S) on blood glucose values (mg/100 ml) at the successive 5 h OGTT. Values represent mean ± SEM. p values are calculated by a two way analysis of variance

Groups	n	Time (min) after glucose							
		0	15	30	60	120	180	240	300
a) at 2 months from baseline									
with B	58	95 ± 2	118 ± 6	154 ± 4	172 ± 5	123 ± 4	74 ± 3	70 ± 2	77 ± 2
without B	58	96 ± 2	117 ± 6	156 ± 4	175 ± 5	120 ± 4	73 ± 2	72 ± 2	75 ± 2
significance									
with S	55	94 ± 2	117 ± 3	155 ± 4	173 ± 5	123 ± 4	73 ± 5	69 ± 2	74 ± 1
without S	61	97 ± 2	119 ± 2	155 ± 4	173 ± 5	120 ± 4	75 ± 2	73 ± 1	77 ± 1
significance									
b) at 14 months from baseline									
with B	48	89 ± 2	117 ± 3	157 ± 4	160 ± 5	113 ± 4	69 ± 3	68 ± 2	75 ± 2
without B	48	95 ± 2	124 ± 3	156 ± 4	172 ± 5	123 ± 4	73 ± 3	70 ± 2	73 ± 2
significance									
with S	46	89 ± 2	118 ± 3	149 ± 4	159 ± 5	114 ± 4	66 ± 3	70 ± 2	72 ± 2
without S	50	95 ± 2	124 ± 3	157 ± 4	173 ± 5	121 ± 4	75 ± 3	72 ± 2	76 ± 2
significance		$p<0.05$					$p<0.05$	$p<0.05$	
c) at 26 months from baseline									
with B	45	94 ± 2	127 ± 3	167 ± 4	176 ± 5	115 ± 4	71 ± 3	71 ± 2	78 ± 1
without B	41	93 ± 2	119 ± 3	156 ± 4	175 ± 6	113 ± 4	71 ± 3	71 ± 2	76 ± 2
significance									
with S	44	92 ± 2	120 ± 3	157 ± 4	170 ± 6	114 ± 4	71 ± 3	69 ± 2	76 ± 2
without S	42	95 ± 2	127 ± 3	166 ± 4	182 ± 6	114 ± 4	72 ± 3	73 ± 2	78 ± 2
significance									

Table 7. Plasma insulin values (μU/ml) at the successive 5 h OGTT in the 4 groups of treatment: placebo (P), biguanide (B), sulphonylurea (S) and combined therapy (B + S). Values represent mean ± SEM

Group	n	Time (min) after glucose							
		0	15	30	60	120	180	240	300
a) at 2 months from baseline									
P	30	16 ± 1	40 ± 4	64 ± 10	94 ± 11	65 ± 8	21 ± 2	14 ± 1	13 ± 1
B	27	13 ± 1	36 ± 3	58 ± 7	76 ± 10	65 ± 8	23 ± 3	10 ± 1	10 ± 1
S	24	15 ± 2	32 ± 3	49 ± 7	64 ± 7	56 ± 8	25 ± 5	11 ± 1	10 ± 1
B+S	25	13 ± 1	36 ± 5	47 ± 6	82 ± 9	58 ± 7	26 ± 5	13 ± 1	12 ± 1
b) at 14 months from baseline									
P	26	16 ± 1	41 ± 5	62 ± 8	76 ± 6	57 ± 5	23 ± 3	15 ± 1	13 ± 1
B	23	12 ± 1	32 ± 4	59 ± 6	86 ± 10	57 ± 7	19 ± 3	11 ± 2	13 ± 3
S	19	15 ± 2	46 ± 10	65 ± 12	72 ± 10	77 ± 14	19 ± 3	12 ± 2	11 ± 2
B+S	24	13 ± 2	37 ± 4	47 ± 5	66 ± 7	54 ± 7	21 ± 4	11 ± 1	10 ± 1
c) at 26 months from baseline									
P	19	16 ± 2	34 ± 5	53 ± 6	75 ± 7	61 ± 10	19 ± 3	13 ± 2	11 ± 1
B	23	13 ± 1	30 ± 5	55 ± 7	82 ± 10	58 ± 8	19 ± 3	11 ± 1	11 ± 1
S	21	15 ± 2	31 ± 5	48 ± 7	69 ± 10	55 ± 8	20 ± 4	11 ± 1	10 ± 1
B+S	21	10 ± 1	34 ± 5	51 ± 8	60 ± 8	44 ± 6	14 ± 5	10 ± 1	9 ± 1

Efficiency of the Experiment

In order to investigate if the absence of significant effect of treatments on blood glucose could be due to a lack of power of the study test, theoretical differences which would have been significant with a probability equal to 0.95 were calculated. An example of these minimal differences is indicated for 2 months in table 10. They are small enough to be reasonably expected if the therapies used were minimally efficient.

Table 8. Effect of biguanide (B) and sulphonylurea (S) on plasma insulin values (μU/ml) at the successive 5 h OGTT. Values represent mean ± SEM. p values are calculated by a two any analysis of variance

Groups	n	Time (min) after glucose							
		0	15	30	60	120	180	240	300
a) at 2 months from baseline									
with B	52	13 ± 1	36 ± 3	53 ± 5	79 ± 7	62 ± 6	24 ± 3	12 ± 1	11 ± 1
without B	54	15 ± 1	36 ± 3	57 ± 5	80 ± 7	61 ± 5	23 ± 3	13 ± 1	11 ± 1
significance									
with S	49	14 ± 1	34 ± 3	48 ± 6	73 ± 7	57 ± 6	25 ± 3	12 ± 1	11 ± 1
without S	57	14 ± 1	38 ± 3	62 ± 5	85 ± 7	65 ± 5	22 ± 3	12 ± 1	11 ± 1
significance									
b) at 14 months from baseline									
with B	47	12 ± 1	35 ± 4	53 ± 6	75 ± 6	56 ± 6	20 ± 2	11 ± 1	11 ± 1
without B	45	16 ± 1	43 ± 4	64 ± 6	74 ± 6	66 ± 6	22 ± 2	14 ± 1	12 ± 1
significance		$p<0.05$							
with S	43	14 ± 1	41 ± 4	55 ± 6	69 ± 6	64 ± 6	20 ± 2	12 ± 1	10 ± 1
without S	49	14 ± 1	37 ± 4	61 ± 6	80 ± 6	57 ± 6	21 ± 2	13 ± 1	13 ± 1
significance									
c) at 26 months from baseline									
with B	44	11 ± 1	32 ± 3	54 ± 5	72 ± 6	51 ± 5	17 ± 2	11 ± 1	10 ± 1
without B	40	15 ± 1	33 ± 3	51 ± 5	72 ± 7	58 ± 6	20 ± 2	12 ± 1	10 ± 1
significance									
with S	42	12 ± 1	32 ± 3	50 ± 5	65 ± 6	49 ± 6	17 ± 2	11 ± 1	9 ± 1
without S	42	14 ± 1	33 ± 3	54 ± 4	79 ± 6	59 ± 6	19 ± 2	12 ± 1	11 ± 1
significance									

Table 9. Effect of biguanide (B) and sulphonylurea (S) on the slope of I on G regression line

	Time of examination (in months from baseline)							
	n	0 m ± SEM	n	2 m ± SEM	n	14 m ± SEM	n	26 m ± SEM
P	33	0.59 ± 0.09	29	0.76 ± 0.11	25	0.53 ± 0.06	19	0.50 ± 0.06
B	30	0.66 ± 0.07	26	0.66 ± 0.07	24	0.69 ± 0.07	22	0.62 ± 0.10
S	28	0.56 ± 0.06	24	0.55 ± 0.10	19	0.75 ± 0.16	21	0.52 ± 0.08
B+S	29	0.60 ± 0.08	25	0.64 ± 0.07	24	0.59 ± 0.08	20	0.55 ± 0.11
with B	59	0.63 ± 0.06	51	0.65 ± 0.07	48	0.64 ± 0.06	42	0.59 ± 0.06
without B	61	0.58 ± 0.06	53	0.67 ± 0.07	44	0.63 ± 0.07	40	0.51 ± 0.06
p value								
with S	57	0.58 ± 0.06	49	0.60 ± 0.07	43	0.66 ± 0.07	41	0.53 ± 0.06
without S	63	0.63 ± 0.06	55	0.71 ± 0.06	49	0.61 ± 0.06	42	0.57 ± 0.06
p value								

Discussion

In the present study, sulphonylurea had no effect – even an adverse effect – on weight reduction, while administration of biguanide is accompanied by weight reduction, in accordance with the results reported by Feldman [24] and Clarke [36]. Blood glucose improvement was only observed in the S group at the 14 months test. A significant level was reached only at fasting and at 180 and 240 min after oral glucose. Under the null hypothesis (i. e. no effect) the probability of observing three significant differences of identical sign among the 48 involved comparisons was equal to 11%. Under the alternative hypothesis (i. e. efficacy of drugs as defined in table 10), the probability of obtaining only three significant differences was near zero. So there was no evidence of the effectiveness of oral hypoglycaemic drugs either in lowering blood glucose or in improving insulin secretion in borderline diabetic patients. These results are also in agreement with Feldman's study [24]. However, some differences which might

Table 10. Lower limits of differences of blood glucose values which would have been detected with a probability of 95% when groups with S are compared to groups without S – or groups with B are compared to groups without B

	Time (min) after glucose load							
	0	15	30	60	120	180	240	300
Differences in blood glucose levels (mg/100 ml)	8	12.5	19	27	21	12	7	7

These values are given to appreciate the efficiency of the study. For instance, let be 21 mg/100 ml the true difference (unknown) due to treatment at 120 min after glucose. In this study, with the number of subjects examinated at 2 months, the probability to observe a significant difference was equal to 95%. In the same conditions, a true difference equal to 11 mg/100 ml had only a probability of 50% to be detected

have interfered with the results are notable between these two trials. Among them are the different patterns of drug intake before the test: in Feldman's study treatments were discontinued 3 days before each OGTT showing the absence of a permanent effect of drugs on glucose tolerance. In the present study, drugs were *not* discontinued before the tests except before the last test. Nevertheless no striking effectiveness of the drugs in lowering blood glucose was shown, although the overall procedure of the trial was accurate enough to disclose small differences between the groups. This is of interest because the doses of drugs we used were similar to those usually given in asymptomatic diabetes.

In the present study, a sulphonylurea-biguanide association previously advocated [25] could be tested and was found to lack totally any synergic effect on blood glucose. There was no evidence of a significant effect of drugs on insulin levels and the insulin-glucose relationship evaluated by an index currently used [26–27] was not altered by drugs. Thus, in a long-term experiment, biguanide was not able to diminish plasma insulin level, and sulphonylurea had no apparent stimulatory effect on insulin secretion. This failure of sulphonylurea to increase insulin secretion under chronic administration has been previously demonstrated by CHU et al. [28] and emphasized by PROUT [29].

This study shows that there is no clear beneficial effect of oral hypoglycaemic drugs on blood glucose levels in borderline diabetics confirming previous findings [37, 24]. In view of the disturbing UGDP [30–32] findings which suggested a possible toxic effect of oral hypoglycaemic drugs, our results support the concept that there is no rational basis for the use of those agents in patients with mild impairment of glucose tolerance [33].

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