Is Combination Sulfonylurea and Insulin Therapy Useful in NIDDM Patients?

A metaanalysis

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OBJECTIVE— To assess the efficacy of combination therapy with insulin and sulfonylurea in the treatment of NIDDM.

RESEARCH DESIGN AND METHODS— Studies published between January 1966 and January 1991 were identified through a computerized Medline search and by hand searching the bibliographies of identified articles. We identified 17 eligible randomized, controlled trials of combination therapy in NIDDM. These trials had a minimum duration of 8 wk and at least one of three outcome measures (fasting glucose, HbA_1, or C-peptide) with SD or SE of the mean reported to do metaanalysis. With standardized forms, three independent reviewers abstracted measures of study quality and specific descriptive information about population, intervention, and outcome measurements.

RESULTS— We calculated effect size and weighted mean changes of the three outcome measures for control and treatment groups. In the treatment group, the fasting plasma glucose decreased from a mean of 11.4 mM (206 mg/dl) at baseline to a mean of 9.16 mM (165 mg/dl) posttreatment, whereas the control group decreased from (11.3 to 10.8 mM) (204 to 194 mg/dl) (effect size 0.39, $P < 0.0001$). For HbA_1, the treatment group decreased from a baseline of 11.0 to 10.2% compared to 11.0 and 11.2% in the control group (effect size 0.43, $P < 0.0001$). For fasting C-peptide, the treatment group increased from 0.49 to 0.58 nM (1.45 to 1.75 ng/ml) compared with 0.47 and 0.43 (1.42 and 1.30) for the control group (effect size 0.26, $P < 0.017$).

CONCLUSIONS— Combined insulin-sulfonylurea therapy leads to modest improvement in glycemic control compared with insulin therapy alone. With combined therapy, lower insulin doses may be used to achieve similar control. Obese patients with higher fasting C-peptides may be more likely to respond than others.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; CI, CONFIDENCE INTERVAL.

NIDDM affects 5% of the U.S. adult population (1). The recommended initial treatments are diet and exercise (2). If these fail to achieve glycemic control, then sulfonylureas are often prescribed (2). However, 20% of people with NIDDM have minimal initial response to sulfonylureas and another 5–10%/yr become secondary failures (2). Generally, insulin therapy is initiated in sulfonylurea failures. Even with insulin, it is often difficult to achieve adequate control because many patients with NIDDM have pronounced insulin resistance. Theoretically, in patients capable of partial response to sulfonylureas, the combination of sulfonylurea and insulin might achieve better glycemic control at lower doses of insulin. The sulfonylureas increase endogenous insulin secretion (2,3), reduce the accelerated rates of hepatic glucose production in NIDDM, partially reverse the postreceptor defect in insulin action, and lead to an increase in the number of cellular insulin receptors (2). These actions should complement the effect of exogenous insulin. To determine whether this theoretical advantage is a practical reality, we reviewed all available studies of the efficacy of combination therapy.

Previous reviews often stated that the results of the available trials are conflicting (4–8). These reviews failed to address indepth design issues that may have led to these conflicting results. First, previous reviews included before-after or uncontrolled trials. Uncontrolled trials are more likely than controlled trials to overestimate the efficacy of a therapy (9). Second, the study populations may have intrinsic differences (differing duration of disease, differing initial responses to sulfonylureas) that might contribute to different treatment responses. Third, the treatment regimens themselves may vary enough to cause conflicting results; for example, adding a small dose of insulin to a sulfonylurea versus adding a sulfonylurea to a large dose of insulin. Fourth, most trials have had small sample sizes (<30), for which

there is an increased likelihood of failing to demonstrate a statistically significant difference between treatment and control groups due to inadequate sample size. One way to overcome the problem of small sample size short of conducting a large multicenter trial is to perform a metaanalysis. Metaanalysis is a quantitative method of integrating data from similar trials to overcome the problem of low sample size (10). This report is a metaanalysis of randomized controlled trials studying combination insulin and sulfonylurea therapy in NIDDM. Explicit selection criteria were used to obtain a relatively homogeneous set of trials, for which it makes sense to integrate data. In this way, it is possible to achieve a more definitive answer than previous reviews regarding the efficacy of combination insulin-sulfonylurea therapy.

RESEARCH DESIGN AND METHODS

Data retrieval

We performed a Medline (computerized) search from January 1966 to January 1991. We included all languages but only human subjects. The indexing terms we used were sulfonylurea compounds, hypoglycemic agents, insulin, and/or combination therapy. We also reviewed the bibliographies of diabetic textbooks, review articles, and articles obtained by our search. The titles of the articles were reviewed for relevance. To check for any incorrectly indexed articles, we reviewed the abstracts of a 10% sample of those studies whose titles we felt to be irrelevant. No relevant articles were identified in this manner. If a relevant reference was an abstract, we attempted to obtain more complete data from the authors.

All potentially relevant articles were reviewed against explicit inclusion criteria: the article must be a treatment trial, subjects must have NIDDM, the trial must be randomized and controlled but could be either crossover or noncrossover, the duration of the treatment trial had to be a minimum of 8 wk (16 wk for crossover), the treatment comparison must be between insulin plus sulfonylurea versus either insulin alone or insulin plus placebo, and at least one of three outcome measures (fasting glucose, HbA_1, fasting C-peptide) had to be available with either SE or SD. (SE or SD is necessary to perform metaanalysis.) Many other outcome measures were available for individual trials (mean values of self-monitored blood glucose over variable periods of time, mean values of glucose monitoring during inpatient stays over variable periods of time, area under the curve of a 2-h glucose tolerance test after a 75-g glucose load, 2-h glucose after a standard meal, insulin requirement determined by automated external feedback mechanism, glucose utilization rates, glucagon-stimulated C-peptide) but could not be used to pool data.

Data extraction

Standardized data abstracting and quality rating forms were developed. The data abstracting form included sample size, patient characteristics, study design, subject inclusion-exclusion criteria, dropouts, compliance, duration of treatment, statistical methodology, and specific levels of outcome measures (fasting glucose, HbA_1, and fasting C-peptide). The quality rating form included trial design, adequacy of randomization, post-hoc adjustment for baseline inequities, blinding, adequacy of description of patient selection and source, enumeration of dropouts, method of analysis of dropouts, treatment duration, sample size calculation presentation, presence or absence of SD or SE of the outcome measures, adequacy of description of subject baseline characteristics, cointerventions and study intervention, appropriateness of statistical analysis, and adequacy of raw data presentation. The range of possible quality scores was 0–26, with 26 representing the highest quality possible on this scale. After evaluating each trial independently, a final quality score for each trial was arrived at by consensus of three reviewers. The reviewers checked each quality item for agreement. If there was disagreement, the article in question was reviewed together and all three reviewers then decided which score they agreed on for that item.

Data analysis

Overall means for all of the trials, weighted for sample size, were derived for the three outcome measures. For each individual trial, the effect size was calculated for each outcome measure, weighted by the inverse of the effect size variance (11). Effect size is a measure of the amount of change in the outcome measure (11). Before pooling the results, we calculated a homogeneity score for each outcome measure (11). Because the studies were homogeneous, we then calculated an average weighted effect size, its 95% CI, and its statistical significance (Z score) (11). With a standard normal cumulative distribution function table, the pooled effect size was converted to a percentage expected improvement of the control group if the control group had received combination therapy. To determine the number of trials that would be needed to overturn or disprove the results, we calculated a "fail-safe N" with the method of Orwin (12). To test the effect of study quality on outcome, we performed linear regression analyses with SAS (13).

RESULTS

Search results

Three hundred twenty-two titles were identified by the Medline search, of which 91 were relevant, and 11 more were found by searching bibliographies. Nineteen of 102 met criteria for further study, but 2 of 19 were presentations of the same data for a total of 17 original studies. Of the relevant titles excluded, there were 8 abstracts (2 of which were randomized trials with incomplete data), 24 review articles, 2 case reports, 4 letters, 16 studies without control groups, 3

Table 1—*Study characteristics*

Ref.	N	Sulfonylurea	Duration of trial (wk)	Study design	Location	Quality score
14,15	22	Glyburide	16	NB	US	14.0
16	20	Glyburide	46	NB	Sweden	11.5
17	16	Glyburide	16	CB	US	22.5
18	11	Tolazamide	8	CB	US	12.5
19	9	Glyburide	8	CB	Finland	12.5
20	22	Glyburide	16	NB	Belgium	5.0
21	13	Glyburide	8	CB	Finland	7.5
22	13	Glyburide	8	CU	Finland	7.0
23	12	Tolazamide	12	CU	US	2.5
24	15	Chlorpropamide	8	CU	UK	11.0
25	30	Glicazide	52	NU	Italy	16.5
26	15	Glyburide	16	CB	Finland	12.0
27,28	20	Glyburide	16	NB	US	9.5
29	21	Glyburide	16	CB	US	18.5
30	64	Glyburide	52	NB	US	20.5
31	31	Glyburide	12	CB	Australia	16.0
32	20	Glyburide	12	NB	Sweden	12.0

N, noncrossover; C, crossover; B, blinded; U, unblinded. All studies were randomized and controlled. Quality score, range 0–26, with 26 representing the highest quality study possible.

controlled but nonrandomized studies, 9 that were not trials of combination therapy with insulin and sulfonylurea, 7 studies of insulin-dependent diabetic patients, 6 studies of <8 wk duration, and 4 randomized trials with inadequate data presentation. (A list of excluded articles is available from the authors on request.)

Design of included studies and baseline characteristics of subjects

Table 1 displays characteristics of the 17 trials (14–32). Study size ranged from 9 to 64 subjects. The most frequently used sulfonylurea was glyburide (glibenclamide). Only 3 trials lasted >4 mo. Only 2 studies achieved quality scores ≥20 (maximum quality score was 26). Two studies added insulin to subjects who had just failed sulfonylureas (16,24), whereas all the others added sulfonylureas to existent insulin regimens. However, 2 of these latter studies started insulin as part of the study in patients who recently failed sulfonylureas (21,32). Some studies allowed decreases in the insulin dose for hypoglycemia. A few studies also allowed increases in the insulin dose to achieve better glycemic control.

Table 2 displays the baseline characteristics of the study subjects. Most of the studies enrolled older, obese individuals who were poorly controlled on moderate-to-large daily doses of insulin. In four studies (16,21,24,32), subjects were begun on insulin as part of the study.

Treatment results

Table 3 presents pre- and posttreatment values for each study and means weighted for sample size, and Table 4 presents the effect sizes for fasting glucose, HbA_1, and fasting C-peptide. In all of the studies, the achieved glucose and HbA_1 were better in the treatment than in the control group, although sometimes minimally. For glucose, the weighted mean at baseline was 11.4 mM (206 mg/dl) and decreased to 9.16 mM (165 mg/dl) after treatment compared with 11.3 and 10.8 mM (204 and 194 mg/dl) in the control group. The effect size was 0.39 ($P < 0.0001$). An effect size of 0.39 is interpreted to mean that the average person in the treatment group has a fasting glucose that is better than 65% of the members of the control group. Similarly for HbA_1, the treatment group decreased from a baseline value of 11.0 to 10.2% compared with 11.0 and 11.2% in the control group. The effect size was 0.43 ($P < 0.0001$), or the average member of the treatment group had a higher C-peptide level than 67% of the control group. C-peptides increased in the treatment group (from 0.49 to 0.58 nM [1.45 to 1.75 ng/ml]) but declined in the control group (from 0.47 to 0.43 nM [1.42 to 1.30 ng/m]) for an effect size of 0.26 ($P < 0.017$). The average member of the treatment group had a C-peptide level that was higher than the C-peptides of 60% of the control group.

A different way to express the effect size is to calculate the percentage expected improvement if the control group was given the treatment (10). This conversion is made with a standard normal cumulative distribution function table. For fasting glucose, the percentage improvement is 30% (CI 16, 43), for HbA_1 34% (CI 20, 46), and for C-peptide 20% (CI 4, 37).

To assess the strength of our conclusions, we estimated the number of additional studies that would be needed to disprove the results of our analysis. This is called the "fail-safe *N*." The number of studies needed is dependent on both the outcome measure used and the expected difference between the groups. Eleven studies, each reporting no difference between the control and treatment groups, would be needed to reduce the expected clinical improvement in HbA_1 from 34 to 20%. Similarly, to reduce the expected clinical improvement to 10%, 39 studies with no difference between the control and treatment groups would have to be published. The corresponding numbers for fasting glucose are 8 and 32 studies and for C-peptide 1 and 13 studies. Because three of the randomized trials (33–35) excluded (due to inadequate

Table 2—*Mean baseline subject characteristics*

Ref.	Age (yr)	% Ideal body weight*	Duration of NIDDM (yr)	Insulin (U/day)
14,15	58	129	13	55
16	57	117	14	62
17	48	132	10	55
18	62	147	12	64
19	73	(32)	11	58
20	61	122	11	
21	56	123	8	
22	52	109	8	36
23	51	172	10	84
24	57	128	8	
25	57	(29)	12	95
26	58	(23)	9	32
27,28	59	112	9	42
29	61	124	6	0
30	56	(30)	13	67
31	67	(27)	9	47
32	64	105	10	
Mean	60.8	124.6	10.6	56.2

* Numbers in parentheses are body mass index values rather than ideal body weight.

reporting of the chosen outcomes but no other methodologic problems) also showed a positive effect of combined therapy on glycemic control, it is highly unlikely that the conclusions of this metaanalysis will be overturned.

Linear regression analysis showed no correlation between effect size and study quality ($r^2 = 0.058$, $P = 0.37$), therefore the quality score was not used to exclude studies or weight the effect size.

CONCLUSIONS— This metaanalysis shows that combination insulin and sulfonylurea therapy for NIDDM results in a significant but modest improvement in glycemic control. The results of the "fail-safe *N*" analysis show that 8–39 studies, all of which would have to find no response to combination treatment, would be necessary to overturn this conclusion. Overturning our conclusion is unlikely because, as noted above, there are at least

Table 3—*Pre- and posttreatment values*

	Fasting glucose (mg/dl)				HbA_1 (%)				C-Peptide (nM)			
	Treatment		Control		Treatment		Control		Treatment		Control	
Ref.	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
14	286	252	268	250	10.9	9.6	10.4	10.5	0.52	0.67	0.31	0.25
16	232	193	221	196	11.1	9.1	10.3	8.9	0.26	0.26	0.28	0.21
17	262	232	262	262	10.6	10.2	10.6	10.9		0.63		0.56
18	272	222	260	268	12.7	12.4	12.4	12.8	0.09	0.28	0.14	0.13
19	266	212	247	295	13.8	12.4	13.5	14.1	0.77	0.92	0.77	0.75
20	179	147	195	175					0.47	0.60	0.34	0.32
21	196	187	196	194	13.7	13.3	13.7	13.5		0.38		0.36
22	162	130	162	146	13.1	11.0	13.1	11.5	0.28	0.62	0.28	0.40
23					10.7	8.8	10.7	9.2				
24	196	94	196	92	11.7	9.5	11.7	10.1				
25					12.2	9.0	11.8	11.5				
26	158	142	158	173	9.2	8.3	9.2	9.1	0.10	0.21	0.10	0.16
27	118	119	115	152	8.9	8.9	9.9	10.9				
29	243	144	243	200	10.6	9.8	10.4	10.6	0.68	0.56	0.68	0.46
30	226	173	223	192	10.9	12.9	11.4	14.4				
31	160	140	160	182	9.9	9.1	9.9	10.3	0.75	0.89	0.75	0.69
32	166	151	157	187	8.3	7.0	8.2	8.4	0.40	0.63	0.40	0.55
Weighted mean	206	165	204	194	11.0	10.2	11.0	11.2	0.49	0.58	0.47	0.43

Table 4—*Effect sizes and their interpretation*

Outcome measures	Weighted average effect size	Clinical improvement (%)	Better than control (%)
Fasting glucose	0.39 (0.2,0.57)	30 (16,43)	65
Range	−0.02 to 0.94		
HbA_{1c}	0.43 (0.25,0.61)	34 (20,46)	67
Range	0.07 to 0.82		
C-Peptide	0.26 (0.05,0.48)	20 (4,37)	60
Range	0.07 to 0.88		

Values in parentheses are 95% CIs.

3 other randomized trials of >8 wk duration with positive results. However, some important questions regarding duration of response, individual predictive characteristics of response, and appropriate insulin dosing need to be addressed.

Most of the studies were short term (8–16 wk) and therefore cannot address the long-term benefit of such therapy. Of the three trials with durations of 46–52 wk (16,25,30), two showed favorable responses. The third trial (30) showed a worsening of glycemic control in both treatment groups, but this change was of smaller magnitude in the group receiving combined therapy. The weighted mean effect size for glucose in the longer-duration trials was 0.21 (CI −0.21, 0.64) compared with 0.43 (CI 0.22, 0.64) in the shorter trials, not a significant difference, although trending to a smaller effect. However, for HbA_1, the effect size for the longer-duration trials was 0.45 (CI 0.07, 0.82) compared with 0.43 (CI 0.22, 0.63), an almost identical effect size. The stimulation of insulin secretion by sulfonylureas may decline after 1–18 mo of therapy (3,36–38). If most of the effect of combined therapy is due to increased insulin secretion, then the long-term benefit may be even smaller than reported here, although our data do not show a significant decline in effect.

Four of the studies used patients who had recently failed sulfonylureas and were placed on insulin as part of the study. We found no significant difference in effect size for glucose (0.19 [CI −0.21, 0.60] vs. 0.42 [CI 0.21, 0.63]) or for HbA_1 (0.27 [CI −0.13, 0.67] vs. 0.47 [CI 0.27, 0.68]), although both had a trend toward a lower effect size.

Some individuals have large responses to combination therapy, whereas others have none. This was dramatically illustrated by Schade et al. (17) and Riddle et al. (29). Clinically, it would be very useful to be able to choose combination therapy on the basis of known predictive patient characteristics. The studies included herein did not use a uniform definition for identifying responders nor did they explore the same predictors of response. One used either a decrease of 2.78 mM (50 mg/dl) in the fasting glucose or an absolute value of ≤7.77 mM (140 mg/dl) (14,15). Another study used a fasting glucose of <7.77 mM (140 mg/dl) at three visits and a 25% reduction in total daily insulin dose at some time during the study (30). Others used any decrease over baseline (17,18). In two studies, instead of defining response at a particular level, correlations were performed between prognostic factors and outcomes (16,22). None of the studies compared responders in the treatment group to responders in the control group. Even given these limitations, some interesting hypothesis-generating observations emerged. In six of the randomized studies (14,15,18,19, 23,31), fasting C-peptide predicted response. In one (30), fasting C-peptide showed a "clinical but not statistical" correlation with response. One study did not show an effect of C-peptide (19). One study (27,28) showed that urinary C-peptide before treatment (but not C-peptide response to sulfonylureas) predicted ability to discontinue insulin while maintaining euglycemia. In three studies, obesity predicted response (16,19,31), but in one study it did not (17). Degree of hyperglycemia (worse initial control) was positively correlated with response in two studies (16,31) but not in another (18). In one of the studies, this effect was no longer found when multivariate analysis was performed (31). In one study (31), duration of insulin therapy <8 yr predicted better response. Of the predictors studied, fasting C-peptide was the most consistent.

One problem with most of the studies was that the insulin doses were not increased aggressively to achieve euglycemia. Seven of the studies did not allow the insulin dose to be increased after randomization. Although 9 allowed the dose of insulin to be increased, only 5 of the studies achieved normalization of the glucose in a substantial number of the patients; in 8 of 17 studies, the mean fasting glucose was <8.33 mM (150 mg/dl), but in only one was HbA_1 <8. In the one study in which glucoses were normalized before addition of sulfonylurea, the combination group had less deterioration of their glucoses than the insulin-only group while receiving less insulin. Theoretically, the combination of insulin and sulfonylurea might result in lower circulating insulin levels with the same or lower glucose. This would occur because the subjects would require less exogenous insulin through increased secretion of insulin and possibly improving insulin sensitivity and decreasing hepatic glucose production. However, this effect cannot be adequately assessed in the absence of euglycemia due to the suppression of endogenous insulin secretion by hyperglycemia, so-called pancreatic glucotoxicity. As pointed out above, only 1 study achieved HbA_1 <8. Four studies

measured posttreatment free insulins (16,17,24,26) and did not find significant differences between the groups. No studies measured portal insulins. The theoretical benefit of lower insulin levels (and therefore less hypertension and cardiovascular disease) with combination therapy remains unproved. Furthermore, the benefit of aggressive insulin therapy (enough insulin to achieve euglycemia) versus combination therapy is also not proved.

One possible side effect of combination therapy is weight gain. However, in 12 of 17 studies used in this metaanalysis, no significant differences in weight gain were seen between the control and treatment groups (14,17–19,21–23,25–27,30,32). One study did not report weights at all (24). Four studies showed a significant increase in weight with combination therapy compared to insulin alone (16,20,29,31). The mean weighted effect size for increase in weight with combination therapy was 0.08 with a CI of −0.13 to 0.29, showing no significant effect. We conclude that the risk of weight gain with combination therapy is similar to that with insulin alone.

In conclusion, this metaanalysis shows that combination therapy is more effective than insulin alone in the treatment of patients with NIDDM, but further studies are needed to confirm the predictors of individual response. Further study is justified because, if combination therapy can be shown to reduce complications, it might be more cost-effective, despite higher costs of the drugs themselves. To answer these important questions, a large randomized trial needs to be performed. The intervention should be a maximal dose of sulfonylurea (or placebo) plus insulin varied by standard algorithm as necessary to achieve euglycemia but avoid significant hypoglycemia. Outcomes in both the treatment and placebo groups should be correlated with possible prognostic factors. In the absence of a large trial, the available data suggests that combination therapy may be most beneficial in the obese patient with NIDDM who still has residual insulin secretory capacity.

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