Effect of Metformin in Pediatric Patients With Type 2 Diabetes

A randomized controlled trial

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OBJECTIVE — Metformin is the most commonly prescribed oral antidiabetic agent in the U.S. for adults with type 2 diabetes. The incidence of type 2 diabetes in children has increased dramatically over the past 10 years, and yet, metformin has never been formally studied in children with type 2 diabetes.

RESEARCH DESIGN AND METHODS — This study evaluated the safety and efficacy of metformin at doses up to 1,000 mg twice daily in 82 subjects aged 10–16 years for up to 16 weeks in a randomized double-blind placebo-controlled trial from September 1998 to November 1999. Subjects with type 2 diabetes were enrolled if they had a fasting plasma glucose (FPG) levels ≥7.0 and ≤13.3 mmol/l (≥126 and ≤240 mg/dl), HbA_{1c} ≥7.0%, stimulated C-peptide ≥0.5 nmol/l (≥1.5 ng/ml), and a BMI >50th percentile for age.

RESULTS — Metformin significantly improved glycemic control. At the last double-blind visit, the adjusted mean change from baseline in FPG was −2.4 mmol/l (−42.9 mg/dl) for metformin compared with +1.2 mmol/l (+21.4 mg/dl) for placebo ($P < 0.001$). Mean HbA_{1c} values, adjusted for baseline levels, were also significantly lower for metformin compared with placebo (7.5 vs. 8.6%, respectively; $P < 0.001$). Improvement in FPG was seen in both sexes and in all race subgroups. Metformin did not have a negative impact on body weight or lipid profile. Adverse events were similar to those reported in adults treated with metformin.

CONCLUSION — Metformin was shown to be safe and effective for treatment of type 2 diabetes in pediatric patients.

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The incidence of type 2 diabetes in children has increased dramatically over the past 10 years. This increase has been linked to increasing prevalence of obesity and progressively sedentary lifestyle in American children (1–6). Insulin, the only FDA approved medication for the treatment of diabetes in children, is the current standard of care, despite its parenteral route of delivery and association with the side effects of weight gain and hypoglycemia. Children with type 2 diabetes need alternative therapies that improve glycemic control, facilitate administration and compliance, do not promote weight gain, and address comorbid conditions.

Metformin hydrochloride is an oral antihyperglycemic agent that has been used in many countries for >40 years, and it has been marketed in the U.S. for the treatment of adult type 2 diabetes since 1995. Metformin improves glycemic control by reducing hepatic glucose production, increasing insulin sensitivity, and reducing intestinal glucose absorption, without increasing insulin secretion (7–9). In adults, metformin is effective as an initial monotherapy to improve glycemia, with a low risk of hypoglycemia, and with potential independent benefits of a lack of weight gain and improved lipid profile (10–13).

The phenotypic constellation of type 2 diabetes (hyperglycemia, obesity, dyslipidemia, and insulin resistance) is similar in adults and children (14). Therefore, it has been reasonable to presume that the pharmacodynamic response to metformin therapy in children would be similar to that documented in adults. This randomized placebo-controlled study was designed to investigate, in a rigorous clinical trial, the safety and efficacy of using metformin for the treatment of children with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— This multicenter randomized double-blind placebo-controlled trial randomized subjects from 44 sites (35 in the U.S. [$n = 62$], 6 in Russia [$n = 13$], 1 in the Ukraine [$n = 4$], 1 in Belarus [$n = 2$], and 1 in Poland [$n = 1$]) under a uniform protocol. Subjects were identified through a screening program involving large numbers of children who were not known to have type 2 diabetes but had recognized risk factors. Those eligible for the study included male and female subjects aged 8–16 years of age at screening, with a previous or new diagnosis of type 2 diabetes, who met the following inclusion criteria: FPG levels 7.0–13.3 mmol/l (126–240 mg/dl); HbA_{1c} ≥7.0%; stimulated C-peptide ≥0.5 nmol/l (≥1.5 ng/ml); BMI >50th percentile for age; and informed consent

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Abbreviations: ADA, American Diabetes Association; ANCOVA, analysis of covariance; DSMB, Data and Safety Monitoring Board; FPG, fasting plasma glucose;

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

signed by the subject and subject's parent or legal guardian.

Subjects were excluded if they had one or more positive immune marker(s) for type 1 diabetes; had diabetic ketoacidosis within ≤8 weeks before screening; were currently on insulin; received metformin within 3 months, troglitazone within 6 months, or sulfonylurea within 28 days of randomization (prior sulfonylurea was permitted if the subject had HbA_{1c} ≥7.5% and gained weight while on treatment, justifying a change of therapy); or if they had known hypersensitivity to biguanides or insulin, renal insufficiency (serum creatinine ≥76.26 μmol/l and abnormal creatinine clearance rate), hepatic dysfunction (>3 times upper limit of normal for aspartate aminotransferase and alanine aminotransferase), the presence of chronic diarrhea, or life-threatening or serious conditions that could affect study participation.

Subjects were instructed at randomization on the technique for home capillary blood glucose monitoring, which was performed twice daily at least every other day, and counseled on dietary and exercise practices at each study visit.

Subjects were randomized to either metformin (≤2,000 mg/day) or placebo in a ratio of 1:1 across sites in accordance with a schematic based on a permuted block design. Subjects were titrated at 1-week intervals beginning with two tablets/day to a maximum of four tablets/day (500 mg metformin or placebo per tablet) and remained on the highest tolerable dose of study medication for the remainder of the treatment period. Rescue therapy was instituted for subjects who exceeded predetermined glycemic thresholds of ≥12.8 mmol/l (≥230 mg/dl) at week 2, ≥10.0 mmol/l (≥180 mg/dl) at week 4, or ≥7.8 mmol/l (≥140 mg/dl) after week 6.

All laboratory measurements were performed by Quintiles Laboratories (Smyrna, GA, and Edinburgh, U.K.), except for autoimmune antibody assays, which were performed at the Barbara Davis Center (Denver, CO) (15). All blood samples for laboratory measurements were collected in the fasting state, except at screening. The HbA_{1c} measurements were made on a Bio-Rad Variant II instrument (normal range 4.3–6.1%). Stimulated C-peptide levels were measured 90 min after a standardized 12-oz Sustacal challenge and analyzed using radioimmunoassay methodology (normal range 0.26–1.33 nmol/l). Safety assessments included physical examination, weight measurements, laboratory tests, and adverse events.

For safety purposes, an interim analysis, planned for when half of the subjects had completed 8 weeks of follow-up, included safety and demographic data, and change in FPG from baseline at the last double-blind visit at or before week 8. At that time point, 70.0% of the placebo subjects had required rescue medication compared with 15.8% of metformin subjects. The adjusted mean change in FPG at week 8 for the interim cohort was −2.8 mmol/l (−50.4 mg/dl) for metformin subjects and +1.0 mmol/l (+17.4 mg/dl) for placebo subjects ($P = 0.001$). The independent Data and Safety Monitoring Board (DSMB) recommended early termination of the trial, based on convincing efficacy results and lack of safety concerns, to reduce the number of trial subjects exposed to placebo. At the recommendation of the DSMB, all subjects in the double-blind period as of 25 November 1999 were switched to open-label metformin.

Statistical analysis

The primary analysis of efficacy included all randomized subjects who had a baseline and at least one postbaseline measurement during the double-blind period. Analysis of demographic characteristics and baseline characteristics were performed using all randomized subjects. Baseline was defined as the last measurement at or before the randomization visit. The primary efficacy variable, the change in FPG from baseline at the last double-blind visit at or before week 16, was evaluated by an analysis of covariance (ANCOVA), using a term for treatment and the baseline FPG as a covariate. The 95% CI around the adjusted mean change from baseline was obtained for each treatment group and for the difference between treatment groups, based on the ANCOVA model. The statistical test was two-sided at a significance level of 0.03355 adjusted for one interim analysis. Secondary efficacy variables, HbA_{1c} levels and changes from baseline for weight, height, BMI, lipid, and stimulated C-peptide at the last double-blind visit, were analyzed using a similar statistical model. All statistical analyses were performed using statistical software, SAS version 6.12 (SAS Institute, Cary, NC).

The safety assessment of adverse events, physical examinations, and laboratory values included all subjects who were randomized and had taken at least one dose of study medication (metformin or placebo). The proportions of subjects requiring rescue therapy or discontinuing therapy due to treatment-related adverse events were compared between treatment groups using Fisher's exact test.

The planned sample size of 72 subjects (36 subjects/treatment) was estimated to provide 80% power to detect a difference between metformin and placebo groups at a two-sided 0.05 significance level, for mean change from baseline in FPG (primary efficacy variable) if the true difference is 2.2 mmol/l (40 mg/dl), assuming a SD of 3.3 mmol/l (60 mg/dl).

RESULTS — Of 481 subjects enrolled, 399 were excluded, including 305 (76.4%) who had FPG <126 or >240 mg/dl, 286 (71.7%) with HbA_{1c} <7%, 43 (10.8%) who were positive for islet cell antibodies, and 38 (9.5%) for other reasons. A total of 42 subjects were randomized to metformin, and 40 subjects were randomized to placebo (Fig. 1).

Six (14.3%) metformin subjects and four (10.0%) placebo subjects discontinued prematurely from the study before 16 weeks. One metformin and two placebo subjects discontinued due to serious adverse events, all judged to be unrelated to the study drug. Of the placebo subjects, 26 (65%) required rescue medication before week 16 compared with 4 (9.5%) metformin subjects. More subjects randomized to metformin completed the double-blind study or were switched to open-label treatment before week 16 based on the DSMB recommendation to terminate the double-blind period (Fig. 1).

Baseline demographic characteristics were similar for the two treatment groups (Table 1). Although the 20 (24%) subjects recruited from outside the U.S. tended to be leaner, these subjects did not differ meaningfully from the U.S. subjects in regard to treatment effects, mean final doses, or rescue rates. Differences between the two treatment groups were seen in the baseline diabetes characteristics obtained at or before the randomization visit (Table 1); eligibility for the study was de-

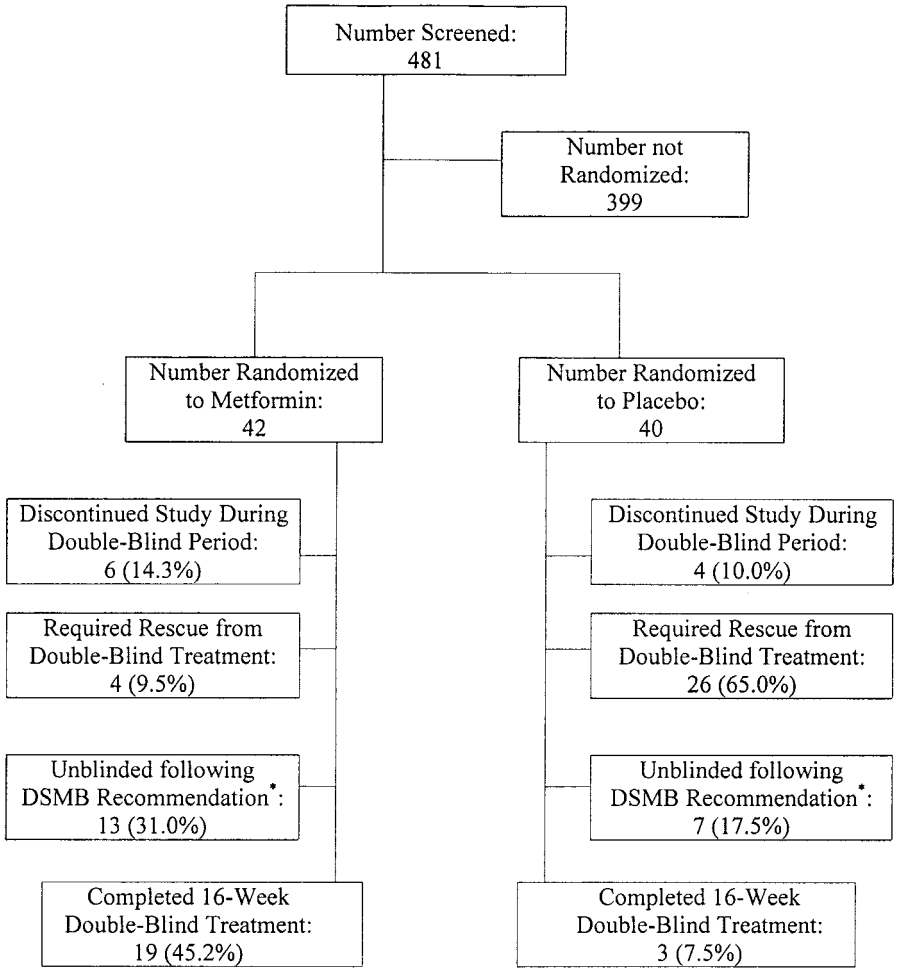

Figure 1—*The dispositions of subjects who were screened and of subjects who were randomized in this study are graphically displayed. Of the 399 subjects excluded from randomization at screening, 76% had FPG <7.0 or >13.3 mmol/l (<126 or >240 mg/dl), 72% had HbA_{1c} <7%, 11% were positive for islet cell antibodies, and 10% had other reasons for exclusion. *The DSMB, after reviewing results of an interim analysis performed when 39 patients had potentially completed 8 weeks of therapy, recommended that the study be unblinded and all patients taking placebo be switched to metformin therapy.*

termined from screening data. The subjects randomized to placebo had higher mean baseline FPG levels; over twice as many subjects with FPG ≥11.1 mmol/l (≥200 mg/dl) were randomized to placebo (n = 20 vs. n = 9 for metformin). Similarly, a greater number of subjects randomized to placebo had HbA_{1c} ≥8.0% (n = 32 vs. n = 23 for metformin). The mean stimulated C-peptide level was higher in the metformin group, but the difference was due to one subject with a level of 5.5 nmol/l; the median values were similar in the two treatment groups. The higher mean level of triglycerides in the placebo group was also the result of one subject whose triglyceride level was 11.99 mmol/l (1,061 mg/dl). These baseline differences between the treatment groups were adjusted using covariates in the statistical analysis.

Exposure to study treatment

The mean length of exposure to metformin was 80 days (range 0–134) and to placebo it was 44 days (6–125). The mean final dose of metformin was 1,798 mg; 83% of the subjects randomized to metformin were taking 2,000 mg/day at their last double-blind visit.

Glycemic control

At the end of double-blind treatment, the mean FPG (adjusted for baseline) had significantly decreased from baseline in the metformin subjects while increasing in the placebo subjects (−2.4 mmol/l vs. +1.2 mmol/l; $P < 0.001$) (−42.9 mg/dl vs. +21.4 mg/dl; $P < 0.001$) (Table 2). A notable decrease in the mean FPG from baseline was seen with metformin by week 2 (−0.5 mmol/l [−9.3 mg/dl] compared with −0.07 mmol/l [−1.2 mg/dl] with placebo) and continued through the length of the double-blind period.

The reduction in FPG that occurred with metformin was seen in both men (−2.5 mmol/l) and women (−2.3 mmol/l) and all races (white [−1.9 mmol/l], black [−3.0 mmol/l], Hispanic/Latino [−3.1 mmol/l), and other [−1.9 mmol/l]). Among subjects with baseline FPG ≥11.1 mmol/l (≥200 mg/dl), FPG was reduced by −3.6 mmol/l (−65.3 mg/dl) from a mean baseline of 13.5 mmol/l (243 mg/dl) during metformin treatment (n = 7), and it increased by 0.3 mmol/l (5.6 mg/dl) from a mean baseline of 13.0 mmol/l (234 mg/dl) during placebo treatment (n = 17). For those subjects with baseline FPG <11.1 mmol/l (<200 mg/dl), the mean FPG was reduced by −1.6 mmol/l (−29 mg/l) from a mean baseline of 8.0 mmol/l (144 mg/dl) during metformin treatment (n = 30) and increased by 1.2 mmol/l (22 mg/dl) from a mean baseline of 8.6 mmol/l (155 mg/dl) during placebo treatment (n = 19).

The mean HbA_{1c} level (adjusted for baseline mean difference) at the end of the double-blind period was significantly lower in the metformin group compared with the placebo group (7.5 vs. 8.6%, respectively; $P < 0.001$) (Table 2).

The proportion of subjects who met at least one of the American Diabetes Association (ADA) glycemic target levels (FPG <7.0 mmol/l [<126 mg/dl] or HbA_{1c} <7.0%) by their last double-blind treatment visit was 84% (31 of 37) for the metformin group compared with 22% (8 of 36) for the placebo group. The number of subjects who met the HbA_{1c} <7.0% target level increased from 5 of 42 (12%) at the start of the study to 24 of 37 (65%) during metformin treatment, whereas 4 of 36 (11%) achieved HbA_{1c} <7% during placebo treatment.

Four (10%) subjects in the metformin group and 26 (65.0%) subjects in the placebo group required rescue from double-blind treatment because of inadequate glycemic control (Fig. 1). The majority of those subjects required rescue medication by week 6. No between-group difference was seen in the adjusted mean stimulated

Table 1—*Demographic and baseline characteristics (all randomized subjects)*

Characteristic	Metformin	Placebo
Sex	42	40
Male	12 (28.6)	13 (32.5)
Female	30 (71.4)	27 (67.5)
Age (years)		
Mean	13.9 ± 1.8	13.6 ± 1.8
Median	14	14
Range	10–16	10–17*
Age (years)		
8 to <10	0	0
10 to <12	5 (11.9)	7 (17.5)
12 to <14	9 (21.4)	12 (30.0)
14 to <16	18 (42.9)	14 (35.0)
≥16	10 (23.8)	7 (17.5)
Race		
White	17 (40.5)	13 (32.5)
Black	11 (26.2)	13 (32.5)
Asian/Pacific Islander	3 (7.1)	1 (2.5)
Hispanic/Latino	9 (21.4)	9 (22.5)
Other	2 (4.8)	4 (10.0)
Weight (kg)		
Mean	92.8 ± 31.8	90.3 ± 38.1
Median	91.0	87.9
Range	43.0–160.5	32.0–196.4
BMI		
Mean	34.2 ± 10.6	33.9 ± 12.7
Median	33.2	32.0
Range	19.2–58.4	18.1–82.8
BMI (kg/m^2)		
<75th Percentile for age	6 (14.3)	8 (20.0)
≥75th Percentile for age	36 (85.7)	32 (80.0)
FPG (mmol/l)†		
Mean	9.2 ± 2.8	11.0 ± 3.3
<7.0	10 (23.8)§	4 (10.0)§
7.0 to <8.9	12 (28.6)	7 (17.5)
8.9 to <11.1	11 (26.2)	9 (22.5)
11.1 to <13.3	2 (4.8)	11 (27.5)
≥13.3	7 (16.7)	9 (22.5)
HbA_{1c} (%)†		
Mean	8.3 ± 1.3	9.0 ± 1.4
<7.0	5 (11.9)§	1 (2.5)‡
7.0 to <8.0	14 (33.3)	7 (17.5)
8.0 to <9.0	12 (28.6)	17 (42.5)
9.0 to <10.0	5 (11.9)	7 (17.5)
≥10.0	6 (14.3)	8 (20.0)
Stimulated C-peptide (nmol/l)	2.4 (1.1)	2.2 (1.1)
Total cholesterol (mmol/l)§	4.5 (1.0)	4.9 (1.0)
HDL cholesterol (mmol/l)§	1.1 (0.3)	1.1 (0.3)
LDL cholesterol (mmol/l)§	2.6 (0.8)	2.9 (0.7)
Triglycerides (mmol/l)‖	1.7 (1.3)	2.3 (2.2)¶

Data are *n* (%) or means ± SD, unless otherwise indicated. *One subject was 16 years of age at the time the informed consent was signed, but had a birthday between the signing date and the screening visit. †The FPG and HbA_{1c} values provided were the values at the randomization visit (visit 2). The inclusion criteria had to be met only at screening (visit 1); consequently, at randomization some subjects had levels outside the range given in the inclusion criteria. ‡Number and percentage of subjects who fell in to each category. §To convert cholesterol levels from millimoles per liter to milligrams per deciliter, divide by 0.259. Data are rounded. ‖To convert triglyceride levels from millimoles per liter to milligrams per deciliter, divide by 0.0113. ¶One subject had a triglyceride level of 12.0 mmol/l, which contributed to the higher mean for the placebo group.

C-peptide change from baseline (−0.2 nmol/l for both groups [−0.7 ng/ml vs. −0.6 ng/ml]).

Other metabolic effects

Mean total serum cholesterol decreased from baseline levels in the metformin group (−0.25 mmol/l [−9.7 mg/dl]) compared with a slight increase in the placebo group (+0.01 mmol/l [+0.7 mg/dl]; $P = 0.043$). The adjusted mean difference in total cholesterol was reflected in the mean decrease in LDL cholesterol seen with metformin, which came close to reaching significance over placebo (−0.11 mmol/l [−4.2 mg/dl] vs. +0.10 mmol/l [+4.0 mg/dl]; $P = 0.053$). No between-group differences were seen in the mean adjusted changes in HDL cholesterol levels (−0.06 mmol/l [−2.5 mg/dl] vs. −0.04 mmol/l [−1.6 mg/dl]), or triglyceride levels (−0.04 mmol/l [−3.9 mg/dl] vs. +0.00 mmol/l [+0.2 mg/dl]). Mean weight change from baseline (−1.5 kg metformin vs. −0.9 kg placebo) and mean BMI change from baseline (−0.5 kg/m^2 metformin vs. −0.4 kg/m^2 placebo) were also comparable between the two treatment groups.

Safety evaluations

The percentage of subjects with at least one adverse event was higher in the metformin group (70 vs. 60%). Some of that difference may be explained by the fact that the length of exposure to metformin was almost double the length of exposure to placebo because more subjects randomized to placebo required early institution of rescue medication as compared with subjects randomized to metformin.

The most commonly reported adverse events were abdominal pain, diarrhea, nausea/vomiting, and headache. Higher percentages of metformin subjects experienced abdominal pain (25 vs. 12%) and nausea/vomiting (17 vs. 10%). Adverse events were considered serious in five subjects (two metformin and three placebo subjects), but none of them were considered related to the study drug. One metformin subject became seropositive for hepatitis B (day 15), and the other had severe abdominal pain with diarrhea considered related to a viral infection (day 47). All three serious adverse events experienced by the placebo subjects were related to a diabetic condition; one subject developed ketoacidosis (day 16), one had an increase in serum glucose (day

Table 2—*Glycemic control measurements at baseline and last double-blind visit*

Variable	Metformin	Placebo	Difference (metformin – placebo)
Baseline mean FPG (mmol/l)	9.0 ± 2.7	10.7 ± 2.7	
Last double-blind visit mean FPG (mmol/l)	7.0 ± 2.2	11.5 ± 4.5	
Adjusted mean* FPG change from baseline (mmol/l)	−2.4 ± 0.5	1.2 ± 0.5	−3.6 ± 0.8
95% CI	−3.5 to −1.3	0.1 to 2.3	5.1 to −2.0
P†			<0.001‡
Baseline mean HbA_{1c} (%)	8.2 ± 1.3	8.9 ± 1.4	
Last double-blind visit mean HbA_{1c} (%)	7.2 ± 1.2	8.9 ± 1.6	
Adjusted mean* HbA_{1c} (%)	7.5 ± 0.2	8.6 ± 0.2	−1.2 ± 0.2
95% CI	(7.2–7.8)	(8.3–9.0)	(−1.6–−0.7)
P§			<0.001

Data are means ± SD unless otherwise indicated. *Mean adjusted for baseline FPG or for baseline HbA_{1c}. †The *P* value is based on an ANCOVA, comparing metformin to placebo using baseline FPG as the covariate and treatment as the main effect. ‡Significance level $P < 0.03355$, where the testwise critical value was adjusted for an 8-week interim analysis of FPG, to preserve an overall α level of ≤0.05 using the O'Brien-Fleming method with an α of 0.025 at the interim analysis. §*P* value is based on an ANCOVA, comparing metformin to placebo using baseline HbA_{1c} as the covariate and treatment as the main effect.

28), and the other subject experienced problems associated with diabetes and increased liver function enzymes (day 2). Three of the five subjects discontinued the study because of the serious adverse event. No cases of clinical hypoglycemia, lactic acidosis, or clinically significant changes in physical examinations occurred during the study.

CONCLUSIONS — This is the first multicenter controlled clinical trial of the safety and efficacy of metformin in pediatric subjects with type 2 diabetes. The study demonstrates that metformin, titrated up to 2,000 mg/day (in addition to standard dietary therapy and exercise), improves glycemic control in pediatric subjects with type 2 diabetes, starting within 2 weeks after initiation of therapy. The improvement with metformin was evidenced by significant reductions in FPG and HbA_{1c}, similar to the decreases reported for adult subjects. The largest published controlled study of metformin monotherapy in adults with doses up to 2,500 mg/day reported mean decreases from baseline of 2.9 mmol/l (52 mg/dl) for FPG and of 1.4% for HbA_{1c} (10). The corresponding reduction in FPG in children in this study, using doses up to 2,000 mg/day, was 2.4 mmol/l (42.9 mg/dl).

Identifying subjects who met the inclusion criteria proved difficult. Because it was considered inappropriate to remove subjects from existing antidiabetic therapy to enter them into a placebo-controlled clinical trial, subject recruitment included screening large numbers of children who were not known to have type 2 diabetes, but were identified as having recognized risk factors. Consequently, 481 subjects were identified for participation, but only 17% met the inclusion criteria at screening. The majority of the subjects failing to qualify did not have the required FPG level ($n = 305$); ~85% of those subjects not meeting the FPG criteria had levels of <7.0 mmol/l, with the remaining subjects having FPG >13.3 mmol/l.

No potential problems were identified with the randomization process. The balance between treatment groups in demographic characteristics, including a balanced distribution of subjects with BMI ≥75th percentile for age, supports the success of the randomization process. However, there were between-group differences in the mean and median baseline diabetes characteristics. Subjects randomized to metformin had lower mean FPG and HbA_{1c} levels than subjects randomized to placebo. Changes from baseline in FPG and HbA_{1c} levels were analyzed using ANCOVA, with the baseline FPG or HbA_{1c} level as a covariate, which served to correct for the between-group difference at baseline. The glycemic improvement seen in the metformin group alone was highly clinically meaningful. Almost 85% of the metformin-treated subjects achieved either the FPG or the HbA_{1c} target level defined by the ADA (6) compared with only 22% of the placebo-treated subjects.

Near normalization of blood glucose has also been associated with a less atherogenic lipid profile (6). In this study, the improvement in glycemic control with metformin occurred without the increase in body weight that is frequently observed with insulin, and it had no adverse effect on the lipid profile.

The adverse events experienced by subjects in this study were consistent with adverse events reported for adults. Of concern with biguanides, such as metformin, is the occurrence of gastrointestinal side effects, most commonly diarrhea, which has been reported in up to 30% of adult patients (9). Diarrhea and/or abdominal pain were reported by up to 25% of the pediatric metformin-treated subjects. Such gastrointestinal effects typically occur with the start of metformin and are significantly reduced with the passage of time and appropriate dosing schedules. No safety issue arose that might indicate metformin is not suitable for use in pediatric patients with type 2 diabetes.

In summary, metformin is effective and safe for the treatment of pediatric type 2 diabetes. The present findings confirm the ADA's recommendation for the use of metformin to treat type 2 diabetes in children and adolescents (6).

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