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Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: A meta-analysis

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ABSTRACT

Background: Metformin is recommended as first-line treatment in type 2 diabetic patients. Several agents can be used as add-on treatments in metformin monotherapy failure. Most available clinical trials on the hypoglycemic efficacy of different drugs were performed either in monotherapy or in combination with agents other than metformin. Aim of the present meta-analysis is to collect available information on the efficacy of different hypoglycemic drugs, in combination with metformin, in patients failing to metformin, or to other oral monotherapies.

Methods: An extensive Medline search, together with manual search of references from retrieved articles, was performed to identify randomized clinical trials comparing the efficacy on HbA1c of different agents, compared with placebo or with other active drugs, in combination with metformin, in patients failing to oral hypoglycemic therapy. HbA1c reduction at 16–36 months was considered for meta-analysis.

Results: A total of 27 clinical trials were retrieved. Combining the results of different placebo-controlled trials, sulphonylureas, α-glucosidase inhibitors and thiazolidinediones induced a reduction [95%CI] of HbA1c of 0.85 [0.78; 0.94], 0.61 [0.55; 0.67], 0.42 [0.40; 0.44]%, respectively. In direct comparisons, sulphonylureas induced a greater reduction of HbA1c (of 0.17 [0.16; 0.18]%) than thiazolidinediones, and had a similar effect as insulin.

Conclusions: When combined with metformin, sulphonylureas and α-glucosidase inhibitors show a similar efficacy on HbA1c. The effects of drugs used as add-on to metformin monotherapy could be different from those observed in monotherapy.

1. Introduction

Metformin is recommended by most guidelines as the drug of choice for monotherapy in patients with type 2 diabetes. The International Diabetes Federation (IDF) suggests to use metformin in all cases inadequately controlled by non-pharmacological treatments [1] while a recent consensus document of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends to prescribe metformin at diagnosis, together with lifestyle interventions [2].

On the other hand, in most patients with type 2 diabetes, monotherapy with metformin, as well as any other hypoglycemic drug, is capable of maintaining a good metabolic control only for a limited period of time [3,4]. For this reason, most type 2 diabetic patients, after a few years from diagnosis, require combined treatments in order to reach therapeutic goals. Treatment options for metformin monotherapy failure

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include the addition of sulphonylureas, glinides, thiazolidinediones, acarbose, glucagon-like peptide-1 (GLP-1) analogues, dipeptidyl peptidase IV (DPP-IV) inhibitors, or insulin. The EASD/ADA consensus document suggests to add sulphonylureas (least expensive), thiazolidinediones (no hypoglycemic risk), or insulin (most effective). Other agents, such as α-glucosidase inhibitors and glinides, are not recommended as first-choice therapy because of a lower efficacy on HbA1c, while GLP-1 analogues and DPP-IV inhibitors are not considered because of the limited amount of evidence presently available [2].

Most available trials on hypoglycemic drugs for type 2 diabetes have been performed in monotherapy, often in drug-naïve patients. The efficacy of a drug when combined with other agents can be different from that of the same drug prescribed as monotherapy. In most instances, hypoglycemic agents show a smaller effect on HbA1c when used in combination [5]. Furthermore, patients failing to metformin monotherapy could have different characteristics in comparison with individuals failing to other forms of monotherapy, or with drug-naïve subjects, and they could therefore show a different response to hypoglycemic agents. Aim of the present meta-analysis is to collect available information on the efficacy of different hypoglycemic drugs, in combination with metformin, in patients failing to metformin.

2. Materials and methods

A Medline search of randomized clinical trials was performed on 2 January 2007, with no time limits, using as a keyword ''metformin'', associated with any one of the following: glibenclamide, glyburide, glipizide, gliclazide, chlorpropamide, tolbutamide, glimepiride, gliquidione, repaglinide, nateglinide, acarbose, miglitol, pioglitazone, rosiglitazone, troglitazone, exenatide, liraglutide, sitagliptin, vidagliptin, muraglitazar, pramlintide, insulin, glargine, lispro, aspart, glulisine and detemir. Retrieved articles were manually searched for further relevant references.

Clinical trials were included in the analysis provided that they were fully published in English, and that they fulfilled the following criteria:

(1) Design as randomized clinical trials, either cross-over or in parallel-series.
(2) Comparison of a hypoglycemic agent with placebo, or with another active drug, in combination with metformin in both treatment arms. Trials in which patients were treated with more than one agent in combination with metformin (i.e., the so-called ''triple therapy'') were excluded.
(3) Duration of treatment of at least 16 weeks. Trials in which treatment lasted more than 36 weeks were included only if HbA1c data at 24 (±4) weeks were available.
(4) Enrolled patients affected by type 2 diabetes, and failing to therapy with metformin or with other oral hypoglycemic agents (i.e., with inadequate HbA1c levels after treatment with oral agents). If inclusion criteria were wider, enrolling patients who were drug-naïve, or already insulin-treated, only those trials reporting a sub-group analysis of patients on oral therapy failure were included. A further analysis was performed including only trials reporting the effects of different treatments on patients failing to metformin monotherapy.

In order to be included in the meta-analysis, papers should report at least baseline and post-treatment HbA1c, together with a dispersion measure (either S.D. or S.E.M.), for both treatment arms. For studies reported in more than one paper, only the first publication with full available data on HbA1c was considered.

The meta-analysis was performed according to the methods described by Hedges and Olkin [6] to determine the effect size for each study. The mean of a control group (M_c) was subtracted from the mean of experimental group (M_e) and divided by the pooled S.D. of both groups: $d = (M_e - M_c)/\text{S.D.}$ In this case S.D. is the square root of the weighted average of the two variances: $s^2 = [(n_e - 1)(s_e^2) + (n_c - 1)(s_c^2)]/(n_e - n_c - 2)$, where n_e and n_c are the number of cases in experimental and control groups, respectively, and s_e and s_c are their standard deviations.

Between-group comparisons of effects on HbA1c were performed with ANOVA, with a significance level of $\alpha < 0.05$, using baseline HbA1c (mean of active treatment and placebo) as a covariate. Statistical analysis was performed using SPSS 12.0.1.

A separate analysis was performed including only trials on patients failing to metformin monotherapy. This analysis was aimed at assessing possible differences in response to treatment of patients failing to different oral monotherapies.

3. Results

A total of 16 placebo-controlled trials [7–22] exploring the effect of different agents in combination with metformin in patients failing to oral therapy was identified (Table 1). Drugs studied included sulphonylureas (five trials), α-glucosidase inhibitors (five trials), thiazolidinediones (three trials), glinides (two trials) and GLP-1 agonists (one trial). No trials on pramlintide or DPP-IV inhibitors fulfilling the above-specified criteria were identified. Two studies [8,20] did not report dispersion data for HbA1c, and they could not be included in the analysis. The effect of different drugs, in comparison with placebo, in individual studies is reported in Fig. 1. When combining all available trials, reduction of HbA1c [95%CI] with sulphonylureas, thiazolidinediones, and α-glucosidase inhibitors, was 0.85 [0.78; 0.94], 0.42 [0.40; 0.44] and 0.61 [0.55; 0.67]%, respectively. After adjustment for baseline HbA1c, the reduction of HbA1c obtained with sulphonylurea, with respect to placebo, was significantly ($p < 0.05$) greater than that of thiazolidinediones; conversely, differences between sulphonylurea and α-glucosidase inhibitors, and between α-glucosidase inhibitors and thiazolidinediones, were not statistically significant. A statistical comparison with glinides and GLP-1 analogues was not possible, because only one trial, in which dispersion measures of $HbA1_c$ was reported, was available for meta-analysis in each of those two categories.

A separate analysis was performed for the assessment of effects of different treatments on HbA1c in patients failing to