Efficacy of benfluorex in combination with sulfonylurea in type 2 diabetic patients: An 18 to 34-week, open-label, extension period

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Abstract

Aim. – The aim of this trial was to obtain further data on the efficacy and safety of benfluorex as an add-on therapy in type 2 diabetic patients insufficiently controlled by sulfonylurea monotherapy who had a limitation for the use of metformin during a 4-month extension period following a 4-month double-blind trial.

Methods. – Patients who completed the 18-week double-blind period entered the 16-week extension period. Patients in the benfluorex group during the double-blind period continued benfluorex 450 mg/day (B-B group), whilst patients in the placebo group switched to benfluorex 450 mg/day (P-B group). The main efficacy criterion was HbA\textsubscript{1c}, analyzed as the change from week 18 (W18) to the end of treatment using a two-sided Student paired t-test. Secondary criteria were fasting plasma glucose (FPG), insulin resistance and lipids.

Results. – Between W18 and the end of treatment, HbA\textsubscript{1c} decreased in the P-B group from 8.53 ± 1.37% to 7.49 ± 1.04% (P < 0.001) and remained stable in the B-B group from 7.52 ± 1.07% to 7.53 ± 1.14% (NS). In the P-B group, parameters of glycemic control showed improvements from W18 to week 34 (W34) which were similar to those observed from baseline to W18 in the B-B group. Overall, the target HbA\textsubscript{1c} (≤ 7%) was achieved in 36% (103 of 289) of patients and a decrease in HbA\textsubscript{1c} of at least 1% was seen in 44% (128 of 289) of patients. Digestive disorders were the most common adverse events and the incidence of diarrhoea was 4.9% in patients receiving benfluorex for 34 weeks.

Conclusion. – The beneficial effect of benfluorex as add-on therapy in lowering HbA\textsubscript{1c} at W18 was maintained at W34 without evidence for a loss of efficacy or an increased incidence of side effects over a 34-week follow-up.

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Résumé

Éfficacité de l’association du benfluorex aux sulfamides hypoglycémiants chez des diabétiques de type 2 : période d’extension 18 à 34 semaines, en ouvert.

Objectif. – L’objectif de cette étude était de disposer de données supplémentaires sur l’efficacité et la tolérance de benfluorex en association à un sulfamide hypoglycémiant chez des patients imparfaitement contrôlés en monothérapie par sulfamide hypoglycémiant et intolérants ou présentant une contre-indication à la metformine, au cours d’une période de quatre mois faisant suite à une période de quatre mois en double-insu.

Méthodes. – Les patients ayant terminé la période en double-insu ont été inclus dans la période d’extension. Les patients sous benfluorex pendant la période double-insu continuaient de recevoir benfluorex 450 mg/j (groupe B-B) alors que ceux qui étaient préalablement sous placebo recevaient benfluorex 450 mg/j (groupe P-B). Le critère principal d’efficacité était la variation de l’HbA\textsubscript{1c} de la semaine 18 à la fin du traitement et était analysé selon un test t de Student bilatéral. Les critères secondaires étaient la glycémie à jeun, l’insulinorésistance et les lipides plasmatiques.

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1. Introduction

Due to the rising number of diabetes cases worldwide (approximately 171 million in 2000) [1], the burden of diabetes is growing and there is an enhanced need for effective diabetes management. This burden is mainly related to chronic microvascular and macrovascular complications, and the UKPDS and the ADVANCE studies have established that a decrease in HbA1c decreases the incidence of microvascular complications [2,3].

Accordingly, international and French guidelines for the management of type 2 diabetes include maintaining glycaemic levels as close to the non-diabetic range as possible by targeting HbA1c to less than 7% [4] and more recently to less than 6.5% [5,6]. To achieve such goals, there is an increasing need for different molecules in order to optimize treatment combinations according to the clinical setting and the tolerance of each subject, hence the early initiation of combined therapy is being gradually recognized.

Benfluorex [1 (3-trifluoromethylphenyl)-2-(benzoxyloxyethyl)-aminopropane] is a compound with blood glucose lowering actions. In preclinical and clinical studies, benfluorex has been shown to improve insulin sensitivity, to decrease hepatic glucose production and to improve aerobic glucose utilization in skeletal muscle [7–10]. The mechanisms of these metabolic actions in liver and muscle differ from those of metformin. In particular, benfluorex decreases gluconeogenesis by affecting expression of genes encoding phosphoenolpyruvate carboxykinase (PEPCK) and by the inhibition of beta-oxidation [7].

A large-scale 6-month study in diet-failed type 2 diabetic patients demonstrated the efficacy of benfluorex versus placebo in monotherapy, with a significant 0.86% reduction in HbA1c and a good safety profile [11]. A recent double-blind 18-week study confirmed the glycaemic-lowering properties of benfluorex as an add-on therapy in type 2 diabetic patients insufficiently controlled on sulfonylurea monotherapy [12]. The study showed that benfluorex was superior to placebo in lowering HbA1c with a between group difference of 1%. In these two studies the most common side effects were gastrointestinal (GI) disorders, asthenia, somnolence, dizziness and headache.

For ethical reasons, the duration of the double-blind period, which included a placebo arm, did not exceed 18 weeks. Nevertheless, as expected when a chronic disease is concerned, information on long-term effects of any antidiabetic treatment is useful. It was therefore considered of scientific interest to continue the above-mentioned study [12] with an open-label period, in which all patients were given benfluorex as add-on therapy. The results of this 16-week extension period are presented here.

2. Research design and methods

2.1. Study population

Eligibility criteria were type 2 diabetic patients with age greater or equal to 18 years, BMI of 25–40 kg/m², HbA1c of 7–10% (inclusive) and treated by monotherapy with a sulfonylurea at the maximal tolerated dose for at least 4 months. All patients had either a history of gastrointestinal intolerance to metformin or a contraindication to its use, such as renal impairment, or any cardiac or respiratory condition with a potential for tissue hypoxia [13]. Exclusion criteria were severe renal impairment (creatinine clearance < 30 ml/min), an alanine aminotransferase or aspartate aminotransferase plasma level above three times the upper limit of normal, active proliferative retinopathy, uncontrolled high blood pressure (≥ 180/100 mmHg), or any disorder that could interfere with the study conduct or endpoint evaluation. Patients were withdrawn for lack of efficacy, which was defined as two fasting plasma glucose (FPG) measurements greater or equal to 15 mmol/l after at least 1 month of study treatment. All the patients who completed the double-blind period of the study were eligible to continue with the extension period except those judged by the investigator to be insufficiently controlled. Patients in the benfluorex group during the double-blind period continued benfluorex 450 mg/day (B-B group), whilst patients in the placebo group switched to benfluorex 450 mg/day (P-B group).

2.2. Study design

From W18 to W34, a 16-week open-label extension was conducted in 63 centres in seven countries. The double blind of the comparative period was maintained during the extension period. In the B-B group, the benfluorex dose was maintained...
at 450 mg/day (les laboratoires Servier Industrie, Gidy, France). In the P-B group, the dose was increased progressively over the first 3 weeks from one active tablet (150 mg) per day to the recommended dose of one active tablet three times daily (450 mg). A third agent (acarbose, starting dose 50 mg tid) could be added from week 26 (W26) in patients whose HbA1c was greater than 8%, depending on the investigator’s judgment. The dose of sulfonylurea was to be stably maintained throughout the study, except in cases of severe or repeated hypoglycaemia. Subjects were asked to maintain their usual diet and physical activity. The primary efficacy endpoint was HbA1c. The secondary endpoints were FPG, fasting serum insulin (FSI) and lipid profile, each assessed at W0, W18 (end of double-blind period), W26 and W34. The insulin resistance index (HOMA-IR) was also a secondary endpoint and was evaluated at W0, W18 and W34. The trial was conducted in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Edinburgh, Scotland, October 2000. All subjects provided written informed consent.

2.3. Assessments

HbA1c, FPG, FSI, standard biological safety parameters and lipid parameters were assessed centrally (MDS Pharma Services, Hamburg, Germany). Creatinine clearance was calculated according to the Cockcroft formula [14]. HbA1c was assayed using a NGSP certified HPLC method (Biorad Variant I). FPG was assessed by a hexokinase method; all glucose and lipid assays were performed on a Hitachi 747 instrument (Boehringer, Manheim, Germany). FSI was measured by a specific radioimmunoassay; the HOMA-IR was calculated using the classical homeostasis assessment model [15]. Safety was assessed by spontaneous adverse event reporting, physical examinations, recording of vital signs, laboratory tests and 12-lead electrocardiogram (ECG) at W0, W18 and W34. Hypoglycaemic events were recorded from the patient diary and were based on suggestive clinical symptoms only.

2.4. Statistical analysis

The intention-to-treat (ITT) population was defined as all randomized patients exposed to the study drug with a W0 value, a W18 value under treatment and at least one value of HbA1c measured during the extension period. For primary efficacy analyses, the change HbA1c from the W0 and W18 value to the last value under treatment was studied using a two-sided student paired t-test. The secondary analytical approach for efficacy was the percentage of responders defined as patients with an HbA1c value on treatment of less or equal to 7%. Three subgroups were predefined according to regulatory requirements [16]: HbA1c at inclusion (>8%), age at selection (>65 years) and creatinine clearance (≤80 ml/min). Safety analyses were performed on all patients exposed to at least one dose of study treatment. Final values for withdrawn patients corresponded to the last values during treatment. All statistical analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC).

3. Results

3.1. Disposition of patients

Of the 297 patients who completed the W0–W18 period, a total of 296 patients entered the W18–W34 period, with 282 of these patients completing to W34. Overall there were 289 patients (97.6%) in the ITT population. Thirteen withdrawals (4.4%) occurred in the W18–W34 period (five patients in the B-B group and eight patients in the P-B group). Nine patients withdrew due to adverse events (two in the B-B group and seven in the P-B group) and four patients withdrew for non-medical reasons. One patient was lost to follow-up during the W18–W34 period. (Fig. 1).

3.2. Demographic and baseline characteristics

Baseline characteristics were broadly similar between the two groups (n = 145 in the B-B group and n = 151 in the P-B group) (Table 1). Overall, 73% of patients had a metabolic syndrome (modified NCEP III definition [17] – waist circumference criterion was replaced by BMI > 30) and all patients had at least one contraindication (60%) or limitation (56%) to the use of metformin, except for one patient in the B-B group. The
Table 1
Baseline characteristics* in the included population.

<table>
<thead>
<tr>
<th></th>
<th>B-B</th>
<th>P-B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (entered the W18-W34 period)</td>
<td>145</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.2 ± 10.9</td>
<td>64.9 ± 10.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>76/69</td>
<td>66/85</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>6.4 ± 5.5</td>
<td>7.5 ± 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.4 ± 3.7</td>
<td>29.2 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of metabolic syndrome (%)</td>
<td>74</td>
<td>72</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>66.9</td>
<td>69.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sitting systolic blood pressure (mmHg)</td>
<td>138.8 ± 13.4</td>
<td>138.8 ± 13.8</td>
<td>NS</td>
</tr>
<tr>
<td>Sitting diastolic blood pressure (mmHg)</td>
<td>81.2 ± 7.0</td>
<td>80.2 ± 7.3</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease (%)</td>
<td>46 (31.7)</td>
<td>59 (39.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Nephropathy (%)</td>
<td>16 (11.0)</td>
<td>19 (12.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>21 (14.5)</td>
<td>23 (15.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Ophthalmological (%)</td>
<td>15 (10.3)</td>
<td>20 (13.2)</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.37 ± 0.83</td>
<td>8.32 ± 0.87</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>9.95 ± 2.39</td>
<td>9.66 ± 2.34</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>95.4 ± 33.1</td>
<td>85.6 ± 28.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.55 ± 1.03</td>
<td>5.45 ± 1.11</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>3.60 ± 0.80</td>
<td>3.52 ± 0.89</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.25 ± 0.29</td>
<td>1.28 ± 0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.33 ± 1.96</td>
<td>2.12 ± 1.32</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Baseline characteristics are values at the beginning of the double-blind period (W0).

prestudy dose of sulfonylurea was maintained in 97% of patients in both groups. Treatment with acarbose was added at W26 for 17 patients (12%) in the B-B group and 23 patients (15%) in the P-B group (NS).

3.3. Efficacy

The mean HbA1c values between W0 and W34 are shown in Fig. 2. In the B-B group, HbA1c remained stable during the W18–W34 period. In the P-B group, HbA1c decreased from W18 to W34 by an extent of −1.04 ± 1.16% (P < 0.001), which was comparable to that seen in the B-B group between W0 and W18 [11]. Target values of HbA1c less or equal to 7% were achieved under treatment by 36% of patients (103 of 289), with a similar ratio in both groups: 51 of 140 in the B-B group and 52 of 149 in the P-B group.

The mean change in HbA1c from W0 (B-B group) or from W18 (P-B group) to the last value under bitherapy treatment before introduction of acarbose was −0.80 ± 1.11% (n = 140) in the B-B group and −0.95 ± 1.10% (n = 149) in the P-B group (P < 0.001 in both cases).

In the B-B group, FPG remained stable during W18–W34 period. In the P-B group, FPG decreased from W18 to W34 by −1.66 ± 2.74 mmol/l (P < 0.001), which was comparable to that seen in the B-B group during W0–W18 period (Table 2). Similar changes over time in HbA1c and FPG were seen in the subgroups according to HbA1c greater than 8%, age greater than 65 years and impairment of renal function.

Insulin resistance (IR) as assessed by HOMA-IR decreased over the study in both groups (Table 3). HOMA-IR decreased by −1.98 ± 6.63 in the B-B group and by −1.55 ± 9.01 (P = 0.041) in the P-B group over W0–W34. In the B-B group, the beneficial effect of benfluorex on LDL-cholesterol from W0 to W18 was maintained at W34, with no further effect observed during the extension period (Fig. 3). In the P-B group, from W18 to W34 there was a slight reduction in the mean values of...
Table 2
Change in fasting plasma glucose (FPG), total cholesterol, HDL-cholesterol, triglycerides and weight from W18 value under treatment to last value under treatment.

<table>
<thead>
<tr>
<th></th>
<th>B-B group</th>
<th>P-B group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>W0</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td></td>
<td>135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>145</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>136</td>
<td>5.53 ± 1.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>146</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td></td>
<td>136</td>
</tr>
<tr>
<td></td>
<td></td>
<td>146</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>136</td>
<td>2.21 ± 2.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>146</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td>135</td>
</tr>
<tr>
<td></td>
<td></td>
<td>143</td>
</tr>
</tbody>
</table>

* Last value under treatment during extension period.
** Last − W18.

LDL-cholesterol (Fig. 3). In regards to other parameters of the plasma lipids profile: HDL cholesterol decreased significantly but slightly (−3%) from W18 and triglycerides decreased significantly from baseline by 16% and 12% in B-B group and P-B group respectively (Table 2).

3.4. Safety and tolerability

During the extension period, a total of nine patients (3%) were withdrawn due to an adverse event. In three patients, these adverse events were serious but considered as unrelated to the treatment (sudden death, metastases to retroperitoneum and cerebellar infarction). In five patients, minor events considered as related to the treatment by the investigator were reported: GI disorders (n = 2), asthenia (n = 2) or malaise (n = 1). Lastly, one patient experienced a minor event (micturition disorder) which was considered as unrelated to the treatment.

GI disorders were one of the most common adverse events, occurring in 7.3% of patients (n = 11) in the P-B group (W18-W34) and in 18.1% of patients (n = 26) in the B-B group who were exposed longer (W0–W34). These events mostly involved diarrhoea (2.6% of patients in the P-B group and 4.9% of patients in the B-B group). During W18 to W34, GI disorders did not lead to study treatment discontinuation except in two patients (diarrhoea), one from each group. None were reported as serious. During the extension period, five patients (3.5%) in the B-B group and eight patients (5.3%) in the P-B group reported episodes of mild hypoglycaemia.

During the W18 to W34 period, 11 serious adverse events were reported. None were considered by the investigator as being related to the study treatment. There were no significant changes in ECG or laboratory safety parameters, including liver enzymes during the study.

In the B-B group, there was a reduction in mean body weight over W18–W34 of −0.35 ± 2.19 kg. In the P-B group, the change over W18–W34 was −1.34 ± 2.52 kg, which was similar to the change observed in the B-B group over W0–W18.

4. Discussion

This is the first large-scale international study of the efficacy and the safety of benfluorex as add-on therapy in type 2 diabetic patients suboptimally controlled by sulfonylureas, at their maximal tolerated dose, over a 34-week period. It was conducted in accordance with the quality requirements of clinical
trials performance. Thus, there was no attrition of sample size when the patients entered the open-label period. The blindness regarding the treatment received during the comparative period was maintained over the open-label period in order to minimize the risk of bias. Furthermore the compliance with the protocol procedures was respected. The results across the analyses of the two periods are fully consistent. These considerations make the conclusions highly reliable. Moreover, the patient population was representative of patients with type 2 diabetes in terms of disease duration, BMI, presence of diabetic cardiovascular complications and hypertension.

This study demonstrates that benfluorex as add-on therapy behaved throughout the trial as an active glucose-lowering drug that significantly improved glycaemic control, with an HbA1c decrease in the range of 1%. This effect is reproducible and sustained as observed from W18. A decrease of this amplitude in HbA1c has been demonstrated to be of significant clinical benefit. In the UKPDS 35, a 1% reduction in HbA1c corresponded to a 37% reduction in risk of microvascular complications and a 21% reduction in the risk of death related to diabetes [2]. The decrease in the HOMA-IR followed the same trend which was reproducible and sustained. The majority of patients did not have any major plasma lipid abnormalities at baseline, nevertheless a mild improvement was observed, particularly for LDL-cholesterol and plasma triglycerides, which have been shown to be independent risk factors for coronary heart disease in the type 2 diabetes patient population. No deleterious effect was observed on weight and blood pressure.

The reduction of HbA1c with benfluorex in this study is also consistent with the findings of previous studies: $-0.86\%$ (SE, 0.17%; $P < 0.001$) after 29 weeks of monotherapy in 294 patients inadequately controlled by diet alone [10] and, in a study with less power (68 patients), $-0.66\%$ after 12 weeks of combined treatment with sulfonylurea and benfluorex [18]. The magnitude of the effect of benfluorex on blood glucose control is in the range of other recently registered drugs [19]. Trials using metformin or thiazolidinedione in combination with a sulfonylurea showed between group differences of $-1.0\%$ of HbA1c versus placebo in type 2 diabetic patients with a HbA1c around 8% at baseline [20].

This trial was specifically carried out in patients for whom metformin use was inappropriate due to known intolerance or contraindication. As observed during the comparative period [12], there was no overlap between poor GI tolerance to metformin and GI side effects (mainly diarrhoea) related to benfluorex. During the open-label period, GI effects remained moderate. The downward shift in glucose levels over the study combined with the known improvement in insulin sensitivity may explain the small increase in the rate of hypoglycaemia in these patients on sulfonylurea treatment. Previous studies have shown that benfluorex, alone, does not have any effect on insulin secretion. There were no new adverse events identified after a 34-week exposure to benfluorex. Overall tolerance was similar in both groups when the duration of exposure was taken into consideration. Serious adverse events were more frequent in the benfluorex group but without evidence of any causality relationship.

This trial confirms the efficacy of benfluorex in achieving targets for glycaemic control and suggests the possibility of using benfluorex as a first line insulin sensitizer as an add-on therapy, particularly in patients with an unmet medical need such as those for whom metformin is not tolerated or is contraindicated,
or when a glitazone is unsuitable due to oedema. The additional mild LDL-cholesterol lowering effect is of potential interest in the light of other insulin sensitizers known to induce a mild increase in LDL-cholesterol [21]. The neutral effect on weight is an interesting property for the choice of drugs in the management of diabetes. To properly confirm and evaluate the clinical relevance of benfluorex as new authentic antidiabetic agent, additional trials will be required to assess by direct comparison the efficacy and safety profile of this drug versus other insulin sensitizers such as pioglitazone in type 2 diabetic patients.

Acknowledgments

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References