A SECOND LOOK

benfluorex antidiabetic?

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TABLETS

• 150 mg of benfluorex hydrochloride per tablet

Antidiabetic drug?

Licensed indication in diabetes:

"Adjunct to dietary measures in asymptomatic overweight diabetic patients."

Benfluorex (Mediator°, Servier) was marketed in France in 1976 (**a**). Chemically speaking, benfluorex is related to other appetite suppressants like fenfluramine (Servier) (**b**)(1). One of its approved indications, as *"an adjunct to dieting in asymptomatic overweight diabetic patients",* has regularly been promoted over the years (**c**)(2). To reply to readers' questions on the possible value of benfluorex in diabetes, and to answer claims by medical representatives that benfluorex is as effective as metformin, we examined the clinical assessment file (**d**).

The main aims of treating diabetes are to prevent clinical complications and reduce mortality. On the basis of these criteria, the value of the various oral antidiabetics currently on the market is poorly established (3,4). Is benfluorex any different in these respects?

Slight laboratory effects in the short term

Most of the comparative trials mentioned in the Servier information brochure (5) are published.

Placebo-controlled trials. We found 6 trials comparing benfluorex with a placebo in double-blind manner in patients with noninsulin-dependent diabetes (5-10). These trials all had similar designs: after a preinclusion (placebo) phase of 1 month in most cases, aimed at checking the stability of the diabetes, patients received a three-month course of a placebo or benfluorex (450 mg/day by mouth) in double-blind manner. The only end points for efficacy were laboratory criteria (see table page 109). One trial involved patients on a low-calorie diet and no other antidiabetic drugs (6); 3 trials involved overweight patients also receiving insulin (5,7-9); 2 trials involved patients also receiving a glucose-lowering sulphonamide (5,10).

According to the American Diabetes Association, the aim of treatment is to bring fasting blood glucose levels down to 6.7 mmol/l (approximately 1.2 g/l) and glycated haemoglobin down to 7% (11). In only two of the six trials did benfluorex show greater efficacy than the placebo in reducing fasting blood glucose, and average figures fell below 6.7 mmol/l in only one trial (7). In the five trials in which the comparison was possible, the effect of benfluorex on glycated haemoglobin was statistically superior to that of the placebo, but only in one trial did the average level of glycated haemoglobin fall below 7% (7). With the exception of one trial (7), benfluorex failed to influence fasting insulin levels relative to the placebo. Benfluorex yielded a statistically significant reduction in daily insulin requirements in only one of the three trials involving patients treated with insulin (9). None of these placebo-controlled trials showed an effect of benfluorex on morbidity or mortality, but these end points were not provided for by the protocol (**e**).

Trial versus metformin. A trial comparing benfluorex with metformin in 121 patients was published, but the results were uninterpretable because of major sources of bias (12). At baseline the patients in the metformin group had statistically lower postprandial blood glucose levels and a statistically smaller area under the curve for glucose tolerance test than the patients in the benfluorex group. Yet the main end point was changes in blood glucose in an oral glucose tolerance test. Furthermore, the trial was not blinded.

In brief. Available trials show that benfluorex has effects, at least in the short term (3 months), on certain indices of blood glucose balance, particularly glycated haemo-

__a-__ In Europe benfluorex is also marketed in Spain, Greece, Italy, Luxemburg, Portugal and Switzerland (ref 5). It is not available in Anglo-American or North European countries.

__b-__ Benfluorex has an unusual classification in France. It is not officially classified among the appetite suppressants, meaning that it is not subject to restricted prescribing conditions. However, a circular from the Health Directorate on October 25, 1995 (Journal Officiel October 31, 1995, page 15937) includes benfluorex in the list of appetite suppressants and states that it must not be included in extemporaneous preparations. Furthermore, benfluorex is on the World Health Organisation list of appetite suppressants.

1- "Benfluorex°" Micromedex 31/03/1996; **87**: 9 pages.
2- "Mediator° activité ou non ?" *Rev Prescr* 1986; **6** (58): 42.
3- "What use are antidiabetic drugs" *Prescr Intern* 1996; **5** (26): 186-190.
4- "Acarbose" *Prescr Intern* 1996; **5** (26): 164-166.
5- Servier International Research Institute "S780 - benfluorex - brochure pour investigateur" Version n° 1, May 30, 1996 (unpublished): 80 pages.
6- Velussi M et al. "Therapeutic effect of benfluorex in type II diabetic patients on diet regimen alone" *J Diab Complications* 1996; **10** (5): 261-266.
7- Bianchi R et al. "Effect of benfluorex in addition to insulin therapy in obese type II diabetic patients with secondary failure to conventional oral treatment" *Diab Nutr Metab* 1996; **9**: 81-88.
8- Pontiroli AE et al. "Benfluorex in obese non insulin dependent diabetes mellitus patients poorly controlled by insulin: a double blind study versus placebo" *J Clin Endocrinol Metab* 1996; **81**: 3727-3732.
9- Leutenegger M et al. "Intérêt de l'adjonction du benfluorex à l'insuline chez des patients diabétiques insulino-traités ayant un surpoids" *Diab Metab* 1996; **22**: P43: 2 pages.
10- Stucci N et al. "Therapeutic benefit of benfluorex in type II diabetic patients treated with sulfonylrureas" *J Diab Complications* 1996; **10**: 267-273.
11- In: Bailey CJ et al. "Metformin" *N Engl J Med* 1996; **334**: 574-579.

Double-blind comparative clinical trials of benfluorex (B) versus placebo (P)

Réf.	Number of patients	Other treatment	Results after 3 months			
			Fasting blood glucose (mmol/l)	Glycated haemoglobin (%)	Fasting blood insulin	Other results
5.6	32	no	B -1.3 (±1.0) P -0.5 (±1.3) — NS	B -0.6 (±1,0) P +0.3 (±1.1) — p=0.024	B -4.9 (±4.3) P -2.7 (± 5.0) — NS	
5.7	20	insulin	B -3.0 (±1.9) P -1.6 (±3.3) — NS	B -0.6 (±0.6) P +0.3 (±1.0) — p<0.001	B -0.3 (±5.8) P +10.1 (± 10.1) — p=0.02	no difference in insulin requirements
5.8	30	insulin	B -0.5 (±2.5) P +1.7 (±3.0) — NS	B -2.2 (±1.6) P -0.5 (± 0.9) — p=0.006	B -10.2 (±12.7) P -5.0 (±6.8) — NS	no difference in insulin requirements
9	76	insulin	B -1.45 (±5.28) P +0.15 (±3.88) — NS	heterogeneous at inclusion	not stated	lower insulin requirements in the benfluorex group
5 (*)	25	sulphonylurea	B -1.6 (±1.9) P +0.2 (±2.3) — p=0.046	B -0.5 (±1.0) P +1.2 (±2.1) — p=0.023	B -4.8 (±4.7) P -0.7 (±9.6) — NS	
5.10	68	sulphonylurea	B -1.4 (±?) P -0.3 (±?) — p=0.009	B -0.66 (±1.14) P -0.14 (±1.04) — p=0.007	B -0.8 (±4.0) P -1.3 (±5.6) — NS	

* Study by Louvet

NOTHING NEW

A few comparative trials lasting only 3 months showed that benfluorex had, at best, limited effects on fasting blood glucose and glycated haemoglobin levels in patients with noninsulin-dependent diabetes, but no apparent effect on morbidity or mortality. The adverse effects of benfluorex are very poorly documented. After 20 years on the market there is still no reason to prescribe benfluorex to diabetic patients.

globin. However, these effects are only mild and, in the absence of comparative data, it is not known how they compare to the available oral antidiabetics.

Adverse effects? Given the lack of independent data it is impossible to know the precise pattern of adverse effects on benfluorex. According to Servier "*the most common adverse effects of benfluorex are gastrointestinal (nausea, vomiting, gastralgia and diarrhoea) but also include fatigue, drowsiness and dizziness. These only occur at doses of more than 3 tablets a day and vary from patient to patient*" (5). These claims do not match data from four clinical trials in which benfluorex was used at a dose of 3 tablets a day (450 mg) and in which the same adverse effects were observed (10,13-15). In these small trials, involving the recommended dose of 450 mg/day, drowsiness occured in 7 to 10% of patients on benfluorex (1), and diarrhoea was observed in 25% of patients in a non comparative trial (13). In another trial 5 of the 34 patients stopped taking benfluorex because of adverse effects, compared to 2 of the 34 patients in the placebo group (10).

Conclusion. Even though it has been on the market for 20 years, it is unclear whether benfluorex benefits diabetic patients. No long-term trials with morbidity or mortality end points are available.

A few placebo-controlled trials lasting only 3 months and involving noninsulin-dependent diabetics showed that benfluorex alone or in combination with insulin or a glucose-lowering sulphonamide reduced glycated haemoglobin levels. A reduction in fasting blood glucose was observed in only two of the six relevant trials. These effects were only mild, rarely returning these parameters to within "normal" limits. The only trial comparing benfluorex with metformin is uninterpretable.

Benfluorex has adverse effects at the recommended dose of 450 mg/day, including drowsiness and diarrhoea, but neither the frequency nor the type of adverse effects is correctly documented.

There is currently no basis for treating noninsulin-dependent diabetics with benfluorex. The French health authorities should reconsider their decision to license and reimburse this product.

c- *The other approved indication is as an "adjunct to dietary measures in hypertriglyceridaemia. It is essential to continue the diet". We shall examine this use in a coming issue. The two approved indications for benfluorex date back to 1974. As required by European directive 75/319/EEC on drugs registered before December 1 1976, the approved indications for benfluorex were "validated" in 1987.*

d- *Our literature search was based on continuous prospective scrutiny of contents listings of the main international journals and Current Contents, and on routine consultation of reference texts in clinical pharmacology (Martindale The Extra Pharmacopoeia, etc.). We also consulted CD-ROM versions of Medline (1996-March 1997), Embase Drugs and Pharmacology (1991-December 1996) and Cochrane (1996 outlet 3), and Minitel versions of the Pascal and EMC databases up to March 26 1997. Furthermore, Servier provided us with various published and unpublished documents. Two members of ISDB (International Society of Drug Bulletins) — Boletin Terapeutico Andaluz and Informazion sui Farmaci — also gave us relevant documents.*

e- *Some of these trials contained potential biases, making their interpretation hazardous. For example, in one trial the daily insulin dose and glycated haemoglobin levels were statistically higher in the benfluorex group at baseline (ref 9).*

12- Brun JM "Efficacité antidiabétique du benfluorex. Données cliniques" *Presse Med* 1992; **21** (28): 1344-1352.

13- Sommariva D et al. "Effects of benfluorex on serum lipoproteins in diabetic and non-diabetic hypertriglyceridemic patients" *Curr Ther Res* 1986; **39** (3): 281-287.

14- Giustina A et al. "Effects of benfluorex on glucose tolerance, metabolic control, beta-cell secretion, and peripheral sensitivity to insulin in obese type II diabetic patients on a body weight-maintaining diet" *Curr Ther Res* 1989; **45** (1): 33-42.

15- Cavallo-Perin P et al. "Benfluorex and blood glucose control in non insulin-dependent diabetic patients" *J Endocrinol Invest* 1991; **14**: 109-113.