necessitating blood transfusions occurred in 37% of patients (9).

The most frequent non haematological side effects were nausea (68.1% of patients, severe in 6.1% of patients), vomiting (44.3%, severe in 4.5%), hair loss (56.9%), fatigue (44.5%, severe in 6%), diarrhoea (26.1%, severe in 3.4%), and stomatitis (20.2%, severe in 2%) (9).

Paclitaxel solution contains a solvent, Cremophor EL°, that is incompatible with the use of PVC infusion devices and warrants prior steroid administration because of its high sensitising potential (3). This is not the case with topotecan.

In all, 0.9% of patients died from proven or probable toxicity on topotecan, an incidence similar to that reported with paclitaxel (9,11). And 5% of patients discontinued treatment with topotecan because of severe adverse events (9).

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Literature

Our literature search was based on systematic scrutiny of contents listings of the main international journals and Current Contents at the Prescrire library, and on reference texts in clinical pharmacology (Martindale The Extra Pharmacopoeia 31st ed., etc.). We also consulted CD-ROM versions of Medline (1981-March 1998), Embase Drugs and Pharmacology (1991-January 1998), Cochrane (1998, issue 1), Medidoc (1991-1994) and Reactions (1983-June 1997), and the Minitel version of the Pascal database up to September 16 1997. SmithKline Beecham provided us with published and unpublished documents, including the clinical expert report. We also used the European public assessment report (EPAR) available from the European medicines agency.

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benfluorex: what use?

A SECOND LOOK

POOR ASSESSMENT FILE

Abstract

● **The clinical file on the value of benfluorex for hypertriglyceridaemia is highly inadequate. No clinical trials have been done with morbidity or mortality as end points. Available placebo-controlled trials are small, methodologically weak in most cases, and their results regarding triglyceride levels are contradictory. None of the three trials comparing benfluorex with a fibrate is interpretable, because of methodological problems.**

NOTHING NEW

There is no reason to prescribe benfluorex for hypertriglyceridaemia and diabetes.

Tablets

- **150 mg per tablet**

Biopharma

■ licensed indication in lipid disorders

"Adjunct to appropriate dietary measures in hypertriglyceridaemia. The dietary measures must be continued. NB. There is no proven efficacy in primary or secondary prevention of complications of atherosclerosis."

lipid-lowering drug?

Benfluorex (Biopharma, Servier group), has been marketed in France since 1976, as tablets containing 150 mg (**a**). Chemically, benfluorex is similar to other appetite suppressants (**b**)(1). In France benfluorex has two approved indications. We recently took another look at the file on the indication worded "*adjunct to dietary measures in asymptomatic overweight diabetic patients*", and concluded that its slight effects on surrogate end points in no way warranted prescription to diabetic patients (2).

The second approved indication for benfluorex is in the treatment of hypertriglyceridaemia (see inset opposite). The most important question is the following: does benfluorex have proven ▶▶

a-In Europe, benfluorex is also marketed in Spain, Greece, Italy, Luxemburg, Portugal and Switzerland (1). Benfluorex is not marketed in English-speaking countries or Northern Europe.

b- In France benfluorex has a peculiar classification. It is not officially classified among the appetite suppressants, meaning that its prescription is not restricted. However, the authorities decided on October 25, 1995 (Journal Officiel, October 31, 1995: 15 937) to place benfluorex on a list of substances that must not be used in freshly prepared mixtures, a list composed only of appetite suppressants. Furthermore, the suffix -orex is attributed to international nonproprietary names of appetite suppressants by the World Health Organisation (WHO) (1), and benfluorex is on the list of doping substances, together with amphetamines and other stimulants (Dictionnaire Vidal, French data sheet compendium, 1997 edition, page 6).

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► beneficial effects on the only clinically relevant end point, i.e. cardiovascular morbidity and mortality, in patients with or without a history of cardiovascular disease?

A consensus conference in the United States was devoted to hypertriglyceridaemia (3). According to the conclusions, only marked hypertriglyceridaemia warrants treatment, with the aim not only of reducing the hypertriglyceridaemia, but more importantly of reducing LDL-cholesterol levels and increasing HDL-cholesterol levels. This is because the link between cholesterol fractions and cardiovascular morbidity is better established than for triglycerides. First-line management of hypertriglyceridaemia is based on lifestyle measures (giving up smoking and alcohol, taking exercise, etc.) and dietary advice (increasing oily fish consumption). According to the American consensus conference, drugs are useful only when these measures are inadequate (3).

Lipid-lowering drugs known to induce a marked reduction in hypertriglyceridaemia are the fibrates, nicotinic acid and fish oils (**c**)(3,4). Gemfibrozil, a fibrate, is the only drug having shown a preventive action, based on clinical criteria, in a trial involving patients with hypertriglyceridaemia (**d**)(3,5).

We examined the clinical file on benfluorex for answers to the following questions: Does benfluorex have a proven effect on cardiovascular morbidity? and Has it at least been compared with other triglyceride-lowering drugs on the basis of surrogate end points, i.e. triglyceride and triglyceride-rich lipoprotein levels (VLDL and chylomicrons)?

Poor-quality, generally uninterpretable clinical trials

The clinical file is of poor methodological quality.

Placebo-controlled trials: no convincing evidence. Benfluorex has been compared with a placebo in about ten clinical trials, most of which have been published, but often vaguely described (6-11). The trials involved between 7 and 50 patients with various conditions (glucose and lipid overload, hyperlipidaemia, obesity with or without carbohydrate disorders) treated in parallel groups or cross-over studies, for 7 to 50 days. The results are difficult to interpret, as most of the studies have major methodological biases. At the end of treatment, five trials showed a statistically significant difference in triglyceride levels between benfluorex and the placebo, while five showed no such difference.

Trials versus other lipid-lowering drugs: uninterpretable results. Three trials comparing benfluorex with other lipid-lowering drugs have been published in detail (12-14). Two of these trials compared benfluorex with clofibrate in patients with hypertriglyceridaemia (at least 1.5 g/l) and/or hypercholesterolaemia (cholesterol level above 2.5 g/l) (**e**). The first trial was single-blind and involved 40 patients (**f**)(12). While total triglyceride levels fell more strongly on benfluorex (52.7% versus 38.5% on average; $p<0.001$), the result was meaningless for at least two reasons: firstly, 15 of the 20 patients received only 1.5 g of clofibrate daily, an inadequate dose (**g**); secondly, patient recruitment was highly heterogeneous, the clofibrate group comprising more patients with type IIb hyperlipidaemia and fewer patients with type IV hyperlipidaemia than the benfluorex group (**h**).

The second trial, involving 28 patients, is also uninterpretable: blinding was not mentioned and this leads us to believe that it was not done; the daily dose of clofibrate was probably inadequate for a number of patients; and the distribution of the various types of dyslipidemia was not clearly stated (13).

The third trial involved 28 patients with type 2 diabetes treated for 1 month with benfluorex (450 mg/day), fenofibrate (300 mg/day), or bezafibrate (600 mg/day) (14). The paper mentions no statistical analysis of intergroup differences and, in any event, it seems impossible to show significant differences between such small groups.

There are no clinical trials of benfluorex using clinical end points in patients with hypertriglyceridaemia.

In a recent article we underlined the lack of clear and independent data on the adverse effects of benfluorex (1). We were unable to find any new information to contradict this judgement.

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c- hMG-CoA reductase inhibitors (statins) have mild effects on triglyceride levels.

d- In the "Helsinki heart study", although gemfibrozil reduced triglyceride levels by 35% its protective effect on the cardiovascular risk was attributed to its actions on cholesterol fractions (ref 5).

e- In these trials the patients were treated in parallel groups for 2 months with either benfluorex (450 mg/day in 3 doses) or clofibrate (1 500 mg/day in 3 intakes).

f- The report does not state whether the investigators or the patients were blinded.

g- The patients weighed at least 65 kg, in which case the recommended dose of clofibrate is 2 g/day.

h- The authors themselves stated that the probability of a response to pharmacological treatment was higher in the case of type IV dyslipidaemia than in type IIB dyslipidaemia.

Literature

Our literature search was based on systematic scrutiny of contents listings of the main international journals and Current Contents at the Prescrire library, and on reference texts in clinical pharmacology (Martindale The Extra Pharmacopoeia, etc.). We also consulted CD-ROM versions of Medline (1966-January 1998), Embase Drugs and Pharmacology (1991-December 1997), Reactions (1983, December 1997), and Cochrane (1998, issue 1), and the Minitel version of the Pascal and EMC databases, up to October 18, 1997. Servier sent us published and unpublished documents. Two ISDB members (International Society of Drug Bulletins) - Boletin Terapeutico Andaluz and Informazion sui Farmaci - sent us their documentation.

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