struction. Etamiphylline does not liberate theophylline in the body. Etamiphylline camsilate is used in veterinary medicine.

The hydrochloride salt has also been used.

Preparations

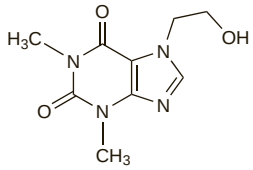
Proprietary Preparations (details are given in Part 3)
Spain: Solufilina.

Etofylline *(BAN, rINN)*

Aethophyllinum; Etofilina; Etofilinas; Etofillin; Etofylin; Etofylliini; Etofyllin; Étofylline; Etofyllinum; Hydroxyaethyltheophyllinum; Hydroxyéthylthéophylline; Oxyetophylline. 7-(2-Hydroxyethyl)-1,3-dimethylxanthine; 3,7-Dihydro-7-(2-hydroxyethyl)-1,3-dimethyl-1*H*-purine-2,6-dione; 7-(2-Hydroxyethyl)theophylline.

Этофиллин

$C_9H_{12}N_4O_3$ = 224.2.
CAS — 519-37-9.
ATC — C04AD04.
ATC Vet — QC04AD04.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Etofylline). A white or almost white, crystalline powder. Soluble in water; slightly soluble in alcohol. Protect from light.

Profile

Etofylline is a derivative of theophylline (p.1140) that is an ingredient of preparations promoted for respiratory and cardiovascular disorders. It is not converted to theophylline in the body.

Etofylline nicotinate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Oxyphyllin.

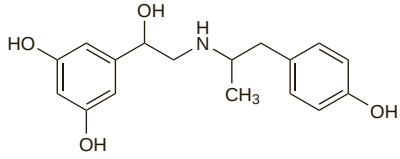
Multi-ingredient: ***Austria:*** Instenon; ***Cz.:*** Ersilan; Oxantil; ***Hong Kong:*** Instenon; ***India:*** Albutamol; Bronchilet†; Dericip; Deriphyllin; Etyofil†; Terphylin; ***Rus.:*** Instenon (Инстенон); ***S.Afr.:*** Actophlem; Alcophyllex; Dilinct; Solphyllex; Solphyllin; Theophen; Theophen Comp; ***Thai.:*** Instenon†.

Fenoterol *(BAN, USAN, rINN)* ⊗

Fénotérol; Fenoteroli; Fenoterolum. 1-(3,5-Dihydroxyphenyl)-2-(4-hydroxy-α-methylphenethylamino)ethanol.

Фенотерол

$C_{17}H_{21}NO_4$ = 303.4.
CAS — 13392-18-2.
ATC — G02CA03; R03AC04; R03CC04.
ATC Vet — QG02CA03; QR03AC04; QR03CC04.



Fenoterol Hydrobromide *(BANM, rINNM)* ⊗

Fénotérol, bromhydrate de; Fenoterol-hidrobromid; Fenoterol-hydrobromid; Fenoterol-hydrobromid; Fenoteroli hydrobromidum; Fenoterolihydrobromidi; Fenoterolio hidrobromidas; Fenoterolu bromowodorek; Hidrobromuro de fenoterol; TH-1165a. 1-(3,5-Dihydroxyphenyl)-2-(4-hydroxy-α-methylphenethylamino)ethanol hydrobromide.

Фенотерола Гидробромид

$C_{17}H_{21}NO_4$,HBr = 384.3.
CAS — 1944-12-3.
ATC — G02CA03; R03AC04; R03CC04.
ATC Vet — QG02CA03; QR03AC04; QR03CC04.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Fenoterol Hydrobromide). A white or almost white, crystalline powder. Soluble in water and in alcohol. A 4% solution in water has a pH of 4.2 to 5.2. Protect from light.

Adverse Effects and Precautions

As for Salbutamol, p.1131.

Increased mortality. Since the introduction of metered-dose aerosols of beta agonists there have been two reported epidemics of increased morbidity and mortality in asthmatic patients associated with their use. The first occurred in the 1960s and was linked with the use of high-dose isoprenaline inhalers.[1] The use of isoprenaline was subsequently largely stopped in favour of more selective beta$_2$ agonists.

The second epidemic occurred in New Zealand in the late 1970s and 1980s and was associated with the use of fenoterol.[1-5] When use of fenoterol fell in New Zealand, so too did the asthma mortality rate.[5] Heavy or regular use of fenoterol was implicated.[6,7] Fenoterol was also implicated in increased asthma morbidity and mortality in a study in Canada,[7] as was salbutamol, and results from Japan also suggested a relation between asthma deaths and excessive use of beta agonists, particularly fenoterol.[8] However, an analysis of the New Zealand deaths could not identify such a risk with beta agonists other than fenoterol.[5]

There is still debate about this second epidemic. The individual case control studies, including the one from Canada,[7] showed an increased morbidity and mortality in patients taking fenoterol, but a meta-analysis of the accumulated data to 1992 suggested that the increase in mortality in the patients taking beta$_2$ agonists was slight and only significant when they were given by nebulisation.[9] Also a working party of the UK CSM considered[10] that a causal link between asthma mortality and beta-agonist use could neither be confirmed nor refuted.

Not surprisingly there are different views on the cause of the increased asthma mortality. The cardiotoxicity of the beta agonist might have to be considered, although evidence for such an effect is felt by some to be slight.[11] The severity of the asthma might have been a factor in two different ways. One hypothesis is that patients used more fenoterol because they had severe asthma and were already at increased risk of dying.[12] Another proposes that heavy beta-agonist use led to an increase in asthma severity[13] which could be explained by a down regulation of beta receptors.[14]

This may appear to be only of historical interest since mortality rates have fallen and current recommendations for the use of short-acting beta$_2$ agonists, which are generally more selective than fenoterol, are for them to be taken as required rather than on a regular basis; indeed increasing use of such drugs is seen as an indication to amend the treatment schedule. Moreover, the dose of fenoterol has been reduced in recent years. However, controversy over regular use of short-acting beta$_2$ agonists continues to be fed by conflicting studies of their benefit. More recently 2 further observational studies have reported an association between use of short-acting beta$_2$ agonists and adverse effects on mortality.[15,16] A cohort study,[15] designed to evaluate the effect of respiratory medications on asthma death, found an association between the excessive use of short-acting beta$_2$ agonists and an increased risk of asthma death; no additional risk was found with fenoterol beyond the risk associated with beta$_2$ agonists as a class. It was unknown whether excessive use was a symptom or a cause of worsening asthma. A case-control study[16] similarly found a modestly increased risk of mortality associated with use of short-acting beta$_2$ agonists in the previous 1 to 5 years. However, the study had insufficient power to come to any conclusions regarding the effects of fenoterol, which was rarely prescribed alone, and concluded that evidence for a direct adverse effect of beta$_2$ agonists was inconclusive; other explanations might include lack of more appropriate asthma care, more severe disease or increasing severity of disease, or a tendency for patients whose disease was not responding to receive a wider range of treatments.

For discussion of similar concerns about the use of *long-acting* beta$_2$ agonists in asthma, see Salmeterol, p.1135.

1. Pearce N, *et al.* Beta agonists and asthma mortality: déjà vu. *Clin Exp Allergy* 1991; **21:** 401–10.
2. Crane J, *et al.* Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. *Lancet* 1989; **i:** 917–22.
3. Pearce N, *et al.* Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977–81. *Thorax* 1990; **45:** 170–5.
4. Grainger J, *et al.* Prescribed fenoterol and death from asthma in New Zealand, 1981–7: a further case-control study. *Thorax* 1991; **46:** 105–111.
5. Pearce N, *et al.* End of the New Zealand asthma mortality epidemic. *Lancet* 1995; **345:** 41–4.
6. Sears MR, *et al.* Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990; **336:** 1391–6.
7. Spitzer WO, *et al.* The use of β-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; **326:** 501–6.
8. Beasley R, *et al.* β-agonist therapy and asthma mortality in Japan. *Lancet* 1998; **351:** 1406–7.
9. Mullen M, *et al.* The association between β-agonist use and death from asthma: a meta-analytic integration of case control studies. *JAMA* 1993; **270:** 1842–5.
10. Committee on Safety of Medicines. Beta-agonist use in asthma: report from the CSM Working Party. *Current Problems 33* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 15/01/08)
11. Sears MR, Taylor DR. The β -agonist controversy: observations, explanations and relationship to asthma epidemiology. *Drug Safety* 1994; **11:** 259–83.
12. Fuller RW. Use of β agonists in asthma: much ado about nothing? *BMJ* 1994; **309:** 795–6.
13. Sears MR. Asthma deaths in New Zealand. *Lancet* 1995; **345:** 655–6.
14. Tattersfield AE. Use of β agonists in asthma: much ado about nothing? *BMJ* 1994; **309:** 794–5.
15. Lanes SF, *et al.* Respiratory medications and risk of asthma death. *Thorax* 2002; **57:** 683–6.
16. Anderson HR, *et al.* Bronchodilator treatment and deaths from asthma: case-control study. Abridged version: *BMJ* 2005; **330:** 117. Full version: http://www.bmj.com/cgi/reprint/330/7483/117 (accessed 15/01/08)

Pulmonary oedema. Pulmonary oedema has occurred in women given beta agonists, including fenoterol,[1] for premature labour. The risk factors, the most important of which is fluid overload, are discussed under Precautions for Salbutamol, on p.1132.

1. Hawker F. Pulmonary oedema associated with β -sympathomimetic treatment of premature labour. *Anaesth Intensive Care* 1984; **12:** 143–51.

Interactions

As for Salbutamol, p.1132.

Pharmacokinetics

Fenoterol is incompletely absorbed from the gastrointestinal tract and is also subject to extensive first-pass metabolism by sulfate conjugation. It is excreted in the urine and bile almost entirely as the inactive sulfate conjugate. Fenoterol is distributed into breast milk.

◊ References.

1. Warnke K, *et al.* The pharmacokinetics of the beta 2-adrenoceptor agonist fenoterol in healthy women. *Eur J Clin Pharmacol* 1992; **43:** 663–5.
2. Hochhaus G, Möllmann H. Pharmacokinetic/pharmacodynamic characteristics of the beta-2-agonists terbutaline, salbutamol and fenoterol. *Int J Clin Pharmacol Ther Toxicol* 1992; **30:** 342–62.
3. Hildebrandt R, *et al.* Pharmacokinetics of fenoterol in pregnant and nonpregnant women. *Eur J Clin Pharmacol* 1993; **45:** 275–7.

Uses and Administration

Fenoterol is a direct-acting sympathomimetic with beta-adrenoceptor stimulant activity largely selective for beta$_2$ receptors (a beta$_2$ agonist). It has actions and uses similar to those of salbutamol (p.1133) and is used as a bronchodilator in the management of reversible airways obstruction, as occurs in asthma (p.1108) and in some patients with chronic obstructive pulmonary disease (p.1112). On inhalation, fenoterol acts rapidly (5 minutes) and has a duration of action of about 6 to 8 hours.

In the management of **reversible airways obstruction,** fenoterol hydrobromide may be given from a *metered-dose aerosol* in a dose of 1 or 2 inhalations of 100 micrograms up to 3 or 4 times daily, to a maximum of 800 micrograms daily. Current asthma guidelines recommend that inhaled short-acting beta$_2$ agonists such as fenoterol be used on an 'as-required', not regular, basis. In those patients requiring more than occasional use of fenoterol, anti-inflammatory therapy is also needed. An increased requirement for, or decreased duration of effect of, fenoterol indicates deterioration of asthma control and the need for increased anti-inflammatory therapy.

Fenoterol hydrobromide may be given as a *nebulised solution*; the usual dose for inhalation by this route is 0.5 to 1 mg. In more refractory cases up to 2.5 mg may be given. Treatment may be repeated every 6 hours as required.

Fenoterol hydrobromide may also be given *orally* for the relief of bronchospasm at a dose of 2.5 to 5 mg three times daily.

For doses in children, see Administration in Children, below.

Fenoterol hydrobromide has also been used similarly to salbutamol, in the management of **premature labour** (see p.2003). A suggested dose, by intravenous infusion, has been 1 to 3 micrograms/minute, up to a maximum of 5 micrograms/minute, followed by oral doses of 5 mg every 3 to 6 hours.

Administration in children. In some countries fenoterol has been given via a metered-dose inhaler to children over 6 years of