Fenoterol: Pharmacology and Clinical Use

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INTRODUCTION

Fenoterol is a selective β₂-adrenoceptor agonist that has been in clinical use for decades. It belongs to a family of compounds that have comparable pharmacological properties, such as terbutaline or salbutamol. The well-characterized, therapeutically useful pharmacological effects are bronchodilation and relaxation of the pregnant uterus. Therefore, fenoterol’s most important indications are bronchodilation (by inhalation, i.v., or p.o.) and tocolysis during premature labor (by i.v. infusion or p.o.). Fenoterol may also be used in states of acute hyperkalemia in patients with chronic renal failure, an indication that has not been thoroughly investigated. The side effects of fenoterol are typical for β₂-adrenoceptor agonists, e.g., hypokalemia, cardiac acceleration, hypotension, and tremor.

This review will summarize the current basic and clinical knowledge about fenoterol with a focus on the features that are most important therapeutically. It is surprising that human pharmacokinetics has received little attention. At the time of the development and initial marketing of fenoterol, it was technically difficult to detect small concentrations of the drug, particularly if it was administered by inhalation. Although this technical problem has been overcome, there are still no sensitive and enantioselective methods for detecting small amounts of fenoterol in the plasma to study its pharmacokinetics.

Concerns over the safety of short-acting β₂-adrenoceptor agonists, particularly fenoterol, have surfaced mainly in relation to their inhalation by asthmatics. This debate appears to be resolved after confusing and lengthy investigations and commentaries. The present review will attempt to report the current views on the use of short-acting β₂-adrenoceptor agonists in asthma, with a focus on fenoterol.

Pharmacology

Fenoterol, a 4-hydroxyphenyl derivative of orciprenaline (Fig. 1), is a resorcinol derivative with β-adrenoceptor agonist activity. The basic structural nucleus of β-adreno-
ceptor agonists comprises a benzene ring substituted with an ethyl amino group. Fenoterol belongs to the group of $\beta_2$-selective adrenoceptor agonists, which were synthesized to avoid the cardiac effects of $\beta_1$ adrenoceptor agonists. Its large N-substituent is a p-hydroxyphenylisopropyl moiety. Such bulky substitution of the amino group leads to an increase in the $\beta_2$-adrenoceptor potency and decreased activity to $\alpha$-adrenoceptors. In addition, this constituent reduces monoaminooxidase metabolism.

The hydroxyl groups in positions 3 and 5 are typical for $\beta_2$-adrenoceptor agonists with resorcinol-like structures; they reduce metabolism of the drug by catechol-O-methyltransferase (COMT). The hydroxyl groups serve for coupling with sulfuric acid. These modifications of the structure confer resistance to MAO and COMT and thereby enhance the availability of these drugs and increase their duration of action. The fenoterol molecule has two asymmetric C-atoms (Fig. 1). The marketed form is a racemate and consists of SS’(+)fenoterol and RR’(−)fenoterol. In analogy to other adrenergic agonists, the latter enantiomer represents the pharmacologically active component (65).

In vitro comparison of various $\beta_2$-adrenoceptor agonists reveals that isoproterenol has equal affinity for $\beta_1$- and $\beta_2$-adrenoceptors, orciprenaline is slightly more selective for $\beta_1$-adrenoceptors, and fenoterol is 59 times and salbutamol 107 times more selective for $\beta_2$-adrenoceptors (100,101). These in vitro tests used guinea pig isolated atria for $\beta_1$-adrenoceptors and tracheal preparations for $\beta_2$-adrenoceptors, respectively. Relative selectivity varies considerably among species.

**FIG. 1.** Chemical structures of orciprenaline and fenoterol (asterisk denotes the optically active C-atoms of fenoterol).
The relative potency of fenoterol is similar to that of other β₂-adrenoceptor agonists such as albuterol (salbutamol) and terbutaline. Fenoterol has a 2.7 times higher potency in vitro on guinea pig tracheal β₂-adrenoceptors than does salbutamol (102).

The β-adrenoceptors have been cloned. The β₂-adrenoceptor gene is located on chromosome 5. It encodes a protein of 413 amino acids, only 54% of which are shared with the β₁-adrenoceptor (4). The β₂-adrenoceptor belongs to the superfamily of receptors with seven lipophilic transmembrane domains. β₂-Adrenoceptor agonists fit in a cleft between the transmembrane segments of the receptor and interact with transmembrane helices II and IV. The intracellular segment interacts with a G protein that links receptor activation to adenylate cyclase. The activation of adenylate cyclase induces the conversion of ATP to the second messenger, cyclic AMP, which activates protein kinase A (PKA) leading to the biological response, e.g., bronchodilatation. It has recently been proposed that the classical cAMP-PKA phosphorylation cascade is not the only system that mediates the response of smooth muscle to β-adrenoceptor agonists (133). According to the current evidence there may be two cAMP-dependent pathways, served by distinct protein kinases, which may act in concert with at least one cAMP-independent pathway.

β-Adrenoceptors can be desensitized by several mechanisms (4). The receptor is phosphorylated very shortly after exposure to an agonist. The phosphorylation interferes with its coupling to stimulatory G proteins (56). Minutes after exposure, the receptors are internalized; this process can be completed within 30 min (120). Also, longer exposure (several hours) of hamster vas deferens cells to agonists leads to a downregulation of receptors and decreased production of their mRNA (50). It has been reported recently that downregulation of β₂-adrenoceptors by fenoterol in myometrial tissue is not necessarily associated with a reduction in its mRNA levels (31). The authors of this report discuss different types of regulation of β-adrenoceptors by tissue or organ-specific factors (e.g., regulatory proteins such as receptor kinases, phosducins, or mRNA regulatory proteins), which may determine the pattern of receptor desensitization.

Polymorphism of the human β₂-adrenoceptor gene has been reported. In a group of 51 patients with asthma and 56 normal subjects, nine different point mutations in the nucleic acid sequence were detected. Four of these mutations resulted in a change in the amino acid sequence. The most frequent changes were arginine 16 to glycine and glutamine 27 to glutamic acid (108). The incidence of β₂-receptor polymorphism was no greater in patients with asthma than in control subjects, although within the asthma group the polymorphism Arg16 → Gly was associated with more severe steroid-dependent asthma. Other investigations suggest that this polymorphism may lead to an enhanced downregulation of the receptors and may be abundant in patients with nocturnal asthma (134), whereas the polymorphism Gln27 → Glu may be associated with lower airway reactivity in asthmatic subjects (52,129). The most recent investigation found neither an association between genotype coding for amino acids 16 and 27 nor a change in overall asthma control by formoterol, indicating that a deleterious response to an inhaled β₂-adrenoceptor agonist was not related to a polymorphism of the β₂-adrenoceptors (54). Therefore, the clinical relevance of this polymorphism is not yet established.

β-Adrenoceptors are located in a variety of mammalian organs. β₁-Adrenoceptors are found in the heart and in the juxtaglomerular cells. The response to stimulation of these receptors is an increase in the force and rate of contraction and AV nodal conduction velocity. It is now known that β₂-receptors are more widespread than originally assumed.
A number of in vitro and in vivo studies have characterized the role of cardiac \( \beta_2 \)-adrenoceptors. It has been suggested that inotropic effects are at least partially mediated by \( \beta_2 \)-adrenoceptors, along with a dose-related loss of \( \beta_2 \)-adrenoceptor selectivity. Also, the chronotropic effect appears to be predominantly mediated by \( \beta_2 \)-adrenoceptors (81). \( \beta_2 \)-Adrenoceptors are further found in smooth muscle (vascular, bronchial, gastrointestinal and genitourinary), skeletal muscle, and liver. In skeletal muscle \( \beta_2 \)-agonists lead to glycogenolysis and potassium uptake, in the liver to glycogenolysis and glycogenesis (78). Smooth muscles are relaxed by \( \beta_2 \)-adrenoceptor agonists.

In the lung, \( \beta_2 \)-adrenoceptors have been identified on many cells. Their density increases from the large to the small airways and is much higher on the alveolar walls than other structures of the lung (4). The ratio of \( \beta_1 \) to \( \beta_2 \)-adrenoceptors in human lung tissue is about 1:3 (30). The major bronchial effects of agonists, such as fenoterol, or of antagonists are mediated by \( \beta_2 \)-adrenoceptors on the bronchial muscle cell surface (20). Furthermore, \( \beta_2 \)-adrenoceptors mediate numerous nonbronchodilator effects in the lung. They are found on mucous and serous glands and on inflammatory cells. Their activation promotes secretion from serous and, to a lesser extent, mucous cells. They enhance mucociliary beating frequency, and increase the movement of water and chloride ions into the bronchial lumen (see e.g. 58). In addition, \( \beta_2 \)-adrenoceptors inhibit mediator release from various cells, including mast cells and basophils; they interfere with cholinergic neurotransmission, reducing the cholinergic component of bronchoconstriction and enhance vascular integrity by preventing microvascular leakage (96).

**ANIMAL TOXICOLOGY AND KINETICS**

As for many other compounds that have been on the market for decades, there are relatively little systematic data in the public domain on the animal toxicology and pharmacokinetics of fenoterol. Considering the substantial experience with the drug in human therapy, animal toxicology is of limited usefulness for this review. In publications from the seventies, an LD50 of fenoterol in rats and mice was reported to range from 2200 to 3000 mg/kg p.o.; 260 to 530 mg/kg i.p., and 42 to 76 mg/kg i.v. (66).

During the early days of fenoterol use, there was a debate on its possible cardiotoxicity. Many investigations in fetuses or young animals addressed this topic. Arndts et al. (2) were unable to find any cardiotoxicity in fetuses or young animals whose mothers were treated with fenoterol during the perinatal period. In subacute toxicity studies, Kast et al. studied the cardiotoxicity of extremely high doses of fenoterol. At 600 mg/kg/day p.o. for 35 d fenoterol was lethal in adult and newborn rats. Only adult rats, which died after receiving 600 mg/kg of fenoterol, showed extended myocardial scars (67). A review of 92 publications with animal and human data indicated that fenoterol, at doses used in human tocolysis, does not damage the fetal heart (68). Many investigators have studied the myocardial effects of fenoterol. Meinen et al. (88) investigated the ultramorphologic effects on rabbit myocardium. Their experiments did not reveal any myocardial damage after monotherapy with fenoterol or combination therapy with fenoterol and verapamil, or fenoterol and prednisolone.

In other animal experiments, the effects of fenoterol on umbilical blood flow were studied (55). These experiments were carried out in pregnant sheep and demonstrated that continuous infusion of fenoterol to the mother at therapeutically used doses has no effect on the fetal umbilical circulation.
Pulmonary edema may be a rare adverse event during tocolysis with \( \beta_2 \)-adrenoceptor agonists. Its pathophysiology is not fully understood. In an attempt to study the pathogenesis of pulmonary edema, Grospietsch et al. (44) carried out experiments in nonpregnant rabbits and found that hypervolemia during therapy with \( \beta \)-adrenoceptor agonists may contribute to the development of pulmonary edema.

Koster et al. (74) described fenoterol kinetics in rats using HPLC and non-enantiospecific electrochemical detection. They found that after intraduodenal administration only 34–53% of the drug was absorbed. Similar results were obtained in dogs (110) and mice using tritium-labeled fenoterol (73). After intraduodenal administration of fenoterol at 10 mg/kg and 40 mg/kg, the total systemic availability of the drug ranged from 0.8 to 1.2%. The pharmacokinetics of fenoterol i.v. was dose-dependent. The terminal half-life of the drug remained unaltered (about 45 min). These findings suggest that fenoterol is subject to substantial metabolism in the intestinal wall and liver. It is known that glucuronidation is a major component of the intestinal first-pass effect, particularly in rats. The dose-dependent kinetics of fenoterol i.v. in rats is interpreted as evidence of an increased gastrointestinal blood flow. Fenoterol has a high clearance, and its metabolic clearance is likely to be affected by changes in the portal blood flow.

**HUMAN PHARMACOKINETICS**

Most of the published pharmacokinetic data in humans have been obtained using labeled fenoterol (93,111,113). There are no data on the kinetics of fenoterol enantiomers in either animals or humans. It has been shown that the clearance and bioavailability of salbutamol enantiomers differs significantly (13). Recently, new techniques have been used for the detection of \( \beta_2 \)-adrenoceptor agonists (capillary electrophoresis and mass spectrometry, CE-MS; 136) in body fluids, and stereoselective assays are being tested.

The kinetics of fenoterol in humans are not substantially different from animals. The above-mentioned radioimmunoassay (RIA) has a limit of detection of 10–20 pg/ml fenoterol in plasma or urine. It is not selective with respect to the main metabolites of fenoterol, which have to be removed by selective extraction with organic solvents. This assay is valid only if the enantiomer ratio of the racemate is not changed during the passage of the drug through the body. This appears not to be the case, however, in the species tested so far, including humans (113).

Investigations by Buchelt and Rominger (17,18) using radioactively labeled fenoterol led to the conclusion that about 60% of an oral dose is likely to be absorbed. More than 90% of the radioactivity in the plasma appears to be due to metabolites. Fenoterol is metabolized by conjugation reaction, and sulfate conjugates are its main metabolites in humans (17). Following i.v. administration, >60% of a fenoterol dose was recovered in urine as sulphate ester. After oral administration of fenoterol, only 2% of the dose reached systemic circulation as the unchanged drug (110).

Using the non-stereoselective RIA, Hildebrandt et al. (61) reported that in healthy volunteers or patients fenoterol is metabolized to sulphate and glucuronide conjugates and that sulphate ester is the predominant conjugate. These findings indicate an extensive first-pass effect in the gut mucosa and liver. Plasma protein binding of fenoterol is 35–40%. After i.v. injection, its pharmacokinetics has a very fast distribution phase of \(~1\) min, followed by two additional distribution phases with half-lives of 15 min and 3 h, the
latter being the terminal half-life (62,63). In patients with asthma, the total clearance of fenoterol was 63 ± 24 L/h and the steady-state volume of distribution was 140 ± 70 L (62).

Hochhaus et al. (62) suggested linear pharmacokinetics for fenoterol. There are no published pharmacokinetic studies with long-term use of fenoterol. Pharmacokinetics of related compounds were similar in asthma patients and during repeated inhalation (63). After administration of an oral immediate-release formulation of fenoterol, the peak plasma levels were observed at 3 h (12). The effect of food on the pharmacokinetics of oral fenoterol in humans is not known. Experiments in dogs suggest that fenoterol absorption is better in fasting than in fed animals (18).

The major route of administration of fenoterol is by inhalation. There are only a few studies on fenoterol excretion following inhalation. After inhalation, plasma levels of the drug are in the picogram to nanogram per milliliter range, and peak plasma levels are observed at 10–60 min after inhalation (62). This wide range is due to the fact that plasma levels depend heavily on the individual’s inhalation technique. The plasma levels after inhalation do not reflect the effective drug concentration at its site of action. Also, the disease state may alter drug absorption from the lung (116,135). Schmidt et al. (117) compared the efficacy of $\beta_2$-adrenoceptor agonists by i.v. administration vs. inhalation in patients with chronic obstructive airway disease. The duration of bronchodilation was much longer after metered dose inhalation (>4 h) than after i.v. administration. The efficacy of infused fenoterol was maintained only as long as the drug was administered.

Another route of administration is nasal delivery; it is effective and leads to higher plasma levels of fenoterol than does oral administration. The bioavailability of the drug is 10-fold higher, compared with the oral route (62).

Tocolysis represents another form of continuous therapy. The pharmacokinetics of fenoterol by short-term i.v. infusion was studied in healthy women over 3 h using tocolytic doses (0.5, 1.0, and 2.0 $\mu$g/min) (137). The total clearance of fenoterol increased with the dose from 1299 to 1924 ml/min; while the apparent volume of distribution increased from 49 to 85 L. The terminal half-life was 52 min and did not change with the dose. The dose-dependent increase of clearance may be due to increased gastrointestinal and hepatic blood flow, in analogy to earlier experiments in rats (74).

There are also some pharmacokinetic data from pregnant women who underwent i.v. tocolysis with fenoterol (60). Total clearance of fenoterol was comparable in pregnant and nonpregnant women, and there was no correlation between clearance and gestational age. The pharmacokinetic parameters differed from those in healthy male subjects (112). In another study, pregnant women received i.v. fenoterol at 4 $\mu$g/min over 3 h (86) and an RIA was used to determine fenoterol concentrations. Steady-state concentrations reached 2242 ± 391 pg/ml. Mean half-lives were 11.4 min and 4.87 h, i.e., comparable to earlier investigations in nonpregnant women and men. Total clearance was 114.8 L/h. On the basis of this and other studies, gender-specific kinetics of fenoterol can be excluded. During tocolysis with oral fenoterol, 5 mg orally 8 times a day, Dudenhausen et al. (29) reported that maternal plasma concentrations of fenoterol ranged from 130 to 200 pg/ml.

Diaplacental transport of fenoterol during tocolysis is also important. In an earlier investigation plasma concentrations of fenoterol were determined in maternal plasma and blood from the umbilical cord during delivery (85). Following continuous infusion of fenoterol for at least 12 h, average plasma concentrations of the drug in the fetus were
40–60% of maternal concentrations. It appears that the drug is not concentrated in the fetus.

There is still relatively little conclusive data on fenoterol kinetics, particularly with regard to long-term administration, and no detailed information on the kinetics of the two enantiomers.

**PHARMACOLOGICAL EFFECTS IN HUMANS**

β₂-Adrenoceptor agonists such as fenoterol exert a number of well-characterized pharmacological effects in humans. Among these, the most pronounced are bronchodilation and relaxation of the pregnant uterus. It has been shown recently that erythropoietin production could be affected by β₂-adrenoceptor activation. Fenoterol has been shown to increase erythropoietin production in healthy volunteers (41). A similar effect has been reported in pregnant women receiving i.v. tocolysis with fenoterol (42). Other important pharmacodynamic effects of fenoterol lead to clinical side effects: transient hypokalemia, cardiac acceleration, hypotension, ECG changes, and tremor (see below).

Hypokalemia is due to an enhanced uptake of K⁺ into skeletal muscle caused by stimulation of membrane-bound Na⁺/K⁺ ATPase (23). As demonstrated in nephrectomized animals, this effect is due to β₂-adrenoceptor control of extrarenal handling of potassium and not to renal effects (9). Hypokalemia has also been demonstrated in vivo in humans treated with epinephrine due to its β₂-adrenoceptor properties (16,28). Hypokalemia can be prevented by selective β₂-adrenoceptor antagonists, such as ICI 118 551 [erythro-dl-1(7-methylindan-4-yloxy-3-isopropylaminobutan-2-ol], or non-selective compounds such as oxprenolol (15,64).

After inhalation of metered doses of fenoterol by healthy volunteers, Haalboom et al. (48) demonstrated a dose-dependent decrease of plasma potassium levels. The maximum decrease of K⁺ reached 0.9 ± 0.1 mmol/L; it was not predictable from muscle mass or body-mass index. Other investigators (24,115) compared hypokalemic effects of fenoterol or salbutamol at therapeutically equieffective doses and concluded that fenoterol has a more-pronounced hypokalemic effect than salbutamol. After inhalation of 800 μg of either compound, serum potassium levels decreased by 1.13 ± 0.32 mEq/L after fenoterol vs 0.67 ± 0.25 mEq/L after salbutamol (115). This hypokalemic effect was accompanied by increases in plasma cAMP. A stronger hypokalemic effect of fenoterol, in comparison with salbutamol or terbutaline, was also observed in patients in another study (139).

According to the findings of Bauer et al. (6), the hypokalemic effect may differ with different formulations of fenoterol. Inhalation of dry powder appears to result in smaller changes in potassium than does inhalation of metered doses of fenoterol. Bouillon et al. (12) found that in healthy nonpregnant women, fenoterol given by infusion at 2 μg/min for 1.5 h decreases plasma K⁺ to 2.77 mmol/L.

Inhalation of fenoterol slightly increases insulin secretion, an effect that may contribute to hypokalemia. Mg²⁺ concentrations are not altered by inhalation of fenoterol (94).

Cardiovascular effects of fenoterol result from different mechanisms. The fall of serum potassium is accompanied by dose-related electrocardiographic effects such as T wave flattening, U-waves, and S-T segment depression (6,81). Some of the cardiac effects, e.g., an increase in heart rate or in QTc interval, were reported to be more pronounced after
fenoterol than after salbutamol or terbutaline. This finding may not be valid, since the investigators compared the effects of the same number of puffs from metered dose inhalers containing one of the three drugs without considering their concentrations (139). Scheinin et al. (115) found that fenoterol has dose-dependent effects on heart rate, renin activity, and plasma norepinephrine levels. These effects were stronger than those of salbutamol at equal doses by weight (molar ratio 1.0/1.6). The positive chronotropic effect of fenoterol is due to stimulation of cardiac $\beta_2$-adrenoceptors (123). This effect, as well as the rise of the QTc interval, appear to be dose dependent (139). Positive inotropic effects of selective $\beta_2$-adrenoceptor agonists are caused by stimulation of $\beta_2$-adrenoceptors at high doses, as well as by stimulation of $\beta_1$-adrenoceptors (81), since the selectivity is a dose-related phenomenon.

Cardiovascular effects can easily be demonstrated in healthy humans (12,22,33). Fenoterol, 400 $\mu$g q.i.d., slightly increased heart rate and systolic blood pressure because of its positive inotropic effect, and decreased diastolic blood pressure via peripheral vasodilation (inodilatory effect). Mean cardiac output increased by 26% and total peripheral vascular resistance decreased by 18%. After 2 w, there was no evidence of tolerance to these hemodynamic effects (22). In a longer-term study (>14 d) of fenoterol, 400 $\mu$g q.i.d., tolerance to its hemodynamic effects didn’t develop (22). Prednisolone does not alter the cardiovascular responses to $\beta_2$-adrenoceptor agonists (131). At higher than conventional inhalation doses (≥4 mg) there were no differences in the chronotropic or inotropic effects of fenoterol and salbutamol (98).

Skeletal muscle tremor is a typical effect of $\beta_2$-adrenoceptor agonists. Increasing metered doses of fenoterol increase tremor in a dose-dependent manner without any plateau effect (6,139).

In comparison to other $\beta_2$-adrenoceptor agonists, particularly salbutamol, fenoterol by inhalation causes greater $\beta_2$-adrenoceptor-mediated effects at therapeutically equipotent doses (e.g., 128, 130; hypokalemia, heart rate, QTc interval, tremor; 24, 115, 139). The greater efficacy of fenoterol has been attributed to its higher lipophilicity and consequently better absorption of the drug across the lung vascular bed (81) as well as to higher intrinsic activity. Tachyphylaxis to systemic effects (but not airways responses) following inhalation of fenoterol in excessive amounts may be caused by downregulation of $\beta_2$-adrenoceptors (79).

**INDICATIONS**

The main indications for fenoterol are obstructive airway diseases, predominantly bronchial asthma, and since 1974 tocolysis during premature labor. There are also some experimental data that suggest that $\beta$-adrenoceptor agonists may be useful in the treatment of hyperkalemia in patients with chronic renal failure.

**Bronchial Asthma**

In bronchial asthma $\beta$-agonists should be administered by inhalation, since by this route the systemic side effects are reduced. If administered by this route, $\beta$-adrenoceptor agonists are less likely to reach $\beta$-adrenoceptors in the heart or skeletal muscles in clinically relevant concentrations.
The most important therapeutic effect of β₂-adrenoceptor agonists is bronchodilation. A very rapid onset of action is particularly useful when the drug is self-administered in an acute asthma attack. There is little evidence to suggest that alterations in the properties of β-adrenoceptors are of critical importance in the pathogenesis of asthma (4,95). Despite many vascular and cellular nonbronchodilator effects, β₂-adrenoceptor agonists do not affect the chronic inflammation in bronchial asthma that is considered the principal pathophysiological feature of this disease. Antiinflammatory therapy with inhaled steroids and/or cromoglycate is recommended concomitantly with β₂-adrenoceptor agonists, when β-agonists are needed more than three times a week (99). In addition, glucocorticosteroids have been demonstrated in vitro to reverse desensitization of β-adrenoceptors. This is probably due to increased β₂-adrenoceptor transcription, and possibly increased coupling. Such a phenomenon has been observed for β₂-adrenoceptors from human lymphocytes where reversal of terbutaline-induced desensitization can be accelerated by oral prednisone (14). This is an important aspect of glucocorticosteroids action in the treatment of asthma when β₂-adrenoceptor agonists have to be used concomitantly (27).

Tocolysis

The second important indication for β₂-adrenoceptor agonists is tocolysis with the aim to reduce premature labor and fetal mortality. β₂-Adrenoceptors are dominant (80–85% β₂- vs. 15–20% β₁-adrenoceptors in pregnant women) in the uterus, especially in the progesterone-dominant uterus. They mediate muscle relaxation (84,89). In addition, there appears to be a positive correlation between myometrial and β-adrenoceptor density in the lymphocytes of pregnant women (89). The need for pharmacological tocolysis is determined by the degree of cervix incompetence, the cardiotocogram, and in some cases by the subjective complaints of the patients, as well as by the medical history of the individual patient. The recently introduced i.v. bolus tocolysis has the same indications as continuous i.v. tocolysis. The former regimen has been developed to avoid tolerance and to reduce side effects. Its indications are not clearly differentiated from those for continuous tocolysis. Bolus tocolysis appears to require a smaller total dose of a drug for a comparable therapeutic effect; duration of the therapy may also be shorter (121). It is difficult to determine clear differential indications for either bolus or oral tocolysis.

Hyperkalemia in Chronic Renal Failure

β₂-Agonists can be used to reduce serum potassium in patients with hyperkalemia associated with chronic renal failure. A number of clinical studies have demonstrated a clinically relevant effect (1,91). Most studies have been carried out using albuterol, mostly by inhalation. According to Burgess et al. (19), fenoterol or terbutaline are also effective by inhalation. The hypokalemic effect of a single dose (5 mg) of either of the two drugs appear to be stronger and longer lasting (4 h) than that of albuterol (2 h). These findings are supported by studies in volunteers who had a greater hypokalemic response after inhalation of fenoterol than by equal doses of salbutamol (24,115). It can be concluded that β₂-adrenoceptor agonists are efficacious in the treatment of hyperkalemia in some but
not all patients with chronic renal failure. Resistent hyperkalemia may need a more conventional regimen of insulin and glucose.

**DOSING**

Fenoterol is used in the form of fenoterol hydrobromide as i.v., oral, or inhaled aerosol formulations. For bronchodilation in adults and children of six years and older, single inhalation doses between 100 and 400 µg are recommended. The current available metered dose inhalers use 100 or 200 µg fenoterol per puff. The maximum daily dose should not exceed 3–4 times 400 µg; higher doses do not increase the therapeutic effect but tend to increase the risk of side effects. Oral bronchodilator therapy can be carried out with daily doses of 2500–5000 µg fenoterol, divided into 3 or 4 single doses. It should be noted, however, that the onset of action following oral administration of the drug is rather slow compared with inhalation, which leads to an almost immediate relief. According to current knowledge, the dosing of fenoterol as well as that of similar short-acting β2-adrenoceptor agonists should be guided by clinical symptomatology.

For infants, β2-adrenoceptor agonists are recommended predominantly for acute treatment. Fenoterol is available as a 0.5% solution that can be administered by nebulizer at a dose of 0.01–0.03 ml/kg body weight, 3–4 times daily, or as metered doses (using a spacer or face mask) up to 4 times 2 puffs (each 100 µg) per day.

Myometrial relaxation can be achieved by fenoterol at doses of 0.5–4 µg/min by continuous i.v. infusion. Intravenous administration should be carried out using infusion pumps only. Alternatively, bolus tocolysis will require 3–7 µg fenoterol, every 2–24 min, using a special infusion pump that delivers precise amounts at predetermined time intervals (121). Further studies on the dose and dose intervals during bolus tocolysis in healthy nonpregnant volunteers have suggested that dose adjustments should be made by increasing the bolus size rather than by shortening the interval between treatments (7). By the oral route, fenoterol 5 mg, 4 to 8 times daily, has been shown to be effective (29). It is possible to switch from i.v. to oral tocolysis after achieving a sufficient reduction of labor.

For the treatment of hyperkalemia, prior to dialysis albuterol is considered safe and reasonably effective in nebulized doses of 10–20 mg (1). Some studies in healthy volunteers suggest that fenoterol by inhalation decreases potassium levels in a dose-dependent manner (24,115). This indication has not been yet systematically investigated in patients, so no dose regimen can be recommended.

**CLINICAL ISSUES**

**Fenoterol in Asthma Therapy**

Since the late eighties the therapy of patients with bronchial asthma has changed radically. The changes were due to the improved understanding of the pathophysiology of asthma as a predominantly eosinophilic inflammatory disease (5,11). The debate concerning the use of fenoterol and other β2-adrenoceptor agonists has furthered this change. In the mid-1960’s mortality rates, particularly in children and young adults, rose to alarming levels in England, Wales, Australia, and New Zealand (119). This “epidemic” was most likely owing to the introduction of a high-dose formulation of isoproterenol. The second epidemic occurred in New Zealand in the early 1980’s. It has been linked to inhaled
fenoterol rather than to β-adrenoceptor agonists as a class effect (82), creating, therefore, the “fenoterol hypothesis” (25,26). Many of the deceased patients were on combination therapy with theophylline or other drugs (119). Fenoterol may have been prescribed preferentially to more severely ill patients whose disease was difficult to control; this interpretation was suggested by the detailed analysis of risk factors (37).

Due to the uncertainty of the link between inhaled β₂-adrenoceptor agonists (primarily fenoterol) and increased asthma mortality (36,87), Spitzer et al. (122) examined the prescription records of the Saskatchewan province in Canada and found an association between the prescription of a β-adrenoceptor agonist and the risk of dying from bronchial asthma. This case control study suggested an association between the dose of and cumulative exposure to a β₂-adrenoceptor agonist in general, rather than a specific compound. A second pharmacoepidemiological study by the same group appears to confirm that the association between the use of inhaled β-adrenoceptor agonists and asthma mortality is confined primarily to the use of these drugs in excess of the recommended doses (125). These studies could not find an association between nonasthma mortality (including cardiovascular causes) with the inhalation of β-adrenoceptor agonists.

A recent pharmacoepidemiological investigation surveyed the trends of sales of inhaled fenoterol and other inhaled β-agonists and asthma mortality by contrasting New Zealand with nine other countries where inhaled fenoterol has been marketed. The authors came to the conclusion that these international data do not indicate any relation between asthma mortality and sales of inhaled β-agonists in general nor fenoterol in particular (75). A second paper by Suisse and Ernst (126) reanalyzed the data for the New Zealand asthma deaths rates, fenoterol market share, sales of β-adrenoceptor agonists, and inhaled corticosteroids for the years 1976–1991. They found that the use of inhaled corticosteroids was more closely associated with asthma mortality than either fenoterol or all β-adrenoceptor agonists combined. They concluded that the data do not provide evidence for the “fenoterol hypothesis,” in contrast to the analysis made earlier by Pearce et al. using the same data (104). A debate about the “fenoterol hypothesis” and its validity followed (106,127).

A similar debate took place between Pearce et al. (105) and Garrett et al. (38,39). Garrett et al. came to the conclusion that the “fenoterol hypothesis,” as inferred from the New Zealand studies by correlating fenoterol sales and asthma mortality, may be explained by selection bias and inadequate measures of severity (38,39) and that the existing data do not point to fenoterol as a major factor in the New Zealand “epidemic.” Similarly, Garrett et al. (37) pointed out earlier to Suisse and Ernst (126), that the recent decline in hospital admissions and in the mortality rates for asthma in New Zealand (and in other countries) should be ascribed to the use of high doses of steroids rather than to a decrease in the use of either fenoterol or other β-adrenoceptor agonists by inhalation.

Other groups have addressed another aspect of this problem, namely regular vs on demand therapy with β-adrenoceptor agonists in a number of prospective, placebo-controlled, cross-over studies. Sears et al. (118) and Taylor et al. (132) as well as van Schayck et al. (114) demonstrated that regular use of β₂-agonists (fenoterol and salbutamol) accelerated the decline in ventilatory function and of clinical disease control. An important long-term study by Haatela et al. (46,47) confirmed that regular β₂-adrenoceptor agonist therapy with terbutaline leads to deterioration of asthma. The results of this study suggested that short acting β-adrenoceptor agonists should be administered on demand only, so that the exposure to these drugs is reduced in comparison to other
regimens. In fact, regular, long-term treatment with \( \beta \)-adrenoceptor agonists was introduced to the management of asthma in the 1970’s without appropriate scientific proof of its rationale.

Eventually, in 1992, the first NIH guidelines for the treatment of bronchial asthma were issued (99). Currently, the backbone of asthma therapy is a long-term antiinflammatory treatment, preferably with inhaled corticoids. \( \beta_2 \) Adrenoceptor agonists can no longer be considered an alternative to inhaled corticosteroids. \( \beta_2 \)-Adrenoceptor agonists remain, however, essential for the management of acute, severe asthma attacks. They are considered useful on demand (rather than by regular use) for the relief of symptoms and for prophylaxis of exercise-induced symptoms. Regular, long-term treatment with short-acting \( \beta_2 \)-adrenoceptor agonists is now obsolete; it is thought to contribute to the deterioration of asthma in the long run (103). A recent survey documented that physicians are responding to the above-mentioned guidelines and have changed asthma therapy accordingly (49).

More recently, the guidelines have been updated with no specific recommendation for the selection of short-acting \( \beta \)-adrenoceptor agonists, thus reflecting that there are no clear-cut differences among the various members of this group of asthma therapeutics.

**Fenoterol in Tocolysis**

Various studies have shown that myometrial \( \beta \)-adrenoceptor desensitization correlates with the number and function of \( \beta \)-adrenoceptors in lymphocytes (8,89). In a recent paper Engelhardt et al. (31) demonstrated that tocolysis with fenoterol over a few days leads to a selective downregulation of myometrial \( \beta \)-adrenoceptors without a reduction in their mRNA concentrations. These findings were interpreted as downregulation by receptor degradation, caused by tissue- or organ-specific factors that determine the pattern of desensitization of receptors. The limited duration of the tocolytic effect was attributed to this phenomenon. When \( \beta \)-adrenoceptor agonists were administered by intermittent (bolus) infusion, desensitization, as demonstrated in vitro in human myometrium and in vivo in sheep, did not occur (21,69) and the tocolysis with bolus fenoterol required less drug (121).

Cardiovascular side effects of \( \beta_2 \)-adrenoceptor agonists during tocolysis can be prevented by concomitant use of either a \( \beta_1 \)-selective adrenoceptor antagonist (e.g., metoprolol) or a calcium antagonist (e.g., verapamil).

The tocolytic efficacy of other \( \beta_2 \)-adrenoceptor agonists has been compared with that of fenoterol. Hochhaus and Möllmann (63) demonstrated, using a pharmacokinetic/pharmacodynamic model, that fenoterol by constant infusion (but not orally) is 5 times more potent than terbutaline and 6 times more potent than salbutamol. There are some uncertainties concerning the therapeutic benefit of \( \beta_2 \)-adrenoceptor agonists for tocolysis. There is no precise criterion for the selection of pregnant women with premature labor who will profit from tocolysis. This means that due to rather imprecise indications, some patients will be treated unnecessarily. In addition, even though tocolysis has been shown to postpone delivery, no clear-cut beneficial effect of tocolytic drugs on perinatal fetal mortality has been demonstrated (71,72,92). The absence of such critical studies has not affected the use of tocolysis in the clinic.
SIDE EFFECTS

General Side Effects

Major side effects of $\beta_2$-adrenoceptor agonists such as fenoterol can be derived from their action at $\beta_2$-adrenoceptors and from their loss of selectivity at higher doses, thus activating $\beta_1$-adrenoceptors as well.

Tremor, tachycardia, palpitations, and nervousness are among the most common systemic adverse events. They are dose-related and usually disappear during continued therapy. Following inhalation, only 10% of a dose reaches the target organ (53). The remainder is swallowed and metabolized in the gut and liver. Thus, the systemic side effects are less prominent during inhalation therapy (70,109).

The most common adverse reaction is skeletal muscle tremor (58,76). In respect to the tremor, there appear to be no major differences between various short-acting $\beta_2$-adrenoceptor agonists. The tremor is likely to diminish with long-term administration of the drug (see above; 128).

Tachycardia and palpitations can be induced by direct cardiac stimulation or as a reflex response to peripheral dilation via $\beta_2$-adrenoceptors. The incidence is higher after oral or nebulized administration, compared with inhalation. Cardiac side effects are more common following i.v. administration of $\beta$-adrenoceptor agonists (83). Cardiac arrhythmias are uncommon during inhalation of $\beta_2$-adrenoceptor agonists at recommended dose levels. The occurrence of arrhythmias has been linked to the state of oxygenation (97). In adequately oxygenated patients with acute severe asthma fenoterol (as titrated doses $\leq 3200 \text{ mg}$) or salbutamol (at doses $\leq 1600 \text{ mg}$), produced no clinically significant cardiac arrhythmias, despite the fact that a two-fold higher dose of fenoterol produced greater $\beta_2$-adrenoceptor-mediated systemic effects. There were no substantial prolongations of the QT interval with either fenoterol or salbutamol (97). Other reports suggested that arrhythmias can be produced during the administration of nebulized or high-dose $\beta_2$-adrenoceptor agonists (59,130). The concurrent use of methylxanthines (e.g., theophylline) has also been discussed as a cause of arrhythmias (131). Some evidence warrants careful monitoring of patients with severe asthma who are being treated with theophylline and $\beta_2$-adrenoceptor agonists. Laursen et al. (77) observed an increased incidence of ventricular ectopic and supraventricular beats in patients receiving both types of drugs.

$\beta_2$-Adrenoceptor agonists produce no serious central nervous system side effects (83). Nervousness may occur after oral or aerosol (high dose) administration (45,90). A few patients experienced headache. High doses of $\beta_2$-adrenoceptor agonists can produce mild nausea.

As other sympathomimetic amines, $\beta_2$-adrenoceptor agonists by oral, i.v., or nebulized administration may transiently decrease plasma potassium concentrations (see above). This effect may impose a risk for patients on concomitant therapy with digitalis or diuretics (80,83). Hypokalemia may be linked to $\beta_2$-adrenoceptor agonist stimulation of hepatocytes, which leads to glycogenolysis and reactive insulin incretion. This possibility should be considered in the treatment of diabetic patients.

$\beta_2$-Adrenoceptor agonists may also experience increased plasma free fatty acids, particularly in patients with diabetes, asthma, and concomitant pregnancy. It is unclear whether this effect is clinically significant. Monitoring of blood glucose, free fatty acids, and ketone bodies has been recommended in such patients (83).
The cardiac effect of inhaled fenoterol can be enhanced by concomitant medication such as other β₂-adrenoceptor agonists, methylxanthines, or anticholinergics and lead to tachycardia or arrhythmia. Halogenated hydrocarbons used for anesthesia may increase the danger of arrhythmias. Concomitant use of monoamine oxidase inhibitors and tricyclic antidepressants may lead to an increased incidence of cardiovascular side effects.

**Maternal Side Effects During Tocolysis**

During tocolysis, the mother can experience side effects. In addition, the motility of the ureters can be further reduced. Intestinal atonia is occasionally observed. There have been a number of reports, mostly case reports, about maternal pulmonary edema during tocolysis. Pisani and Rosenow (107) published a review of 58 case reports. The most often involved β-adrenoceptor agonist was terbutaline followed by isoxuprine, ritodrine, and albuterol. In rare cases, i.v. infusion of fenoterol into pregnant patients may cause pulmonary edema when the patients receive concomitantly an excessive fluid load and steroids (3). It is of interest that the majority of these patients received steroids to provide the maturation of fetal lungs. Hawker (57) investigated the importance of the total dose and the infusion rate of the β-adrenoceptor agonists and found no increase in incidence with increases in the dosages of these drugs. Women with a twin pregnancy had a higher incidence of pulmonary edema (57,107). Unfortunately, many cases are not well documented and causes other than β-adrenoceptor agonists cannot be excluded.

It can be concluded that pulmonary edema during tocolysis induced by β-adrenoceptor agonists, particularly fenoterol, is a rare event. Twin pregnancies appear to bear a higher risk. In general, the circumstances under which pulmonary edema occurs are unclear; there is no marker or clear predisposition for this side effect.

**Fetal Side Effects During Tocolysis**

Short-lasting fetal hypoglycemia has been reported, particularly after long-term tocolysis that ended shortly before delivery (32). Metabolic acidosis due to increased lipolysis caused by β₂-adrenoceptor agonists does not require correction. There is no indication for a higher frequency of respiratory distress due to a lack of surfactant.

In the past, various investigators were concerned about conceivable fetal myocardial injury by β-adrenoceptor agonists during tocolysis (e.g., 34). Böhm and Adler (10) investigated newborns whose mothers had been treated with β-adrenoceptor agonists for various lengths of time. They provided no specific information on the drugs used. The immediate cause of death could not be directly related to the tocolysis treatment. After tocolysis with fenoterol, Stix et al. (124) were unable to find any unwanted long-term effects of the drug on cardiac function in infants.

Kast and Hermer (68) undertook a comprehensive review of 92 papers concerning this topic. According to them, neither in animal experiments nor during the widespread clinical use of tocolytics for more than two decades, has fetal or neonatal heart damage been reported. The absence of cardiac toxicity may be due to the fact that the sympathetic innervation of the fetus is immature and β-adrenoceptors are not fully expressed before birth. Neither fenoterol nor other β₂-adrenoceptor agonists could, therefore, produce cardiac damage in the fetus or in newborn infants after long-term tocolysis (68).

An unresolved issue is whether the cerebral development of children is influenced by
tocolysis. Groome et al. (43) reported a higher rate of cerebral hemorrhage in infants whose mothers were subjected to tocolysis with β2-adrenoceptor agonists. In contrast, Freyz et al. (35), Hadders-Algra et al. (51), and Gerhard et al. (40) were unable to show negative effects of long-term tocolysis with fenoterol or related drugs on psychomotor and somatic development. Considering the high number of tocolytic treatments carried out for decades worldwide, major effects of these drugs on cerebral development are unlikely. There were also no indications for embryo- or feto-toxic effects of fenoterol. The use of β2-adrenoceptor agonists by inhalation during pregnancy or breast feeding is not likely to endanger the child.

CONCLUSIONS

Fenoterol is a racemic, β2-selective adrenoceptor agonist. Due to its pharmacological profile it has been used clinically for decades as a bronchodilator in bronchial asthma and as an uterus relaxant for preterm labor. Its oral bioavailability is low, only 2%. It is rapidly metabolized to sulphate and glucuronide conjugates. The terminal half-life is ~3 h. To date there are no kinetic data for its stereoisomers.

For the pulmonary indication, various formulations of fenoterol are available. The drug can be applied by metered dose inhalers or nebulizer, as well as orally in the form of a capsule or syrup. It can also be administered i.v. Intravenous or oral formulations can also be used for the second indication, preterm labor.

The major side effects of fenoterol are based on its mechanism of action. They include muscle tremor, tachycardia, palpitations, nervousness, and hypokalemia. Tachyphylaxis has been reported for its systemic effects, but not bronchodilation. It is conceivable that concomitant corticosteroid administration to patients with asthma tends to preserve β2-adrenoceptor sensitivity. It should be noted that at high doses fenoterol loses its β2-adrenoceptor selectivity and may cause pronounced cardiovascular effects typical for β1-adrenoceptor agonists. Maternal pulmonary edema during i.v. tocolysis with β2-adrenoceptor agonists in general, and fenoterol in particular, is a rare event. There is no clinical or laboratory marker for this side effect.

Recently, increased mortality was reported in patients with bronchial asthma treated with short acting β2-adrenoceptor agonists, particularly fenoterol. These findings were not substantiated by many controlled trials and pharmacoepidemiological analyses. A skewed selection of patients may have been responsible for the reported findings. There is no definite evidence for increased mortality during therapy with recommended doses of β-adrenoceptor agonists by inhalation. Physicians should follow accepted asthma management guidelines that limit the excessive use of β2-adrenoceptor agonists and recommend suppression of the underlying inflammatory process by corticosteroid therapy.

Fenoterol appears to be an effective and safe drug for short-term bronchodilation in acute asthma attacks and tocolysis. In many respects it is comparable to other short-acting β2-adrenoceptor agonists.

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