

Bioavailability File : Terbutaline

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Summary : Terbutaline, a synthetic β_2 -adrenoceptor (β_2AR) stimulant, is used mainly in respiratory medicine (bronchial asthma, chronic bronchitis and emphysema) and in obstetrics. It exists as a racemic mixture (+ and - terbutaline). Although (-) terbutaline is responsible for β -agonist activity, (+) terbutaline is devoid of such pharmacological activity. Terbutaline is incompletely absorbed from the gastrointestinal tract. Its bioavailability is low (10-15%) and stereoselective. It is subject to fairly extensive first pass metabolism by sulfate conjugation in the liver and possibly in the gut wall. In this review, physicochemical and pharmacological properties, pharmacokinetics and bioavailability of terbutaline are discussed.

Key Words: Terbutaline, Pharmacokinetics, Bioavailability, β_2 -agonists, Asthma, Enantiomer

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Biyoyararlanım Dosyası : Terbü-talin

Özet: Sentetik bir β_2 -adrenerjik reseptör stimulanı olan terbü-talin, başlıca solunum yolu ilacı olarak (bronşiyal astım, kronik astım ve amfizem) ve obstetrikte kullanılır. Rasemik karışım halinde bulunur (+ ve - terbü-talin). (-) Terbü-talin β -agonist aktiviteden sorumlu olmasına rağmen (+) terbü-talin böyle bir farmakolojik etkiden yoksundur. Terbü-talinin gastrointestinal kanaldan absorpsiyonu tam değildir. Biyoyararlanımı düşük (%10-15) ve stereoselektiftir. Karaciğerde ve muhtemelen barsak duvarında sülfat konjugasyonu yoluyla oldukça fazla derecede ilk geçiş etkisine uğrar. Bu derlemede terbü-talinin fizikokimyasal ve farmakolojik özellikleri, farmakokinetiği ve biyoyararlanımı tartışılacaktır.

Anahtar kelimeler: Terbü-talin, Farmakokinetik, Biyoyararlanım, β_2 -agonistleri, Astım, Enantiomer

INTRODUCTION

Successful treatment of acute, severe asthma with subcutaneous injections of adrenaline started 100 years ago. Over the years, synthetic congeners of adrenaline (i.e. terbutaline, ibuterol, bambuterol) have been produced and tested for their pharmacological properties¹. Because of its relatively high metabolic stability, terbutaline can be systemically administered, and its duration of action is prolonged in comparison to the solely amine-substituted analogues of adrenaline². Terbutaline stimulates β -adrenergic receptors of the sympathetic nervous system and has little or no effect on α -adrenergic receptors³. Despite its low and stereoselective bioavailability, terbutaline is widely used as a bronchodilator for treatment

of bronchial asthma, chronic bronchitis and emphysema. On the other hand, terbutaline has not been approved and should not be used without permission of the patient in preterm labor. Although terbutaline may produce a wide range of adverse effects (e.g. nervousness, tremor, palpitation, tachycardia, headache, nausea, sweating), all these reactions are transient in nature and usually do not require treatment^{3,4}.

Physicochemical Properties

Terbutaline is a synthetic β_2 -adrenoceptor (β_2AR) stimulant that is used as a bronchodilator in the treatment of bronchial asthma. It is known chemically as $-\alpha$ -[(*tert*-butylamino) methyl]-3,5-dihydroxy-

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benzyl alcohol (C₁₂H₁₉NO₃ mol. wt. 225.29). It exists as a racemic mixture [(+) and (-) terbutaline] and has the chemical structure shown below (Figure 1)⁵.

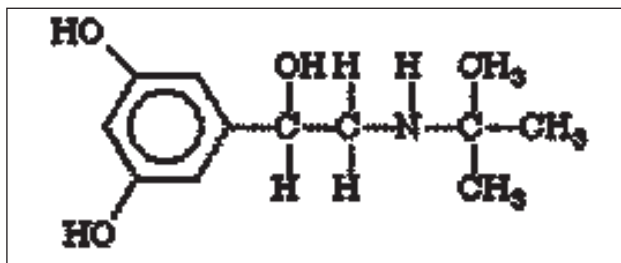


Figure 1. Structural formula of terbutaline.

Terbutaline is given as the sulfate (TBS). It is a white to gray-white, crystalline powder; odorless or with a faint odor of acetic acid; and slightly bitter. It is unstable in light and melts at about 247°C; three pKa values are given: 8.8, 10.1, 11.2⁶. One g of TBS dissolves in 1.5 ml water or 250 ml alcohol. It is soluble in 0.1N hydrochloric acid, slightly soluble in methanol, and insoluble in chloroform^{3,6,7}. Under normal storage conditions, TBS is stable in solid state. No change in chromatographic impurities has been detected even after three years' storage at room temperature. On the other hand, discoloration of aqueous solution is caused by oxidation of terbutaline and is enhanced by low pH and by ultra trace levels of metals in the presence of oxygen. High pressure liquid chromatography (HPLC) analysis of degraded solutions favors oxidative degradation of TBS. In the case of discoloration, drug solution should not be used^{3,8}.

Identification and Quantification Methods

Thin layer chromatography, HPLC, ultraviolet spectrometry (UV)^{9,10} (λ_{\max} = 276 nm in aqueous acid and λ_{\max} = 297 nm in aqueous alkali), infrared spectrometry (principal peaks at wave numbers 1210, 1231, 1155, 1069, 1610, 1042), and mass spectrometry (principal peaks at m/z 30, 86, 57, 41, 29, 39, 192, 42) can be used for identification of TBS. Ultraviolet spectrometry^{9,10} and HPLC (sensitivity about 1 ng/ml, in plasma by electrochemical detection)^{5,11,12-19} can be used for quantification of TBS.

Owing to its potency, terbutaline is employed in very small quantities and its determination in biological fluids requires the detection of nanogram or subnanogram per ml levels²⁰. Therefore, particularly in pharmacokinetic studies, the most usual analytical method for terbutaline is gas chromatography-mass spectrometry (GC-MS)²¹⁻²⁸ (unconjugated terbutaline detection limit in plasma: 100 pg/ml and in postmortem tissues: 1.5 ng/g⁷). Isolation of unchanged compounds and metabolites from biological samples by GC-MS necessitates elimination of matrix interferences by liquid-liquid extraction²⁹, solid phase extraction^{30,31} or both³². Derivatization has an important role in the detection of terbutaline²⁰. Trimethylsilylation is the usual procedure for this purpose^{29,30,32}.

Pharmacological Properties

Noradrenaline and adrenaline (Figure 2) are the two important endogenous compounds mediating β 2AR stimulation. β 1-adrenoceptors are stimulated prima-

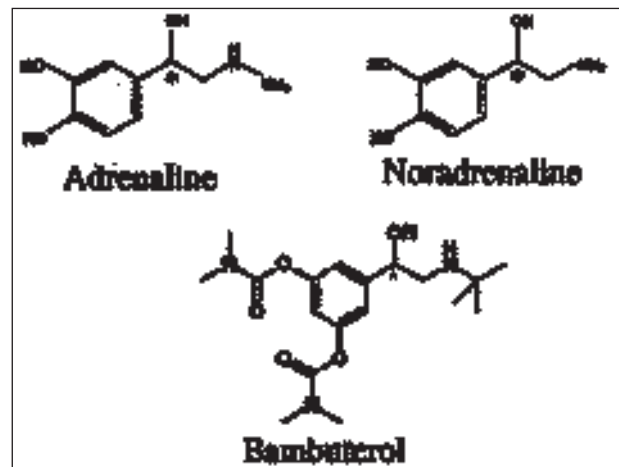


Figure 2. Structural formulas of adrenaline, noradrenaline and bambuterol.

rily by noradrenaline released from nerve endings, β 2AR in blood vessels, the airways, and skeletal muscles are stimulated by circulating adrenaline. Adrenaline, the unselective prototype [stimulates both α - and β -adrenoceptors (β AR)] of all β AR stimulating compounds, is rapidly metabolized by catechol-O-methyl transferase and monoamine oxida-

se, and therefore has a short duration of action. Synthesized analogues of adrenaline (e.g. terbutaline, bambuterol) (Figure 2) have proven useful in the pharmacological treatment of asthma². Of these, terbutaline stimulates β -adrenergic receptors of the sympathetic nervous system and has little or no effect on α -adrenergic receptors. Because of its relatively high metabolic stability, terbutaline can be systemically administered, and its duration of action is prolonged compared with the solely amine-substituted analogues of adrenaline². The main effect of terbutaline is relaxation of the smooth muscles of the bronchial tree and the peripheral vasculature. The drug significantly decreases resistance of the airways as measured by pulmonary function tests such as the forced expiratory volume in 1 second (FEV₁). Terbutaline does not appear to cause changes in arterial oxygen tension. It is believed that β -adrenergic agonists stimulate the production of cyclic adenosine-3',5'-monophosphate by activation of the enzyme adenylyl cyclase. Terbutaline appears to have a greater stimulating effect on β -adrenergic receptors of the bronchial, vascular and uterine smooth muscles (β 2AR) than on the β -receptors of the heart (β 1-receptors). In high doses, however, terbutaline may cause some cardiostimulatory effects and central nervous system stimulation. It is unclear whether the tachycardia that sometimes occurs with terbutaline is caused by β 1 stimulation or by a reflex response to blood pressure changes secondary to peripheral vasodilatation³. Furthermore, diseases (e.g. diabetes) and hormones (e.g. estrogens) may alter the sensitivity of various organ systems to β -receptor stimulation and change the usual relation between terbutaline concentration and effect³³. Although (-) terbutaline is responsible for β -agonist activity, (+) terbutaline is devoid of such pharmacological activity³⁴.

Terbutaline is given as the sulfate for its bronchodilating properties in the management of disorders with reversible airways obstruction such as in asthma and in certain patients with chronic obstructive pulmonary disease³⁵. It has been used intravenously or subcutaneously in selected patients to inhibit contractions in preterm labor (tocolysis), and thus

prolong gestation when such prolongation of intra-uterine life would be expected to benefit pregnancy outcome³. However, terbutaline has not been approved by the Food and Drug Administration (FDA) for use to inhibit preterm labor. Therefore, these agents should be considered experimental and should not be used without the written, informed consent of the patient³⁶.

Clinically, terbutaline is available in formulations for oral intake, inhalation and injection for the treatment of bronchial asthma³³. In the treatment of bronchial asthma, it is given by mouth in a dose of 5 mg two or three times daily. Children's doses may be calculated on the basis of body weight; a dose of 75 μ g per kg three times daily is suggested. A usual dose in children over seven years of age is 2.5 mg two or three times daily. On the other hand, subcutaneous, intramuscular or slow intravenous injection (250 μ g) is required up to four times daily for the treatment of severe forms of bronchospasm. A suggested dose by injection for children over two years of age is 10 μ g per kg to a maximum total dose of 300 μ g. To relieve acute bronchospasm, one or two inhalations of TBS 250 μ g can be taken as required from a metered-dose aerosol. However, if TBS is to be taken more than once daily, the doses recommended by the manufacturers are 250 or 500 μ g every four to six hours, to a maximum of eight inhalations in 24 hours. These doses are suitable, in general, for both adults and children. To arrest premature labor, it is given by intravenous infusion in glucose (5%) 10 μ g per ml³⁵.

Adverse Effects

Sympathomimetics may produce a wide range of adverse effects, most of which mimic the results of excessive stimulation of the sympathetic nervous system. These effects are mediated via the various types of adrenergic receptors, and the adverse effects of an individual drug depend to some extent upon its relative agonist activity on these different types of receptors at a given dose³⁷.

The principal adverse effects of oral or subcutaneous terbutaline are an increase in heart rate, changes in blood pressure, nervousness, tremor, palpitation, and dizziness. Headache, nausea, vomiting, anxiety, restlessness, lethargy, drowsiness, weakness, flushes, sweating, chest discomfort, muscle cramps, and tinnitus have also been reported³. All these reactions are transient in nature and usually do not require treatment⁴. However, pulmonary edema is a risk with β agonists when used for delaying premature labor.

Fletcher et al.³⁸ reported a case of myocardial necrosis in a newborn after treatment of the mother with long-term subcutaneous terbutaline, and speculated that this myocardial damage was due to β -sympathomimetic therapy. Long-term prenatal β -mimetic exposure led to downregulation of fetal β -receptors. This resulted in impaired myocardial function, increased peripheral vascular resistance, and poor cardiac output³⁹. In the rat, β AR stimulation by terbutaline alters cell development in brain and peripheral tissues, with the net effect depending on sex and the timing of exposure. These effects may contribute to neuropsychiatric, cognitive, cardiovascular, and metabolic abnormalities reported in the offspring of women treated with β -agonist tocolytics⁴⁰. On the other hand, when 10 asthmatic children received regular daily therapy with terbutaline aerosol for 50 weeks, no evidence was found for adverse effects of this drug on growth, bone marrow, liver function or the cardiovascular system⁴¹.

Carson et al.⁴² have reported that lone atrial fibrillation is defined as atrial fibrillation occurring in a patient without underlying heart disease and is known to occur during pregnancy. They claimed that atrial fibrillation should be added as a complication of oral terbutaline therapy.

The mutagenicity potential of terbutaline sulfate has not been determined. For the teratogenic effects of TBS, there are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human res-

ponses, this drug should be used during pregnancy only if potential benefits justify the potential risk to the fetus⁴.

It is possible that treatment with uterorelaxing substances, particularly β -adrenergic agonists, may alleviate the uterine discomfort that accompanies dysmenorrhea. However, side effects encountered with oral administration of β -agonists limit their utility. Bulletti et al.⁴³ claimed that intravaginal delivery of β -agonists (terbutaline) could solve this dilemma by enhancing their efficacy and reducing side effects.

Pharmacokinetics and Bioavailability

In healthy subjects the bioavailability of TBS is 10% on average when there are no prandial restrictions, whereas fasting subjects show a mean bioavailability of 14-15%⁴⁴. Similar results were found in children^{27,45}. The low bioavailability of terbutaline may be due to various factors, including stereoselective absorption, but presystemic sulfation certainly limits its bioavailability^{34,45}. Food impairs the bioavailability by about one-third because of reduced absorption. Despite the large variation in the extent of terbutaline bioavailability between subjects, each individual behaves reproducibly from dose to dose⁴⁴. Edema of the bowel and changes in splanchnic blood flow could have important effects on absorption and consequently on bioavailability of TBS³³. Asthmatic patients have the same bioavailability of the drug as healthy subjects⁴⁴. The mean bioavailability results of terbutaline obtained after administration of various dosage forms by different routes are summarized in Table 1.

Although enantiomers have the same physical properties (e.g. lipophilicity) in a non-chiral environment, bioavailability of terbutaline is stereoselective. Borgström et al.²⁸ investigated the pharmacokinetic parameters after intravenous and oral administrations of enantiomers and racemate. Although they observed no significant difference between (-) and (+) TBS in regard to $t_{1/2}$ and V_{ss} , all other pharmacoki-

Table 1. The mean bioavailability results of terbutaline derived from the literature

Route	Dosage Form	Dose (mg)	Disease State	Mean Bioavailability ± Standard Deviation	Ref. No
ORAL	Tablet	5	Volunteers	15.2 ± 8.2	58
	Elixir	1.5	Asthmatic Children	9.5	27
	Aqueous Solution	5	Volunteers	11.2 ± 1.7	28
	CR-granulate	3	Asthmatic Children	10.8 ± 3.1	59
	Tablet	5	Asthmatic	30	44
INHALATION	Aerosol	1	Volunteers	<10	45
	Metered Dose Inhaler			16.5 ± 3.1	60
	Pulmonary component*			9.1 ± 3.1	
	Oral component*			6.7 ± 2.4	

* Contribution of pulmonary and oral components to the metered dose inhaler bioavailability was calculated separately by the authors.

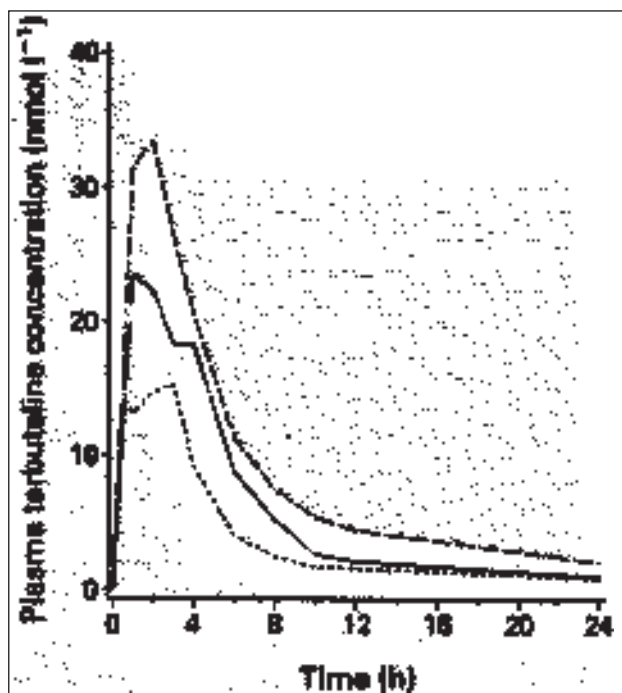


Figure 3. Mean plasma terbutaline concentrations after oral administration of 5 mg of (+), (-) or (±) terbutaline (... (+)T; --- (-) T; _ (±)T)²⁸.

netic parameters were significantly different (Table 2). Further, combination of a higher absorption and a lower first-pass metabolism of (-) terbutaline as compared with (+) terbutaline resulted in a bioavailability of (-) terbutaline which was twice as high as that of (+) terbutaline. The racemate had about the same bioavailability as (-) terbutaline when calculated from plasma data (Figure 3, Table 2).

As terbutaline is an ampholyte and very hydrophilic drug, it passes cell membranes very slowly. A survey of the literature indicated that two prodrugs are available for TBS: ibuterol and bambuterol. Ibuterol, a diisobutyrate ester of terbutaline, is a lipophilic prodrug, and therefore easily passes cell membranes. This prodrug is hydrolyzed to terbutaline in the lung⁴⁶. Bambuterol is an amphiphilic bisdimethyl-carbamate of terbutaline. Pharmacokinetic analysis indicated that absorption of bambuterol was slow and multi-phasic, and that slow biotransformation to terbutaline occurred both presystemically and systemically². Oral administration of bambuterol to patients with asthma prolongs the bronchodilating effect produced by terbutaline, thus making once-daily dosing sufficient¹¹.

After oral administration, peak plasma concentration is reached within 1-4 h. Food reduces peak height by about 40% (Table 3)⁴⁴. Lemmer⁴⁷ reported that not only the pharmacokinetics of the β_2 -sympathomimetic terbutaline but also its effects on peak expiratory flow were circadian phase-dependent (Figure 4). After a seven-day treatment with oral terbutaline, C_{max} was higher after morning than evening drug application with t_{max} being 3.5 h and 6.2 h. These chronopharmacologic data indicate that β -sympathomimetics may/should be dosed higher in the eve-

Table 2. Primary and secondary pharmacokinetic parameters calculated from plasma drug concentration after intravenous (i.v.) and oral administration (p.o.) of (+), (-) or (±) terbutaline in six healthy volunteers²⁸

Parameter	(+) T		(-) T	(±) T observed		(±) T predicted
CL (1h ⁻¹ kg ⁻¹)	0.186 ± 0.044	*	0.125 ± 0.029	0.204 ± 0.034	*	0.155 ± 0.024
CL _R (0-8), i.v. (1h ⁻¹ kg ⁻¹)	0.159 ± 0.034	**	0.088 ± 0.020	0.134 ± 0.015	NS	0.109 ± 0.027
CL _R (0-24), p.o. (1h ⁻¹ kg ⁻¹)	0.148 ± 0.024	***	0.112 ± 0.015	0.148 ± 0.024	NS	0.122 ± 0.017
V _{ss} (1kg ⁻¹)	1.90 ± 0.16	NS	1.76 ± 0.42	1.79 ± 0.13	NS	1.92 ± 0.32
t _{1/2} (h)	12.7 ± 1.5	NS	15.3 ± 2.0	13.7 ± 1.3	NS	14.2 ± 1.7
MRT (h)	10.7 ± 2.7	*	14.4 ± 2.4	9.05 ± 1.74	*	12.7 ± 2.3
F(%)	7.5 ± 2.1	**	14.8 ± 2.0	14.2 ± 1.5	**	11.2 ± 1.7

CL: Clearance, CL_R: Renal Clearance, V_{ss}: Volume of distribution at steady-state, t_{1/2}: Half life, MRT: Mean residence time, F: Recovery

*p <0.05, **p<0.01, ***p<0.0001; NS: not significant

Table 3. Peak plasma concentrations (C_{max}) and peak times (t_{max}) obtained after oral administration of intact terbutaline tablets⁴⁴

Administration (terbutaline sulfate)	Conditions	C _{max} (µg/L)	T _{max} (h)
Single Dose			
5 mg	F	6.6 (4.1-11.2)	2.5 (1.5-4)
5 mg	F	5.8 (3.7-6.8)	2.7 (2-3)
	NF	3.9 (3.1-4.6)	3.7 (3-4)
5 mg	NF	3.3 (2.3-5.5)	3.0 (1-4)
7.5 mg	F	7.9 (5.4-10.0)	3.3 (2-4)
	NF	4.6 (4.3-5.1)	1.7 (1.5-2)
7.5 mg	NF	5.6 (4.4-8.6)	2.1 (1-4)
Steady State			
3 x 5 mg (q.8h)	NF	3.3 (2.9-3.6)	1.8 (1-2)
3 x 5 mg (q.8h)	NF	6.5 (4.7-10.5)	2.5 (2-4)
3 x 5 mg (q.8h)	NF	2.4 (1.9-2.8)	1.5 (1-2)
3 x 5 mg (q.8h)	NF	3.2 (1.9-4.7)	1.5 (1-2)

F = Fasting, NF =Non-Fasting

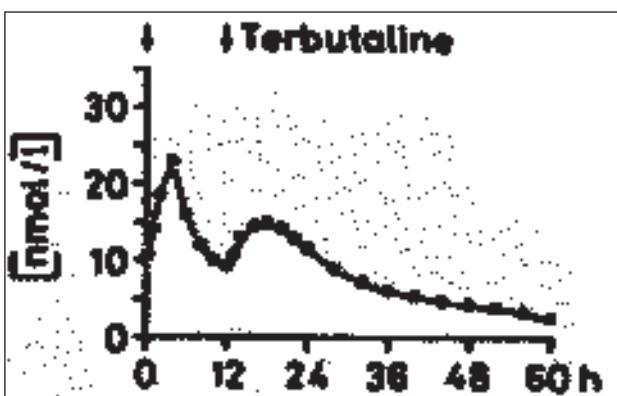


Figure 4. Terbutaline plasma concentrations after a 7-day treatment with oral terbutaline (7.5 mg bid at 7:30 h and 19:30 h, arrows)⁴⁷.

ning than during daytime when asthma is predominantly nocturnal.

Terbutaline sulfate is a very hydrophilic (log *K_d* 3.9) compound and this will influence its distribution⁴⁸. Although plasma protein binding of TBS is low (14-25%), it is bound to erythrocytes and the equilibrium ratios have varied between individuals from 2.0 to 2.6⁴⁹. At steady state, its volume of distribution averages 1.6 l/kg. The volume of distribution exceeding body weights can be taken as an indication of higher affinity to some tissues than to plasma⁴⁴. After intravenous administration, the lung to serum concentration ratio of the unchanged drug was always higher

than unity and increased with time. However, the lung-serum concentration ratio of unchanged terbutaline was about unity after oral administration. When the drug is administered via the air passage, it is retained in the lung for a long period. Higher tissue concentration may be explained by a more rapid clearance of the drug from the blood rather than redistribution from tissues into the blood⁴⁸.

In the literature, a terminal half-life of 2-5 h is usually given for terbutaline after intravenous, subcutaneous and oral administration. It has been claimed that shorter half-lives for terbutaline, as reported in some publications, are due to insufficient sampling periods and lack of sensitive analytical methods, and consequently do not represent the true terminal phase⁴⁵. Recalculation of Fagerströms⁵⁰ data by Nyberg⁴⁴ showed that extrapolation by use of the short half-lives reported in the literature underestimates area under curve (AUC) by 14-20% and area under first moment curve (AUMC) by 57-71% (Figure 5). The deviations in AUC and AUMC will affect the volume-time parameters clearance, mean resi-

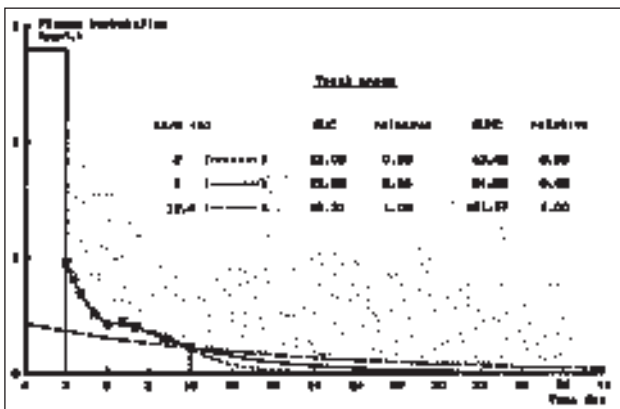


Figure 5. Plasma concentrations of intact terbutaline. The concentrations up to 3 hours have been bulked in to a rectangular area. Results are given from calculations of total areas by use of different terminal half-lives⁴⁴.

dence time and volume of distribution in steady state. The systemic mean residence time of the drug is about 9 h⁴⁴. TBS needs to be administered frequently due to its short biological life (3-4 h). However, such a dosing schedule may be inconvenient for the patients. Therefore, a long-acting TBS formulation is

desirable to improve patient compliance. There are several studies in the literature regarding the prolongation of its release^{9,10,43,51,52}. After administration via the transdermal route, the blood terbutaline level could be maintained at a constant level as reflected in FEV₁ measurements, which remained almost constant for 24 h (Figures 6 and 7)⁵².

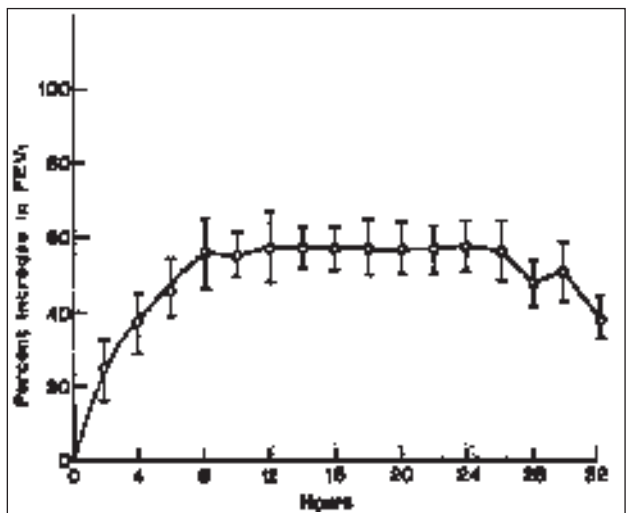


Figure 6. Constant increase in FEV₁ vs time plot following terbutaline patch application⁵².

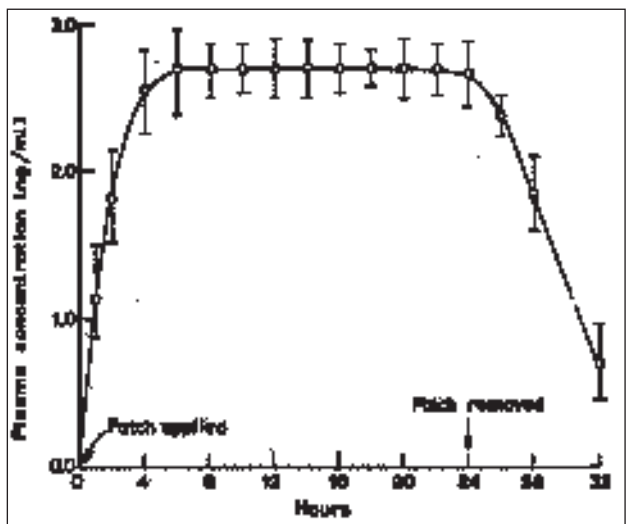


Figure 7. Mean plasma profile of terbutaline following terbutaline patch application⁵².

Nyberg and Kennedy⁵³ compared pharmacokinetic parameters of terbutaline slow-release (SR) tablets after single doses of 5 and 7.5 mg with plain tablets in healthy volunteers (Figure 8). Mean relative bioavailability compared with plain tablets was 76-77%

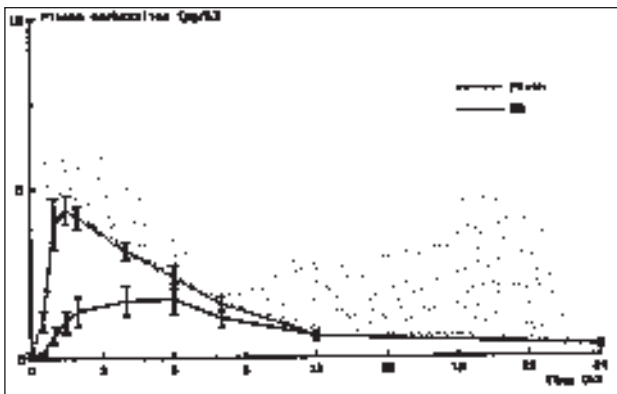


Figure 8. Mean plasma concentrations (\pm SEM) of terbutaline after single doses of 7.5 mg TBS in slow-release (SR) and plain tablets in eight subjects⁵³.

with 7.5 mg SR tablets and 74-80% with those of 5 mg. Variation in bioavailability between and within subjects was the same or smaller with the SR tablets. Despite less frequent dosing, smoother plasma concentration profiles with delayed peaks and the same peak/through concentration ratios as the plain tablets were observed. Although no significant advantages of SR tablets were demonstrated with regard to reduction of objectively measured side effects, they concluded that the main advantage with the SR tablets is the twice-daily dosage regimen. This should increase compliance, facilitate combination therapy with prolonged-action formulations of other drugs and better maintain therapeutic levels during the whole night interval.

Joshi and Misra⁵¹ investigated the drug absorption in rats following intratracheal instillation of terbutaline containing liposomes, and found that absorption prolonged over 12 h. In another study, Palakurthi et al.¹² investigated the disposition kinetics of the free TBS and liposomal TBS preparations in guinea pigs and found that the area under the concentration-time curve AUC_{0-t} with free TBS was 78.58 $\mu\text{g/g/h}$, whereas it was six-fold higher with liposomes (487 $\mu\text{g/g/h}$). Furthermore, in comparison with free TBS, a longer mean residence time was reported with the liposomal TBS formulation (22h vs 11h). Both authors suggested that liposomally encapsulated terbutaline offers a sustained drug concentration profile and can be used for pulmonary delivery for

maximizing the therapeutic efficacy and reducing undesirable side effects^{12,51}.

Recently, prolongation of TBS release from the bovine serum albumin (BSA)¹⁰, PLGA and L-PLA⁹ microspheres was reported. The released amount was decreased with an increase in the crosslinking agent. Biodistribution studies of TBS loaded BSA microspheres indicated that the degree of uptake by the lungs was higher than that of the other organs (Figure 9). Based on these results, the authors suggested that these microparticulate systems can be used for passive lung targeting of TBS.

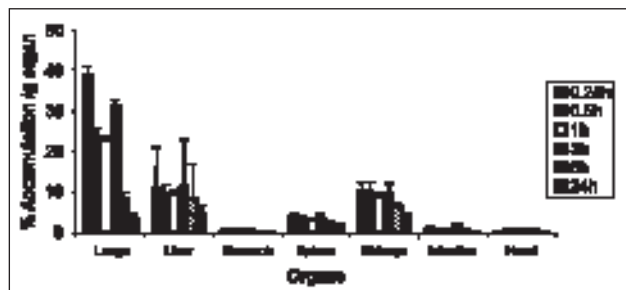


Figure 9. Biodistribution of bovine serum albumin microspheres at various sampling times (0.25, 0.5, 1, 3, 6, 24 hours)¹⁰.

Biotransformation and Elimination

The principle pathway of TBS metabolism is conjugation with sulfuric acid or glucuronic acid⁸. The main metabolite of terbutaline is the sulfate conjugate⁵⁰, which is formed in the liver and, after oral administration, predominantly in the gut wall²⁸. Catechol sulfotransferase plays an important role in the sulfation of terbutaline. Intestinal sulfotransferase accounts for a large part of the presystemic sulfation of terbutaline³⁴. Walle and Walle¹⁴ have shown that the sulfation of terbutaline is stereoselective in human liver cytosol. The rate of sulfation of the (+) enantiomer is greater than that of the (-) enantiomer. In man, the ratio of unchanged terbutaline to conjugate varied with the route of administration. The ratio of 1:0.6 found after intravenous and subcutaneous administration, which changed to 1:4.6 after oral administration, clearly indicates an extensive first-pass metabolism in man⁵⁰. On the other hand, no

detectable biotransformation was noted in the lung⁴⁶.

Following oral administration, approximately 50% of the dose is excreted unchanged in the feces, whereas only 2% of the drug can be recovered following parenteral administration. In a 24-hour collection period, 5.7% of the dose was recovered unchanged in the urine, while 16.8% was recovered as conjugated terbutaline. In a 72-hour collection period, 92% of the dose was recovered with 52% in the feces and 6% in the urine as unchanged terbutaline⁸.

The patterns of metabolism and excretion following intravenous and subcutaneous administration are essentially identical⁸. Over 90% of intravenously injected terbutaline is excreted by the kidneys in man and animals⁵⁴. Only 2% of the drug can be recovered in the feces following parenteral administration⁸. After subcutaneous dosing, approximately 30% of the dose was excreted by glomerular filtration in 12 hours and 40% in 72 hours. Approximately 60% of the administered dose is recovered as unchanged terbutaline in the urine⁸.

Drug Interaction

Terbutaline should not be administered concurrently with other sympathomimetic agents because of the possibility of additive adverse cardiovascular effects. However, an aerosol bronchodilator of the adrenergic stimulant type may be used to relieve acute bronchospasm in patients receiving chronic oral terbutaline therapy³.

Regular use of β_2 -agonists has adverse effects on asthma control due to the cross-talk between cAMP responsive element binding proteins and glucocorticoid receptors. Beta2-agonists interfere with the glucocorticoid receptor function in human bronchial epithelial cells when given simultaneously, with this being overcome by sequential exposure of the cells to first glucocorticoids and later β_2 -agonists⁵⁵. Long-term β_2 AR agonist therapy leads to a desensitization of β_2 AR-mediated cardiovascular and non-

cardiovascular effects in humans in vivo. After a two-week administration of terbutaline, there was a marked and significant attenuation of isoprenaline-induced tachycardia (mean percentage attenuation, 53.3%) and of the isoprenaline-induced decrease in diastolic blood pressure (mean percentage attenuation, 55.6%)⁵⁶.

There is some evidence from animal studies that concomitant administration of terbutaline and a theophylline derivative may produce increased cardiotoxic effects. Although such an interaction has not been established in humans, a few reports have suggested that such a combination may have the potential of producing cardiac arrhythmias. Further clinical data is needed to determine whether this potential interaction occurs in humans³.

Significant synergistic interaction with terbutaline was found for both theophylline (70 or 200 microM), cromakalim (0.1, 0.3 or 1 microM), sodium nitroprusside (30 or 100 nM) and isradipine (1, 3 or 10 nM). Terbutaline can reduce serum-theophylline concentrations by increasing its systemic clearance. This may or may not have clinical implications, as improved clinical scores have still occurred with combined therapy despite the theophylline concentration being lower than when used alone. If respiratory symptoms persist, an increase in dosage may be contemplated while monitoring theophylline side effects and concentration^{35,57}.

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β -agonists, especially when the recommended dose of the β -agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of β -agonists with non-potassium sparing diuretics⁴.

The effects of terbutaline on the vascular system may be potentiated in patients receiving monoamine oxidase inhibitors or tricyclic antidepressants.

Therefore, terbutaline should be administered with caution to patients receiving these drugs^{3,4}.

Conclusions

Terbutaline was the first β_2 -selective adrenoceptor agonist in general clinical use. It exists in a racemic mixture (+ and – terbutaline). Although (-) terbutaline is responsible for β -agonist activity, (+) terbutaline is devoid of such pharmacological activity. Clinically, terbutaline is available in formulations for oral intake, inhalation and injection. Following oral administration, it is subject to extensive first-pass metabolism by sulfate conjugation in the liver and possibly in the gut wall. Hence, its bioavailability is low (10-15%) and also stereoselective. Its prodrugs (ibuterol, bambuterol) can be used to overcome this bioavailability problem. Although it has a wide range of side effects, it is widely used in the treatment of bronchial asthma, chronic bronchitis and emphysema. However, as its use in preterm labor has not been approved, it should not be used without the written consent of the patient.

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