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XOPENEX®: THE BEGINNING OF A NEW TREND IN PHARMACEUTICS OR ALL HYPE ?

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Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.[1] This inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are characterized by reversible airflow obstruction. In the United States more than 11 million people reported an asthma attack in the year 2000, and more than 5 percent of all children younger than age 18 reported having an attack. In 1999, asthma was responsible for 2 million emergency department visits, 478,000 hospitalizations, and 4,426 deaths.[2]

In all forms of asthma, there is some degree of airway inflammation. This inflammation is a result of the infiltration of the airway by inflammatory cells (i.e. eosinophils, activated T cells, mast cells, macrophages, etc.) that cause denudation of the epithelium, deposition of collagen, and hyperplasia and hypertrophy of bronchial smooth muscle. Immunoglobulin E (IgE) binds to mast cells and basophils, signaling the release of histamine and leukotrienes, which results in bronchoconstriction during the acute phase. Mast cells produce interleukin (IL)-1, IL-2, IL-3, IL-4, and IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IF-γ), and tumor necrosis factor-alpha (TNF-α) each of which contributes to acute and chronic inflammation in asthmatic patients.

The initial goals in the treatment of acute asthma are to rapidly reverse airflow obstruction and to correct hypoxemia.[3] Systemic corticosteroids and aggressive use of inhaled β_2-agonists continue to be the cornerstone of therapy for acute exacerbations. Xopenex® (levalbuterol) is the (R)-enantiomer of racemic albuterol and is one of the first in a new trend of pharmaceuticals where a specific stereoisomer is isolated and marketed because it has the potential to be more efficacious or safer than the racemic mixture. Levalbuterol received FDA approval in 1999 for the prevention and treatment of bronchospasm in adults and adolescents 12 years of age and older with reversible, obstructive airway disease. In 2002, levalbuterol received approval for use in children 6 years of age or older.[4] This review will evaluate the evidence supporting levalbuterol's efficacy and safety for the treatment of reactive airway disease.

Mechanism of Action

Levalbuterol activates β_2-adrenergic receptors on airway smooth muscle, leading to the acti-

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Table 1. Mean (SD) values for pharmacokinetic parameters in healthy adults.[5]

	Single Dose	Cumulative Dose		
	Levalbuterol 1.25 mg	Racemic albuterol 2.5 mg	Levalbuterol 5 mg	Racemic albuterol 10mg
C_{max} (ng/ml)	1.1 (0.45)	0.8 (0.41)	4.5 (2.20)	4.2 (1.51)
T_{max} (h)*	0.2 (0.17, 0.37)	0.2 (0.17, 1.50)	0.2 (-0.18†, 1.25)	0.2 (-0.28†, 1.00)
AUC (ng·h/ml)	3.3 (1.58)	1.7 (0.99)	17.4 (8.56)	16.0 (7.12)
$T_{1/2}$ (h)	3.3 (2.48)	1.5 (0.61)	4.0 (1.05)	4.1 (0.97)

T_{max} denotes time to maximum serum concentration. *Median (Min, Max) reported for T_{max}; †A negative T_{max} indicated Cmax occurred between first and last nebulizations.

vation of adenylate cyclase and to an increase in the intracellular concentration of cyclic adenosine monophosphate (cAMP).[4] This increase in cAMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation of smooth muscle in the airways, from the trachea to the terminal bronchioles. Levalbuterol also acts as a functional antagonist by relaxing the airways upon provocation by any number of potential spasmogens, thus protecting against all bronchoconstrictor challenges.

Pharmacokinetics

The inhalation pharmacokinetics of levalbuterol were investigated in a double-blind, crossover, randomized controlled trial in adults and adolescents 12 years of age or older.[5] Thirty healthy adults received a single dose of 1.25 mg and a cumulative dose of 5 mg of levalbuterol and a single dose of 2.5 mg and a cumulative dose of 10 mg of racemic albuterol by nebulization. The drug was administered every 30 minutes for a total of four doses. The pharmacokinetic parameters were determined by noncompartmental analysis and model-fitting. (Table 1) The maximum drug concentration (C_{max}) and area under the curve (AUC) of (R)-albuterol were similar for both levalbuterol and racemic albuterol.

The pharmacokinetic parameters of (R)-albuterol and (S)-albuterol in children, 6 to 12 years of age, with asthma were obtained using population pharmacokinetic analysis.[6] In children, the AUC and C_{max} of (R)-albuterol following administration of 0.63 mg levalbuterol inhalation solution were similar to that of 1.25 mg of racemic albuterol. (Table 2) Following administration of the same dose of 0.63 mg of levalbuterol to children and adults, the predicted C_{max} of (R)-albuterol in children was similar to that in adults, while the predicted AUC was 1.5-fold higher than that in adults. This data supports the use of lower doses in children (6-11 years of age) compared to adults and adolescents.

A comparison of the most clinically relevant inhalation pharmacokinetics demonstrates that there is essentially no difference in onset and duration of action between the two formulations.[7] (Table 3)

Pharmacodynamics

In vitro experiments have compared the binding of (R)-, (S)-, and racemic albuterol to β_1- and β_2-adrenergic receptors in human prostate cells.[8] The results show that (R)-albuterol has a 100-fold greater binding affinity for both types of adrenergic receptors than (S)-albuterol. It has long been thought that (S)-albuterol was pharmacologically inert. This has been disputed given that this assertion is based upon in vitro studies using receptor binding and functional assays, while little is known of the in vivo effects in asthmatic individuals. In isolated smooth muscle cells that (S)-albuterol can promote a cellular influx of calcium. It can also oppose the dose-dependent decrease in calcium that is produced by (R)-albuterol.[9] Other studies have demonstrated that (S)-albuterol decreases the expression and activity of the bronchodilatory pathway involving Gs proteins in vitro and also activates pro-inflammatory pathways involving phosphotidylinositol 3'-OH (PI3) kinase and nuclear factor κB (NF-κB).[10] (R)-albuterol in-

Table 2. (R)-albuterol exposure in adults and pediatric subjects (6-11 years of age).[6]

	Children 6-11 years of age	Adults ≥12 years of age				
	Levalbuterol 0.31 mg	Levalbuterol 0.63 mg	Racemic albuterol 1.25 mg	Racemic albuterol 2.5 mg	Levalbuterol 0.63 mg	Levalbuterol 1.25mg
C_{max} (ng/ml)	0.303	0.521	0.553	1.08	0.56*	1.1†
AUC (ng·h/ml)	1.36	2.55	2.65	5.02	1.65*	3.3†

* The values are predicted assuming linear pharmacokinetics; †These data were obtained from Table 1

hibits airway epithelial cytokine, chemokine and nitric oxide release in vitro, while (S)-albuterol can increase the activity of these mediators, suggesting a possible pro-inflammatory effect.[11] Some in vitro studies have suggested that (S)-albuterol can enhance the contractile effect of spasmogens, while (R)-albuterol can inhibit direct and indirect spasmogen-induced contractions.[12] Other studies have suggested that there are dose-related β_2 responses (i.e. tremor, heart rate, plasma potassium) for (R)-albuterol and racemic albuterol, while (S)-albuterol was similar to placebo.[13] These differences suggest that the (R)-isomer is responsible for the bulk of the pharmacological activity of albuterol.

Clinical Trial Data

The first large scale randomized, double-blind, parallel-group trial enrolled 362 patients with moderate to severe asthma to assess the efficacy and safety of levalbuterol.[14] Eligible patients were nonsmoking males or females 12 years of age or older who had at least a 6-month history of chronic stable asthma (as defined by the American Thoracic Society) requiring pharmacotherapy. Moderate to severe asthma was defined as an FEV_1 between 45% and 70% of the predicted normal value. Patients were allowed to take other medications for asthma or allergic rhinitis if taken as part of a stable regimen; however, this therapy was withheld for an appropriate washout period prior to study visits. All patients were provided with a racemic albuterol metered dose inhaler (MDI) to be used on an as-needed basis for relief of acute asthma symptoms. The mean age of study participants was 36.5 years and 60% were female. Patients were randomly assigned to receive one of 5 treatments 3 times daily for 4 weeks: 0.63 mg levalbuterol, 1.25 mg levalbuterol, 1.25 mg racemic albuterol, 2.5 mg racemic albuterol, or placebo. All active treatment arms resulted in clinically significant improvement (≥15% improvement in FEV_1) immediately after nebulization. The levalbuterol treatment groups had a significantly greater improvement in mean peak FEV_1 than the racemic albuterol groups after the first dose (P=0.03), but not at week 4 (P=0.13). After both the first dose and 4 weeks of treatment, the greatest peak improvement and longest duration of improvement were observed for patients treated with levalbuterol 1.25 mg. The weakest bronchodilator effect and the shortest duration of action were seen in patients receiving racemic albuterol 1.25 mg, which was not significantly better than placebo at week 4. All other active treatment arms were significantly better than placebo at both week 0 and week 4 (P≤0.01). Overall, the rank order of efficacy regarding change in FEV_1 for all analyses was as follows: 1.25 mg levalbuterol > 0.63 mg levalbuterol = 2.5 mg racemic albuterol > 1.25 mg racemic albuterol = placebo. The authors concluded that levalbuterol is approximately 4 times more potent than the 2.5 mg dose of racemic albuterol administered in this study. The study medications were well tolerated with no significant differences in adverse effects across treatment groups.

A large multicenter, randomized, double-blind, controlled trial attempted to establish the efficacy of levalbuterol in 338 children aged 4 to 11 years of age.[6] Selection criteria included a diagnosis of at least mild asthma for ≥60 days before screening and baseline FEV_1 within 40% to 85% of predicted with ≥15% reversibility using racemic albuterol. All eligible patients received 21 days of treatment with levalbuterol 0.31 mg, levalbuterol 0.63 mg, racemic albuterol 1.25 mg, racemic albuterol 2.5 mg, or placebo each administered 3 times daily. All active treatments produced significant improvement in FEV_1. (Table 4) The effect of levalbuterol 0.31 mg on FEV_1 was not signifi-

Table 3. Comparison of inhalation pharmacokinetics for levalbuterol and racemic albuterol[7]

	Onset of Action (mins)*	Time to peak effect (hrs)	Duration of action (hrs)
Levalbuterol 0.63 mg	17	1.5	5
Levalbuterol 1.25 mg	10	1.5	6
Racemic albuterol	5-15	0.5-2.0	2-6

* Defined as ≥15% increase in forced expiratory volume in one second (FEV_1)

cantly different than that of racemic albuterol 2.5 mg at either day 0 or day 21. Clinically significant changes in FEV_1 occurred immediately after nebulization on days 0 and day 21 for all groups except placebo and racemic albuterol 1.25 mg. Levalbuterol 0.31 mg was the only treatment not different from placebo with regards to changes in ventricular heat rate, QT_c interval, and serum glucose. The authors concluded that levalbuterol is 4- to 8-fold more potent than racemic albuterol and exhibits a more favorable safety profile.

Considerable debate has emerged regarding the results of these studies.[15] The 4 to 8 fold difference in potency between levalbuterol and racemic albuterol hass not been universally agreed upon.[14] These trials were designed to assess efficacy and safety compared to placebo, but were not sufficiently powered to compare levalbuterol with racemic albuterol. Doses were near the top of the dose-response curves, and there were no statistically significant differences between doses of the same drug or between different drugs. Conclusions on the relative efficacy of levalbuterol versus racemic albuterol cannot be made due to the lack of statistical power to make this comparison, the lack of a clear dose-response relationship in the active treatment arms, and the presence of an inverse dose-response for levalbuterol. Chowdhurry is not alone as several other authors have voiced concern.[16,17] One group noted that the authors of previous studies failed to address the fact that the (S)-isomer is inactive, and, that in fact previous estimates of the levalbuterol:albuterol potency have been flawed.[17] In addition to these concerns, there were no significant differences in the peak change in FEV_1 after doubling the dose of either levalbuterol or racemic albuterol; therefore, it is not possible to draw conclusions related to relative efficacies of levalbuterol versus racemic albuterol.

Attempts have been made to determine whether or not the in vitro binding assays actually result in clinically significant differences in asthmatics. Lötvall et al sought to compare the bronchodilating and systemic effects of (R)-albuterol and racemic albuterol in a crossover, double-blind, placebo-controlled fashion.[18] Twenty-two patients with a documented history of asthma were randomized to receive (R)-albuterol, (S)-albuterol, racemic albuterol, or placebo for one day in successive fashion. Patients were administered the following doses: (R)-albuterol or (S)-albuterol – 6.25, 12.5, 25, 50, 100, 200, 400, 800, and 1600 μg; racemic albuterol – 12.5, 25, 50, 100, 200, 400, 800, 1600, and 3200 μg. Both (R)-albuterol and racemic albuterol produced significant and dose-dependent increases in FEV_1. There was no plateau at the doses tested. Compared with placebo, (S)-albuterol did not show any consistent effect on FEV_1. At higher doses of (R)-albuterol (≥200 μg) and racemic albuterol (≥400 μg) there were dose-dependent increases in heart rate and decreases in serum potassium. It was determined that (R)-albuterol and racemic albuterol have a 2:1 potency ratio for improvement in FEV_1 in asthmatic patients and that that (R)-albuterol is the pharmacologically active enantiomer. Since half the dose of (R)-albuterol compared with racemic albuterol was required to reach similar bronchodilation, as well as similar systemic side effects on heart rate and plasma potassium level, this tends to support the argument that the (S)-component of racemic albuterol is inert and clinical activity is a function of the (R)-enantiomer.

Recent studies have evaluated the outcome of acute attacks of asthma or COPD following treatment with levalbuterol. A retrospective chart review was performed by Truitt et al. to determine clinical efficacy, patient outcomes, and medical costs in hospitalized patients treated with levalbuterol compared to those treated with racemic albuterol.[19] The length of hospital stay in the levalbuterol group was approximately one day less than

Table 4. Airway function measurements.[6]

Change in FEV_1	Placebo (n=65)	Levalbuterol 0.31 mg (n=70)	Levalbuterol 0.63 mg (n=70)	Racemic 1.25 mg (n=67)	Racemic 2.5 mg (n=66)	P value¶
Day 0						
Median peak change (%)	16.0	27.0*	25.4*	24.2*	26.7*	<0.001
Median time to peak change (%)	118	75*	83*	93*	90*	<0.001
Median change (%), time 0	2.0	19.0*	18.1*	12.4*	15.6*	<0.001
Response (%) at time 0‡	12.3	62.9*†	56.5*	41.8*	54.6*	<0.001
Day 21						
Median peak change (%)	17.9	24.9*	25.7*	22.3*	27.6*	0.02
Median time to peak percent (%)	97	77*	77*	75*	86*	<0.001
Median change (%), Time 0	7.3	17.4*	15.9*	14.4*	16.6*	<0.001
Response (%) at 6ime 0‡	31.2	56.3*	55.2*	47.6*	54.2*	0.02

* P<0.5 vs. placebo; † P<0.05 vs. racemic albuterol 1.25 mg; ‡ Response defined as an improvement of ≥15% from baseline FEV_1: Time 0 is the first FEV_1, completed immediately after nebulization. ¶ P-value denotes treatment versus placebo

those treated with racemic albuterol, and levalbuterol-treated patients required significantly fewer treatments with a β-agonist or ipratropium than did patients treated with racemic albuterol. Significantly more patients were readmitted within 30 days of discharge in the racemic albuterol group compared with the levalbuterol group. Those treated with levalbuterol had a lower mean total cost of nebulizer therapy and lower mean total hospital costs per patient when compared to racemic albuterol. Lastly, regression analysis indicated that levalbuterol was associated with a length-of-stay savings of 0.91 days, a total cost savings of $556, and a decrease in the likelihood of hospital readmission of 67%. Results from this trial must be interpreted in the context of the known limitations of retrospective chart reviews.

The potential of levalbuterol to prevent hospitalizations in the acute management of asthma exacerbations was explored in randomized, double-blind, placebo controlled fashion.[20] Patients 1-18 years of age who presented to the emergency department in an urban tertiary care children's hospital were considered eligible for randomization. A total of 482 patients were selected to receive either 2.5 mg of racemic albuterol or 1.25 mg of levalbuterol every 20 minutes, up to a maximum of six doses. The hospitalization rate was significantly lower in the levalbuterol group than the racemic group (36% vs. 45%, respectively, P=0.02) while the hospital length of stay was not significantly different between the treatment arms.

Adverse Effects

Levalbuterol's pivotal clinical trial systematically collected data on drug-related adverse events in adults and adolescents.[14] (Tables 5 and 6) The events occurred at a similar rate across treatment arms. Other adverse events included nervousness, headache, and tremor. Overall, the study medications were well tolerated.

The following are adverse events, considered potentially related to levalbuterol that occurred in less than 2% of patients: chills, pain, chest pain, EKG changes, hypertension, hypotension, syncope, diarrhea, dry mouth, dry throat, dyspepsia, gastroenteritis, nausea, lymphadenopathy, leg cramps, myalgia, anxiety, insomnia, paresthesia, and ocular itching.

Dosage and Administration

The recommended starting dose of levalbuterol for patients 12 years of age and older is 0.63 mg administered every 6 to 8 hours by nebulization.[4] Those with more severe asthma or those whose response is insufficient may benefit from an increased dose of 1.25 mg three times a day. Patients receiving higher doses should be monitored for systemic adverse effects. Drug compatibility, efficacy, and safety when mixed with other drugs for nebulization has not been established. Safety and efficacy have been established in clinical trials using the PARI LC Jet and PARI LC Plus nebulizers. Safety and efficacy in other nebulizer systems

Table 5. Potential drug-related adverse events.[4]†

	Levalbuterol (n=145)		Racemic albuterol (n=142)		
	0.63 mg	1.25 mg	1.25 mg	2.5 mg	Placebo (n=75)
No adverse effects (%)	12 (6.7)	23 (31.5)	14 (20.6)	20 (27.0)	14 (18.7)
Asthma*	5 (6.9)	4 (5.5)	5 (7.4)	6 (8.1)	7 (9.3)
Asthma increase*	1 (1.4)	3 (4.1)	2 (2.9)	2 (2.7)	2 (2.7)
Nervousness	2 (2.8)	7 (9.6)	3 (4.4)	6 (8.1)	0 (0.0)
Tremor	0 (0.0)	5 (6.8)	0 (0.0)	2 (2.7)	0 (0.0)
Headache	3 (4.2)	4 (5.5)	2 (2.9)	2 (2.7)	3 (4.0)
Tachycardia	2 (2.8)	2 (2.7)	0 (0.0)	2 (2.7)	0 (0.0)
Leg cramps	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	1 (1.3)
Anxiety	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	1 (1.4)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)

*Undefined. † Events listed are those reported by 2% or more of patients in any treatment group.

has not been established.

The recommended dosage of levalbuterol for patients 6-11 years of age is 0.31 mg administered three times daily, by nebulization. In children, routine dosing should not exceed 0.63 mg three times a day. Maximum daily dosage should not exceed 3.75 mg per day via oral inhalation in adults and adolescents 12 years of age or older, or 1.89 mg per day for children 6-11 years of age. The safety and efficacy of levalbuterol in children less than 6 years of age has not been determined.

Drug Interactions

Other short acting sympathomimetic bronchodilators and epinephrine should be used with caution with levalbuterol.[4] β-adrenergic receptor blocking agents can antagonize the pulmonary effects of β-agonists or precipitate bronchospasm. Patients with asthma should not be treated with β-blockers unless there are compelling indications, such as post myocardial infarction or heart failure. If a β-blocker must be used, a cardioselective agent (eg, metoprolol, atenolol, bisoprolol) is preferred. Diuretics (non-potassium sparing) administered along with levalbuterol may potentiate alterations in potassium homeostasis (i.e., hypokalemia); the clinical significance of this interaction is not clear. The concomitant administration of digoxin and racemic albuterol resulted in a mean decrease of 16-22% in serum digoxin levels in healthy volunteers. The clinical significance is unclear, but it is prudent to carefully evaluate serum digoxin levels in patients receiving levalbuterol. Levalbuterol should be administered with extreme caution to patients who are using monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs), or within two weeks of discontinuing such agents.

Cost

The average cost of levalbuterol for inhalation 0.63 mg/3 ml and 1.25 mg/3 ml is $2.27 per unit or approximately $204 per month if dosed three times daily.[21] This is based upon a survey of national community pharmacy prices. Price comparison can be difficult due to differences in dosage and packaging, but the price of levalbuterol is approximately 3-4-fold greater than racemic albuterol. Table 7 depicts a summary of retail prices from several pharmacies located in Gainesville, FL. In general, the average price per unit (3 ml vial) of albuterol is $0.94 while levalbuterol 1.25 mg is $3.16 and levalbuterol 0.63 mg is $3.22.

Summary

Asthma is a major health problem in the United States, affecting millions of people and resulting in significant morbidity and mortality and a reduced quality of life. Levalbuterol is one of the

Table 6. Mean change from baseline in heart rate (15 min.) and glucose and potassium (60 min.) in patients ≥12 years.[4,14]

	Mean Changes (day 1)		
	Heart rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Levalbuterol 0.63 mg (n=72)	2.4	4.6	-0.2
Levalbuterol 1.25 mg (n=73)	6.9	10.3	-0.3
Racemic albuterol 2.5 mg (n=74)	5.7	8.2	-0.3
Placebo (n=75)	-2.8	-0.2	-0.2

first of a new trend in pharmaceutics where a specific isomer has been isolated and marketed. The motivation for developing certain enantiomers has been the desire to improve efficacy and reduce adverse effects. The (S)-isomer is responsible for airway hyperreactivity and decreased efficacy of racemic albuterol if administered on a regular basis. While several studies have demonstrated the therapeutic bronchodilating action is the result of the (R)-isomer, the improved efficacy and possible advantages over racemic albuterol is subject to debate due to study design and conflicting results. The (S)-isomer may also be responsible for adverse effects associated with racemic albuterol, but the data again has proven conflicting on this matter. In the United States, the price of levalbuterol is several times more expensive than generic racemic albuterol. There is a lack of studies proving that the increased drug costs associated with levalbuterol use is offset by decreased downstream medical costs associated with hospitalization, etc. Until this question is settled, there will always be debate as to whether or not its use is justified as first line therapy or if it should be reserved as an alternative for those who suffer adverse effects with racemic albuterol.

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Table 7. Phone survey of drugs costs in selected Gainesville area pharmacies

Drug	Dose	Pharmacy #1	Pharmacy #2	Pharmacy #3	Pharmacy #4	Average
Albuterol	2.5 mg/3 ml	$25.99/25 vials	$26.09/25 vials	$27.99/25 vials	$13.84/25 vials	$23.48
Levalbuterol	1.35 mg/3 ml	$70.99/24 vials	$80.99/24 vials	$77.95/24 vials	$73.34/24 vials	$75.82
Levalbuterol	0.63 mg/3 ml	$75.99/24 vials	$80.99/24 vials	$78.95/24 vials	$73.34/24 vials	$77.32

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Ibandronate (Boniva™), an oral bisphosphonate, has been approved as a once monthly option for the prevention and treatment of postmenopausal osteoporosis. It is the first oral drug for a chronic disease approved in a once monthly dosage form. Boniva had previously been approved for once daily use but was never marketed in the United States. The dose is 150 mg on the same day once each month for both prevention or treatment. If a dose is missed, patients can be counseled to take Boniva™ on the first morning they remember, provided the next dose is not scheduled within the next 7 days. The previous dosing schedule should then be resumed. Boniva™ should be taken on an empty stomach with 6-8 ounces of water immediately upon waking and patients must remain upright for at least 1 hour.

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