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A twelve month comparison of salmeterol with salbutamol in asthmatic patients

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on behalf of a European Study Group

A twelve month comparison of salmeterol with salbutamol in asthmatic patients. M.G. Britton, J.S. Earnshaw, J.B.D. Palmer.

ABSTRACT: The efficacy and tolerability of salmeterol, 50 μg *b.i.d.* was compared for three months with salbutamol, 200 μg *q.i.d.*, administered from metered-dose inhaler. For the following nine months, safety and clinic lung function was monitored on salmeterol, 50 μg *b.i.d.*, compared with salbutamol, 200 μg *b.i.d.* This comparison was made in a multicentre, double-blind, parallel-group study of 667 moderate asthmatics, who had a forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR) >50% predicted, a 15% reversibility to inhaled salbutamol and who were experiencing symptoms.

Throughout the first three month treatment period, both morning and evening PEFR were significantly higher on treatment with salmeterol than salbutamol (mean differences between the treatments 30 $l \cdot min^{-1}$ for morning, $p<0.001$, and 11 $l \cdot min^{-1}$ for evening, $p<0.01$). In addition, the diurnal variation in PEFR, nocturnal and daytime symptoms and use of additional salbutamol were significantly lower in the salmeterol treated group. This improvement was also apparent in the separate subpopulations of patients taking no concurrent glucocorticosteroid or concurrent inhaled and/or oral glucocorticosteroids.

Both treatments were well-tolerated throughout the 12 months of treatment. There was a lower incidence of asthma and related events during salmeterol treatment compared to salbutamol treatment subgroups. The results of the study clearly demonstrate that salmeterol, 50 μg *b.i.d.*, is well-tolerated and more effective than salbutamol, 200 μg *q.i.d.*, in the treatment of moderate asthma.

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Salmeterol is a N-aralkyloxyalkyl analogue of salbutamol [1] and, in preclinical studies, has been shown to have at least a 10–12 h duration of bronchodilator action *in vitro* [1] and *in vivo* [2]. In humans, salmeterol has been shown, in single-dose studies of 25–100 μg, to have a duration of action of at least 12 h with a similar side-effect profile to 200 μg of salbutamol [3, 4]. In addition, one month dosing with salmeterol *b.i.d.* in 692 patients with mild to moderate asthma demonstrated a dose-related increase in morning and evening peak flow, as well as reduction in daytime symptoms, nocturnal wakening and use of additional salbutamol [5].

In this study, a dose of 50 μg *b.i.d.* of salmeterol over one year, was compared in terms of efficacy and safety to salbutamol in mild to moderate asthmatic patients.

Methods

Patients and Materials

A total of 796 patients aged at least 18 yrs with a clinical history of moderate asthma, were recruited at 62 centres in 13 European countries. Regulatory and Ethics Committee approval were obtained in all countries and centres and all patients provided informed consent. Male and female patients (who were neither lactating, pregnant or likely to become pregnant) were included. Patients were excluded if they had a lower respiratory tract infection, required a maintenance dose of oral prednisolone of >20 $mg \cdot day^{-1}$ or had been hospitalized for any aspect of their asthma in the 14 days prior to the trial.

At the first visit, any beta-receptor agonists, methylxanthines or anticholinergics were withdrawn and replaced with a salbutamol metered-dose inhaler (100 μg per actuation), which was to be used for symptomatic relief only. Continued therapy with inhaled glucocorticosteroids, oral glucocorticosteroids at doses of <20 $mg \cdot day^{-1}$ of prednisolone, sodium cromoglycate, nedocromil and/or ketotifen were allowed, providing that the doses remained unchanged. During the two week run-in period (baseline), patients completed diary cards detailing, with the aid of a mechanical counter, the number of actuations of salbutamol required day and night.

In addition, they recorded three peak flow measurements every morning and evening before taking any medication, the number of nocturnal awakenings due to asthma, and estimated the extent of their daytime symptoms using a 0 (no symptoms) to 5 (disabling symptoms) scale. At the end of the run-in period, 667 patients who fulfilled the following inclusion criteria: had a forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR) of >50% predicted; a >15% reversibility in FEV_1 to 200 μg inhaled salbutamol; and either a symptom score of two or more, or a diurnal variation in PEFR of >15%, on four out of the last seven days of the run-in period, were randomized for treatment.

Protocol

The study was of a randomized, double-blind, double dummy, parallel-group design throughout the full year of therapy. During the first three months, diary card measures of efficacy and the safety of salmeterol, 50 μg *b.i.d.*, and salbutamol, 200 μg *q.i.d*, given by identical metered-dose inhalers, were compared.

For the subsequent nine months, lung function, measured in the clinic, and the safety of salmeterol, 50 μg *b.i.d*, and salbutamol, 200 μg *b.i.d.*, were compared. All patients also received salbutamol metered-dose inhalers for symptomatic relief. In addition, they continued their other medication at the same dose as during the run-in period, unless a temporary change in glucocorticosteroids was required to treat any exacerbations of asthma.

Throughout the first three month period, patients completed diary cards recording the same parameters as in the run-in period. For the remaining nine months, patients completed only weekly record cards, recording compliance, additional medication, use of rescue salbutamol and adverse events. Patients also attended the clinic at regular intervals throughout the 12 month period to record any changes in medication, intercurrent illnesses, adverse events or withdrawals. In addition, lung function, blood pressure and heart rate were measured, blood and urine samples taken, and electrocardiograms (ECGs) recorded at the beginning and after 3 and 12 months of treatment.

Statistical analysis

Data from all patients randomized to treatment were used in the analysis of efficacy on an "intend to treat" basis. Assuming a residual standard deviation in morning and evening PEFR of 50 $l \cdot min^{-1}$, it was estimated that a total of 600 evaluable patients would give the study a power of 0.96 to detect a mean difference of 15 $l \cdot min^{-1}$ (this assumes the use of two-sided t-tests conducted at the 5% significance level). To be included in the analysis of a variable, patients were to have at least four days data from the second run-in week and at least 14 days data from the treatment phase. For each patient the mean PEFR in the morning and evening was calculated, together with the mean difference between the treatment groups. These measurements, obtained during treatment, were compared to those recorded in the second week of the run-in period, using analyses of covariance. The mean morning, evening and diurnal variations in predicted PEFR were calculated for each week and for four periods of assessment (weeks 1–4, 5–8, 9–12 and 1–12). These were compared to the second week of the run-in period (baseline) and between each treatment adjusting for baseline and centre variation. The patient's age and sex were also accounted for in the analysis.

Changes in the proportion of nights with no additional salbutamol, proportion of days with no additional salbutamol, additional actuations of nocturnal salbutamol and additional actuations of daytime salbutamol, during treatment, were analysed using Wilcoxon rank sum test. The median daytime and nocturnal asthma scores were analysed by the logistic regression method [6].

Analysis of different doses of steroid

A further analysis was performed to investigate the patient response to salmeterol whilst on different doses of inhaled or oral corticosteroid. Steroid usage of a patient was assessed by determining whether or not a patient was receiving and continuing to receive any form of corticosteroid at the start of the treatment period (Visit 3). Those on glucocorticosteroids were divided into three groups: a) inhaled steroids (<1,000 μg a day); b) inhaled steroids (>1,000 μg a day); and c) on regular oral glucocorticosteroids (table 1).

Asthma exacerbation rates in both treatment groups were also analysed. An exacerbation being defined as any worsening of an asthma symptom, recorded as an adverse event, that required a change in prescribed asthma therapy other than relief β_2-agonists.

Results

Of the 667 patients randomized to treatment, 334 received salmeterol and 333 received salbutamol. The majority of the 129 patients who were withdrawn before randomization did not fulfil the inclusion criteria for the study. The treatment groups were well-matched for all demographic details (table 1) except for sex, where there were more females than males receiving salmeterol compared to salbutamol.

The primary reasons for withdrawal after randomization were similar in the two treatment groups; being asthma and poor compliance with the protocol. During the first 3 months, 33 patients in the salmeterol group and 37 in the salbutamol group withdrew. During the last 9 months, a further 32 in the salmeterol group and 31 in the salbutamol group withdrew.

The difference between the baseline PEFR values in the two treatment groups was due to the patient's sex, age, and height and was accounted for in analysis.

Table 1. – Patient demography

			Salmeterol	Salbutamol
Patients n			334	333
Sex n (%)	M		151 (45)	181 (54)
	F		183 (55)	152 (46)
Age yrs (range)			49 (18–81)	49 (18–79)
Smoking history n (%)	Yes		45 (15)	49 (14)
	No		180 (50)	166 (53)
	Ex		109 (35)	118 (34)
Mean FEV_1 *l*			2.10	2.18
Baseline PEFR am/pm $l \cdot min^{-1}$			336/369	356/387
Concurrent medication				
Glucocorticosteroids n(%)	Oral		49 (15)	47 (14)
	Inhaled	High >1000 $\mu g \cdot day^{-1}$	117 (35)	128 (38)
		Low <1000 $\mu g \cdot day^{-1}$	96 (29)	78 (23)
	None		72 (22)	80 (24)

FEV_1: forced expiratory volume in one second; M: male; F: female.

During the first three months of treatment, salmeterol resulted in significantly higher increases over the run-in values in mean morning PEFR (mean differences between treatments 30 $l \cdot min^{-1}$, 95% confidence interval (95% CI): 24 to 37 $l \cdot min^{-1}$, $p<0.001$) and evening PEFR (mean differences between treatments 11 $l \cdot min^{-1}$, 95% CI: 5 to 17 $l \cdot min^{-1}$, $p<0.001$) compared with salbutamol (fig. 1). Diurnal variation in PEFR was reduced in the salmeterol group to a mean of 13 $l \cdot min^{-1}$ over the three months, whereas in the salbutamol group the mean value was unchanged at 30 $l \cdot min^{-1}$, a difference between the treatments which was statistically significant (95% CI: -22 to -15 $l \cdot min^{-1}$ ($p<0.001$). Figure 2 shows that the improvement in mean morning PEFR on salmeterol treatment compared with salbutamol was independent of the patients' use of concurrent inhaled or oral glucocorticosteroids.

Symptom Scores

This influence on PEFR was also reflected in the symptomatic improvement during both the day and night. In the daytime, the median percentage of days per week with a symptom score of <2 was significantly increased in the salmeterol group (to 92.9%) compared to the salbutamol group (to 83.3%) ($p=0.029$), and this was reflected in a reduction in the requirement for additional rescue salbutamol. In the salmeterol group, the increase in percentage of days with no additional salbutamol was also significantly higher (83.3%) compared with salbutamol (50%), $p<0.001$.

The percentage of nights when patients awoke due to asthma fell to a weekly median of zero for the salmeterol treated group, which was significantly better than that for patients on salbutamol (fig. 3, $p<0.001$).

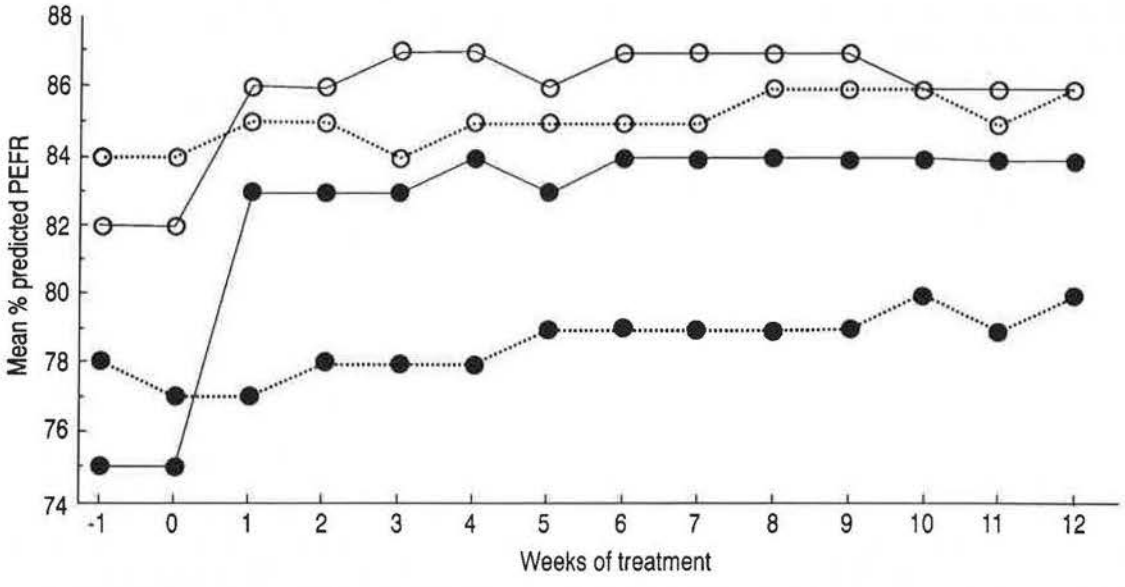

Fig 1. – Shows the morning (closed circles) and evening (open circles) PEFR (*l*) during 3 months therapy with salmeterol (50 μg *b.i.d.*) and salbutamol (200 μg *q.i.d.*). Vertical axis has been below 74% predicted. PEFR: peak expiratory flow rate. —●—: salmeterol (am); ·····●····· : salbutamol (am); —○— :salmeterol (pm); ·····○····· :salbutamol (pm).

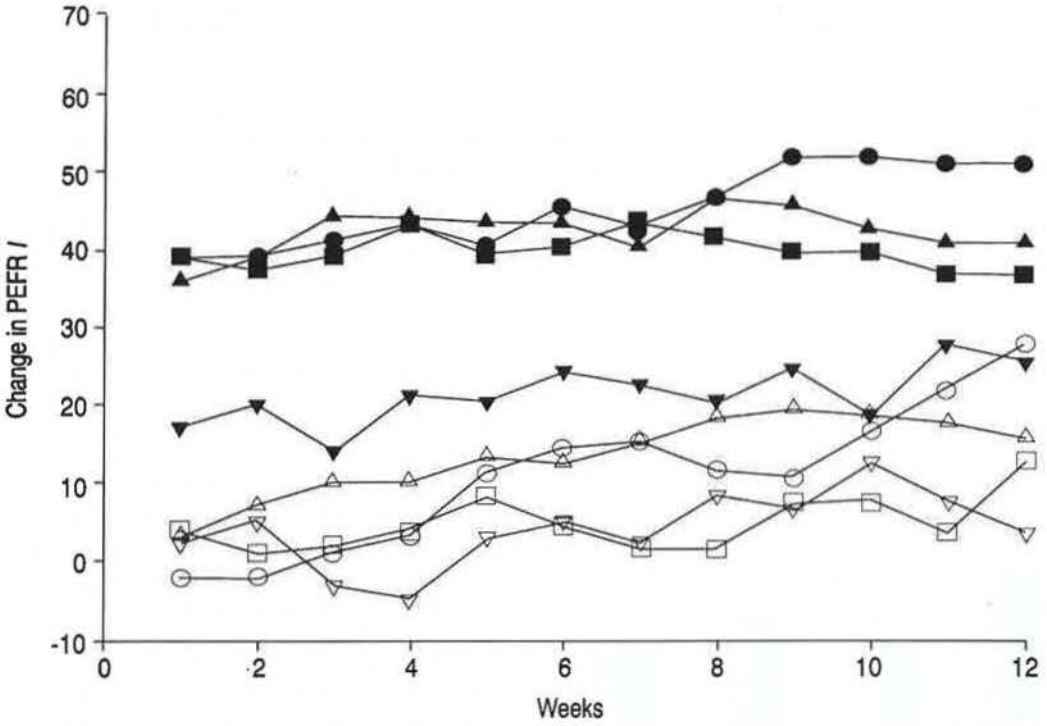

Fig. 2. – Changes in morning PEFR for salmeterol, 50 μg *b.i.d.*, (closed symbols) and salmeterol, 200 μg *q.i.d.*, (open symbols), for patients on no concomitant glucocorticosteroid (○●), <1 mg inhaled glucocorticosteroid (□■), >1 mg inhaled glucocorticosteroid (Δ▲) and oral glucocorticosteroid (∇▼). PEFR: peak expiratory flow rate.

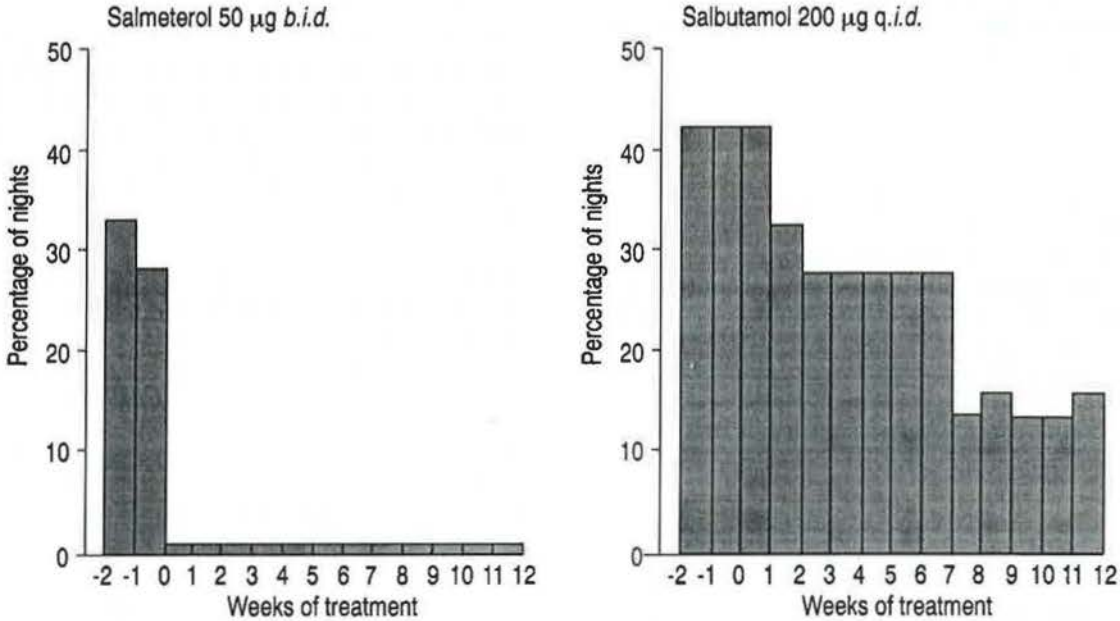

Fig. 3. – Median percentage of nights with awakening due to asthma during three month therapy with salmeterol, 50 μg *b.i.d.*, (left panel) and salbutamol, 200 μg *q.i.d.*, (right panel). Median differences salmeterol-salbutamol, weeks 1–12, p<0.001.

In addition, the median percentage of nights when patients did not require any additional rescue salbutamol rose from 71.4% in the run-in period to 100% on salmeterol, and from 57.1% in the run-in period to 85.7% on salbutamol treatment, a difference between the treatments that was statistically significant (p<0.001)

Clinic lung function

For both treatments, improvements were measured in "clinic visit" lung function data throughout the twelve month treatment period; however, these improvements were greater in the salmeterol group (increases in FEV_1 from baseline to after three months treatment of

2.1 *l* to 2.4 *l* and 2.2 *l* to 2.4 *l* for salmeterol and salbutamol, respectively, (mean difference salmeterol - salbutamol: 0.08 *l*, 95% CI: 0 to 0.16, p=0.04). The proportion of patients experiencing an asthma exacerbation during each of the three monthly intervals did not increase with increasing duration of treatment (fig. 4). In addition, there were more withdrawals due to asthma in the salbutamol group (15 patients, 4.5%) than in the salmeterol group (9 patients, 2.6%).

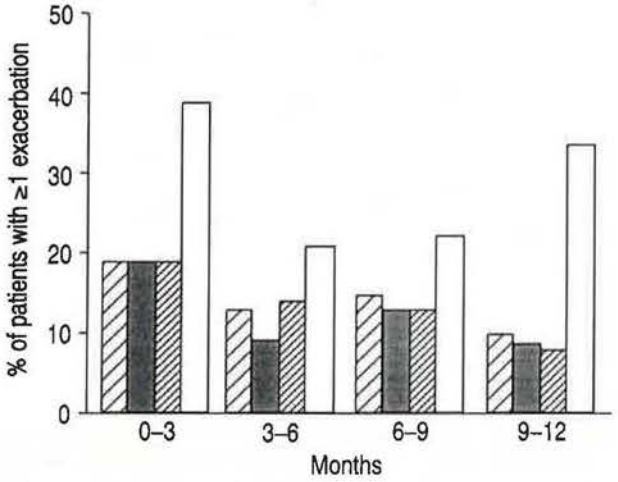

Fig 4. – Percentage of patients with at least one exacerbation during a year's therapy with salmeterol, 50 μg *b.i.d.*, for patients taking no concomitant glucocorticosteroid (▨); <1 mg inhaled glucocorticosteroid (■); >1 mg inhaled glucocorticosteroid; (▨); oral glucocorticosteroid (□).

Safety

Both treatments were well-tolerated throughout the 12 month study, the most common adverse event being asthma, which was not significantly different between the groups, 35% on salbutamol and 32% on salmeterol. The number of pharmacologically predictable adverse events was low for both treatments; muscle cramp (5.4 and 1.8%), subjective tremor (3.6 and 2.1%), palpitations (3.9 and 1.8%), tachycardia (0.6 and 0.9%), and headache (12.3 and 12.9%) for the salmeterol (n=334) and salbutamol (n=333) groups, respectively.

Two patients died during the year of the study, one from a stroke caused by a glioma in the left midbrain after ten months treatment with salmeterol and one from septicaemia and renal failure following an oesophagectomy for an adenocarcinoma after six months treatment with salbutamol.

The incidence of changes in biochemical and haematological parameters to values outside the normal range during the 12 months was similar in the two groups, and in no case were these of any major clinical significance.

There was no change in systolic or diastolic blood pressure or pulse rate during the treatment period. There were no clinically significant changes in ECGs documented during either treatment.

Discussion

The efficacy and safety of salmeterol, 50 μg *b.i.d.*, and salbutamol, 200 μg *q.i.d.*, was evaluated in 667 patients with moderate asthma. Salmeterol treatment produced a greater increase in PEFR and clinic lung function which was associated with a reduction in symptoms scores, nocturnal awakening and additional bronchodilator use. Both treatments were well-tolerated, with a similar incidence of exacerbations of asthma in patients in the two treatment groups.

Nocturnal asthma is a common symptom of poorly controlled asthma and is not prevented by short acting beta$_2$-agonists. In a recent study, 73% of asthmatics woke with asthma at least once a week and 39% woke nightly [7]. In patients receiving salmeterol there were significant improvements in all nocturnal efficacy variables measured, which indicates the superior control of symptoms with this longer acting drug. Daytime symptoms were also better controlled in patients receiving salmeterol, compared to those using regular salbutamol.

The improvement in all the efficacy response variables with salmeterol occurs during the first week of treatment and all of these improvements with salmeterol were maintained throughout the three month treatment period. In addition, lung function measured at each clinic visit was maintained throughout the 12 month period at levels obtained during the first three months of treatment.

When the patients were subdivided by glucocorticosteroid use, the beneficial effects of salmeterol were found in all groups indicating that the benefit was not dependent on glucocorticosteroid use. In the more severe population taking oral glucocorticosteroids, salmeterol showed significant benefit over salbutamol, although the extent of the improvement in morning PEFR was not as great as seen in the groups taking inhaled or no concurrent glucocorticosteroids. However, in more severe asthmatics [8], there is benefit in increasing salmeterol to 100 μg *b.i.d.*

The rate of exacerbations was not different between the two treatment groups. In addition the number of patients experiencing an asthma exacerbation was similar irrespective of the concurrent glucocorticosteroid therapy used. The rate of exacerbations fell rather than increased during the 12 month therapy, suggesting that the regular use of salmeterol is not associated with worsening asthma.

Both treatments were extremely well-tolerated, with a similar incidence of adverse events reported in both treatment groups. The incidence of pharmacologically predictable side-effects was generally low with both treatments (25.7% in the salmeterol group and 19.5% in the salbutamol group).

In conclusion, the results of our study suggest that regular inhaled salmeterol, 50 μg *b.i.d.*, is well-tolerated and more efficacious than inhaled salbutamol, 200 μg *q.i.d.*, in the treatment of moderate asthma. Furthermore, improvements in lung function were maintained throughout the 12 month study period,

there is no evidence of deterioration of asthma control from the long-term administration of inhaled salmeterol or inhaled salbutamol irrespective of concurrent glucocorticosteroid use.

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