

Sodium Fluoride Improves Methacholine Induced Bronchoconstriction Similar To Salbutamol In Patients With Asthma

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Citation

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Abstract

Study objectives: In vitro studies have shown that sodium fluoride (NaF) has a bronchodilatory effect. The aim of this work was to compare the bronchodilatory effects of nebulized NaF and the B₂- agonist salbutamol.

Setting and participants: Fifty eight patients were selected. Forced expiratory volume measurements were performed before and after a bronchial challenge with methacholine. Methacholine challenge continued until the FEV₁ dropped by at least 20%. Patients were randomized to 3 groups, after the bronchial challenge one group inhaled a solution of NaCl 0.9%, another NaF 0.5M for 2 minutes, the third 200 µg salbutamol. FEV₁ were measured 5, 10 and 20 minutes and one hour afterwards.

Results: Both NaF and salbutamol significantly increased FEV₁ by the same amount compared to control ($p < 0.05$).

Conclusion: It appears that NaF and salbutamol have similar bronchodilatory effects when used as bronchodilators after methacholine challenge testing.

INTRODUCTION

NaF is an inhibitor of enolase (Zhao et al. 2002), an enzyme of the glycolysis pathway leading to phosphoenolpyruvate. NaF had been shown to induce bronchial relaxation on precontracted bovine bronchi in vitro (Zhao and Guénard 1997) and in rats in vivo (Zhao et al. 2002). Oral NaF was initially examined in the treatment of osteoporosis (Charles et al. 1989). Cushing et al. 1990, found that NaF relaxed arteries by releasing an endothelium derived relaxing factor and one or more prostanoid (Cushing et al 1990). In Tunisia, where this research was conducted, NaF is an abundant mineral and could be a useful and inexpensive tool for the treatment of asthmatics.

The aim of the study was to compare the effectiveness of NaF as a bronchodilator to the commonly used beta₂-agonist salbutamol in asthmatic patients challenged with methacholine. In this experiment, salbutamol was used as the positive control and isotonic saline was used as a negative control.

METHODS

The research protocol was approved by the institutional ethics committee of Farhat Hached hospital in Sousse (Tunisia) and was in accordance with the recommendations found in the 1975 Helsinki Declaration. Eighty patients were sent by physicians for a routine respiratory testing. Fifty eight asthmatic patients were selected for the study after a response to a standardized questionnaire and a written informed consent obtained from each patient. Exclusion criteria were: age less than 20, pregnancy, cigarette smoking, renal failure, heart failure and coronary disease, current desensitization, alcohol abuse. Patients having received beta-agonists, glucocorticoids, anti-histamines, anticholinergics, calcium, magnesium and beta-blockers over the previous 48 hours were also excluded. Patients were considered asthmatic if they had had intermittent dyspnoea and wheezing which responded to beta agonist inhalations not solely occurring during respiratory tract infection. Patients were randomized into three groups receiving three different products (NaCl 0.9%, beta₂ agonist and NaF 0.5M). Twenty two received beta 2 agonist, 18 received NaCl 0.9% and 18

inhaled NaF after a methacholine challenge.

A daily calibrated portable spirometer (Pal, Mediprom, Japan) was used for all tests. The same researcher conducted each test. Baseline FEV1 was measured first. The patient was asked to perform at least three consecutive manoeuvres with two of the best FEV1 measurements differing by less than 5%. A methacholine challenge test was then carried out with increasing doses of methacholine while maintaining a constant duration of inhalation (one minute, tidal breathing). The results were expressed as a percentage of the baseline FEV1.

The aerosol of methacholine (Allerbio, Lavarene, France) was generated by a calibrated jet nebulizer (Mediprom FDC 88 – Paris France). A DeVilbiss nebulizer (Ref 123016 Marquette Medical products, Englewood Co. USA) was used for the treatments with saline, NaF, and salbutamol. NaF was purchased from Prolabo (Paris, France) and prepared in our laboratory. Firstly dilution was done: 50ml NaCl 0.9% + 1.05g NaF to obtain a 0.5M NaF solution. Then, the solution was filtered with a single use filter unit (Millipore MF membrane for sterilization of aqueous solution, 0.22µm). The tidal breathing method was used for aerosol inhalation. Methacholine challenge was stopped when there was a 20% or greater decrease from baseline in FEV1 (PD20). One of three inhaled treatments was used to reverse the methacholine challenge testing, either saline, NaF, or salbutamol. The first group of patients (G1, N=18) inhaled a saline solution at 0.9%. The second group (G2, N=18) received NaF at a 0.5M concentration, and the third group (G3, N=22), received two puffs of salbutamol (200µg). Reversibility of bronchoconstriction was considered significant when FEV1 increased by 12% and 200ml according to the criteria of the American Thoracic Society [ATS]. Repeated measures of the FEV1 were performed at 0, 5, 10, and 20 minutes after the end of the inhalations and before leaving the laboratory one hour later. If there was no improvement after 20 minutes of the nebulized NaCl and NaF, an inhaled beta2 agonist was given.

Statistical analysis was carried out using the SPSS statistical package. Non parametric statistic tests were used to compare different group results (Kolmogorov-Smirnov two-sample test, Kruskal-Wallis ANOVA by Ranks). A Wilcoxon matched pairs test was used for comparing two dependent samples (FEV1 of the same group of patients was compared at different times: 0, 5, 10, 15 and 20 minutes). For all tests a

p-value of <0.05 was considered significant.

RESULTS

The baseline characteristics of the patients are given in table 1. The three groups were similar in terms of anthropometric characteristics (age, gender, height and weight). All patients had no smoking history.

Figure 1

Table 1: Characteristics of the asthmatic patients studied

	Number	Gender (M/F)	Age (year)	Weight (Kg)	Height (cm)	FEV1 (%)
NaF 0.5M	18	14/4	30 ± 10	70 ± 9	168 ± 9	85 ± 12
NaCl	18	13/5	28 ± 12	69 ± 15	166 ± 8	87 ± 15
Salbutamol	22	16/6	32 ± 10	70 ± 10	160 ± 8	84 ± 9

%FEV1: percentage of predicted value of baseline forced expiratory volume in one second.
M: male
F: female

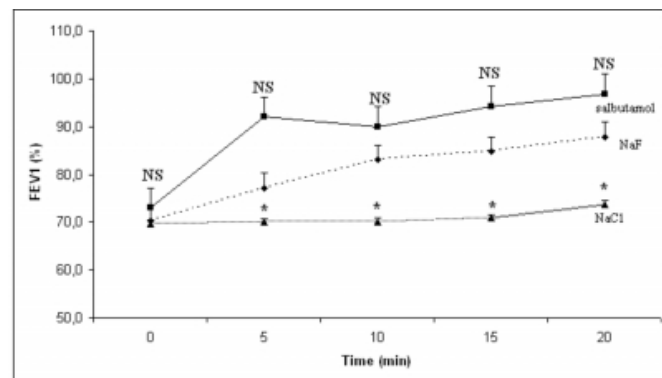
Patients from the three groups had a comparable FEV1 after inhalation of methacholine ($p>0.05$, Kolmogorov-Smirnov Two-sample test) with a mean PD20 of 1.02mg.

A significant increase in FEV1 was observed in patients from the 5th minute after inhalation of NaF ($p<0.05$; $Z=2.20$; Wilcoxon test.) but not in patients after inhalation of NaCl. FEV1 increase after NaF was not significantly different to the one obtained with salbutamol at the 5, 10, 15, and 20 min after inhalation either drugs ($p>0.05$; Kolmogorov-Smirnov test) (Figure 1). The effect of NaF persisted over the 20 minutes observed. Indeed, FEV1 obtained with NaF at 10, 15 and 20 minutes was not different from the FEV1 at the 5th minute ($p<0.05$; Wilcoxon test).

A significant increase in FEV1 was observed 5 minutes after inhalation of NaF ($p<0.05$; Kruskal-Wallis ANOVA by Ranks, 1 d.f but not after inhalation of NaCl. The increase in FEV1 after NaF was not significantly different to the one obtained with salbutamol at the 5, 10, 15, and 20 min after inhalation either drugs ($p>0.05$) (Figure 1). All patients left the laboratory with a FEV1 measured at more than 80% of the original level. Three patients in the NaF group needed salbutamol before leaving, as did all patients having received NaCl (given at the 20th minute).

Figure 2

Figure 1: Effect Of NaCl, NaF And Beta2-Agonists On Airway Obstruction



■ NaF 0.5M ▲ Salbutamol ● NaCl — standard error of the mean bar
 NS : p>0.05, at the 0, 5, 10, 15 and 20th minute there were no differences between FEV1 obtained with NaF and Beta2agonist (Kolmogorov – Smirnov test).
 * : p<0.05, significant differences are present between the FEV1 obtained with either NaF or salbutamol and NaCl at the 5th, 10th, 15th and 20th minute (Kolmogorov – Smirnov test).

DISCUSSION

The two main findings that can be drawn from this study are: 1) NaF induces a significant increase in FEV1 in asthmatic patients challenged with an acetylcholine derivate, and 2) the reversibility obtained with NaF and salbutamol are not significantly different.

The patients included in the three groups were largely homogenous; They were asthmatic, with no significant difference in their methacholine sensitivity, similarly aged, had the same clinical symptoms, and were on no current treatment.

In the present study treatment with NaF led to an increase in FEV1 similar to salbutamol. Salbutamol inhibits bronchoconstriction by stimulating beta2–adrenoceptor (beta2-receptors) located in bronchial smooth muscle. Usually beta2–adrenoceptor agonists (beta2-agonists), such as salbutamol, are characterized by a rapid response but a relatively short duration of action (Sears and Lotvall 2005). In case of acute asthma, some patients could not respond to beta2-agonists because of polymorphisms in the beta2 receptor (Liggett 1997). Indeed, this polymorphism results in increased agonist-dependent down-regulation of beta-receptor expression (William et al. 2003). The bronchodilatory effect of sodium fluoride is thus far poorly documented. NaF has been reported to stimulate adenylate cyclase activity on smooth muscles (Stadel and Crooke 1988) and induce NO synthesis (Cushing et al. 1990) which would relax bronchi. The better known bronchodilatory mechanism of NaF is induced by inhibition of the glycolytic enzyme, enolase, which converts 2-phospho-glycerate to

phosphoenolpyruvate (Gary 1996). The inhibition of glycolysis induced by NaF is illustrated by the sharp decrease in lactate production in its presence (Zhao et al. 2002). The duration of the bronchorelaxant effect of NaF is not known and would need further study as well as the effects of other fluorides.

In Tunisia, NaF is cheaper than beta2-agonists and it could possibly represent a good alternative for the treatment of asthmatics resistant to current treatment in case of acute asthma. Indeed, it could possibly be used alone or as an adjuvant to beta2agonist treatment, as they have two different mechanisms of action.

In conclusion, the bronchodilatory effect of NaF after metacholine challenge is similar to the bronchodilatory effect of salbutamol. The mechanism of action of NaF in asthmatic patients is not yet certain; however experiments in vivo in rats suggested that the inhibition of glycolysis in airway smooth muscles could be responsible (Zhao et al. 2002). NaF should be evaluated further for clinical benefits in obstructive pulmonary disease, and for effects on airway inflammatory markers.

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References

- r-0. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis 1991; 144 : 1202-18.
- r-1. Pak CY, Sakhaee K, Zerwekh JE, Parcel C, Peterson R, Johnson K. Safe and effective treatment of osteoporosis with intermittent slow release of sodium fluoride : Augmentation of vertebral bone masse and inhibition of fractures. J Clin. Endocrinol Metab 1989 ; 68 (1), 150-9.
- r-2. Chung KF, Blanc FX. [Severe asthma: can we do better?] Asthme sévère : comment mieux faire ? Rev Mal Respir 2003 ; 20 : 495-500
- r-3. Cushing DJ, Sabouni MH, Brown GL, Mustafa SJ. Fluoride produces endothelium-dependent relaxation and endothelium-independent contraction in coronary artery. J. Pharmacol Exp Ther 1990; 254, 28-32.
- r-4. Whitford GM. The metabolism and toxicity of fluoride. 2nd, revised edition, Karger. 1996.
- r-5. Liggett SB. Polymorphisms of the bbeta 2-adrenergic receptor and asthma. Am J Respir Crit Care Med 1997; 156: S156-S162.
- r-6. Sears MR, Lotvall J. Past, present and future--beta2-adrenoceptor agonists in asthma management. Respir. Med. 2005; 99 (2):152-70.
- r-7. Stadel JM. Crooke, ST. Differential effects of fluoride on adenylate cyclase activity and guanine nucleotide regulation of agonist high-affinity receptor binding. Biochem. J. 1988; 254(1), 15-20.

r-8. Zhao W., Guenard H. The inhibitory effect of carbachol-induced bovine bronchial contraction. *Respir. Physiol.* 1997; 108 (2) : 171-9.

r-9. Zhao W, Rouatbi S, Tabka Z, Guenard H.. Inhaled sodium fluoride decreases airway responsiveness to acetylcholine analogs in vivo. *Respir. Physiol. Neurobiol.* 2002; 131(3), 245-253.

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