

Comparison of bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics

B. Dahlén, O. Zetterström

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ABSTRACT: Oral challenge with acetylsalicylic acid was compared with inhalation of Lysine acetylsalicylic acid (L-ASA) as a means to diagnose aspirin-idiosyncrasy in the airways. On the basis of history and/or clinical findings (asthma, rhinorrhea, nasal polyposis) 22 consecutive patients were challenged by both routes. Ten of these developed significant bronchoconstriction ($\geq 20\%$ drop in forced expiratory volume in one second (FEV₁)) during either challenge, with the same absolute sensitivity for both tests (9/10). During the bronchial provocations, the reactions developed more promptly (20 min vs 1 h after provocative dose) and were limited to the airways. In contrast, the reactions evoked by the oral provocations were often more pronounced, longer lasting and occurrence of generalized symptoms was more common. Accordingly, the oral tests required more extensive drug treatment for reversal, whereas the bronchial provocations always were reversed by inhalation of bronchodilators. The bronchial method thus resulted in considerably shorter test sessions (4 h vs 8 h). The specificity of the bronchial test was indicated by the observation that a control group of 19 asthmatics with comparable severity of disease failed to bronchoconstrict in response to L-ASA. In conclusion, we have found the bronchial provocation method to be easy to interpret and to control, even in severely asthmatic patients. Consequently, bronchial provocation with L-ASA appears particularly useful in the out-patient office or for research on airway responses to ASA in ASA-sensitive asthmatics.

Eur Respir J., 1990, 3, 527-534.

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Keywords: Acetylsalicylic acid; asthma; bronchial provocation test; diagnostic procedure; drug intolerance; human; lysine-acetylsalicylic acid.

Received: March 1989; accepted after revision December 12, 1989.

This study was supported by grants from the Swedish National Association against Heart and Chest diseases, and Karolinska Institutet. The Swedish Work Environment Foundation (ASF 84-1302), the Swedish MRC (14x-09071).

It has been known for more than 80 years that some asthmatic patients may develop very severe untoward reactions after ingestion of aspirin (acetylsalicylic acid, ASA) [1-3]. The reason why 10-20% of adult asthmatics react in this way is unknown [3, 4], as is the mechanism for how ASA causes the reactions. However, most of the ASA-sensitive patients suffer from a severe, chronic asthma of endogenous type, often associated with nasal symptoms [3, 5-7]. It is also well established that all drugs belonging to the group of non-steroidal anti-inflammatory drugs (NSAIDs) may provoke adverse reactions in sensitive individuals [8-11].

The sensitivity to NSAIDs is not always recognized by the patients, the drugs are commonly used and the reactions are potentially very dangerous. Therefore, it is important to prove the appropriate diagnosis in order to help sensitive patients in avoiding NSAIDs, and also to advise those asthmatics who may use these drugs. However, it is relatively complicated to make the diagnosis of aspirin-intolerance in routine clinical practice. Oral provocations with ASA have been used for many years to diagnose aspirin-asthma [3, 12-14].

However, the challenge procedure is fairly time-consuming and requires considerable experience with ASA-elicited reactions. The risk of eliciting severe bronchial and/or systemic reactions is significant, although it can be decreased by using a protocol where the patient is challenged with increasing doses of ASA over the course of three days [15]. Nevertheless, the same authors have concluded that the oral challenge cannot be recommended for routine clinical provocations [15]. After the introduction of bronchial provocations with L-ASA by BIANCO *et al.* [16], several authors have reported on the usefulness of this approach [17-19]. However, there has not been a formal comparison between oral and bronchial provocations in the same group of patients.

In this study we compared the inhalation method with a protocol for oral provocations which has been used for many years in our out-patient office [13]. In a prospective study, the sensitivity, specificity and safety of the bronchial provocation method was evaluated in 22 patients, all of whom were also challenged by the oral route.

Patients and material

Patients

In a prospective study twenty-two patients (17 asthmatics and 5 with mainly nasal symptoms) agreed to expose themselves to both oral and bronchial provocations with ASA. They were chosen on the basis of history and clinical features suggestive of ASA-intolerance. These patients were selected from consecutive patients with asthma and/or rhinitis who were referred for investigation during a period of 18 months.

All the asthmatic patients were taking medication at the time of ASA challenge. They were asked to refrain from anti-histamines and sodium cromoglycate 24 h before the test, and from bronchodilators and corticosteroids for 10 h. However, because of the severity of their asthma, 5 patients were not able to comply and had to use their inhalant bronchodilators. One patient had to rely on his oral dose of theophylline and β_2 -stimulant in the morning of the day of provocation. However, the prechallenge medication taken by these patients was essentially the same for the two test sessions.

In addition, to gather further information about the specificity of the inhalation method, another 19 asthmatics of comparable severity were challenged by only the bronchial route. These ASA-insensitive patients thus served as a control group.

The study was approved by the local Ethics Committee (Dnr 85:13).

Material

Uncoloured gelatin capsules containing lactose and ASA in doses of 1, 10, and 100 mg were prepared by the hospital pharmacy. The powder of L-ASA was kindly supplied by Maggioni Farmaceutici S.p.A., Milano, (Flectadol[®]) Horby Bayer AG, West Germany, (Aspisol[®]). The samples contained 900 mg of L-ASA (corresponding to 500 mg of ASA), and 100 mg of glycine. Salbutamol (Ventolin[®], Glaxo), adrenalin (Adrenalin[®], ACO), theophylline (Teofyllamin[®], ACO) and hydrocortisone (Solu-cortef[®], Upjohn) were purchased from the manufacturers.

Methods

All the provocations were begun in the morning and performed in hospital under close supervision of the patients with emergency resuscitative equipment readily available. The interval between the two challenge sessions was at least one week and, in the case of a positive reaction, the next challenge was not carried out until 4 weeks had passed.

The oral provocation was started by giving a placebo-capsule containing lactose, and continued by ingestion of capsules with ASA in the doses of 1, 10, 50, 100 and 300 mg. The interval between the doses was generally 30–45 min. However, if there was suspicion

of development of a positive reaction, the observation period was extended up to 90 min.

During the bronchial provocation a freshly made nebulized solution of lysine-ASA (L-ASA) was inhaled by tidal breathing through a mouthpiece without the use of a nose clip. The solution was nebulized by a jet nebulizer (Aiolos, Medicinsk Teknik AB, Karlstad, Sweden) at a driving pressure of 220 kPa (flow rate 8 l·min⁻¹) giving an output of 0.83±0.03 ml·min⁻¹, and with 55% of the particles below 4 and 70% below 6 μ m (Malvern particle- and dropletsize-meter type S.T. 200, Volvo Flygmotor AB, Trollhättan). The L-ASA powder was dissolved in distilled water to a concentration of 200 mg·ml⁻¹ and further diluted 1:4 in 0.9% NaCl solution to a final concentration of 50 mg·ml⁻¹ (corresponding to a concentration of 25 mg·ml⁻¹ of ASA). After placebo challenges with the diluent the patients inhaled successively 1, 3, 9 and 27 breaths and finally 1 ml of the L-ASA solution. The variation in baseline forced expiratory volume in one second (FEV₁) values was <10% before challenge, except in patient no. 10 who showed a 12% decrease in FEV₁ after inhalation of the diluent.

During both challenge procedures the patients were continuously checked for the occurrence of clinical symptoms and serial spirometry was obtained (Vitalograf[®]). Thus, FEV₁ was measured every 10 min during the inhalation challenges whereas during the oral challenges the interval was 30–45 min unless symptoms occurred. A positive reaction was defined as a $\geq 20\%$ decrease in FEV₁ from baseline, or else if apparent naso-ocular or gastro-intestinal symptoms occurred.

Statistical evaluation

Statistical hypotheses were tested with Student's t-test for paired or unpaired variables, and a p-value of less than 0.05 was considered significant. Results are generally expressed as mean±sd.

Results

Overall outcome of provocations (table 1).

Altogether 22 patients were selected for challenge both by the oral and the bronchial route. Five of these were non-asthmatics with histories of rhinitis, nasal polyps and sinusitis whereas all of the remaining patients had asthma.

Among the seventeen asthmatics, ten exhibited clinically significant decreases in FEV₁ ($\geq 20\%$) during at least one of the two challenges. These ten patients were thus diagnosed as aspirin-asthmatics, and the findings in this group will be discussed in detail below. Furthermore, another two of the asthmatics had obvious naso-ocular reactions after the oral provocations but not after the bronchial provocations. However, both of these patients failed to react with bronchoconstriction during either type of provocation. These two asthmatics

Table 1. - Overview and general outcome of oral and bronchial provocations with ASA reported in this study

Group A: Asthmatics with suspected ASA-intolerance (n=17).				
	Oral		Bronchial	
Positive reactions	12		9	
Bronchial		9*		9*
Only naso-ocular		2		0
GI-tract and naso-ocular		1**		
Negative reactions	5		8	
Group B: Non-asthmatics with rhinosinusitis and suspected ASA-intolerance (n=5).				
	Oral		Bronchial	
Positive reactions	2		1	
Bronchial		0		0
Only naso-ocular		2		1
Negative reactions	3		4	
Group C: Asthmatics without ASA-intolerance (n=19).				
	Oral		Bronchial	
Positive reactions		NP		0
Negative reactions		NP		19

*: eight were positive in both provocations; **: this patient responded with bronchoconstriction during the bronchial test; NP: not performed.

were accordingly considered as ASA-sensitive, but, at the time of the study, with preference to extra-pulmonary sites. Five of the asthmatics were entirely negative.

Among the five non-asthmatics with rhinosinusitis there were no bronchial reactions with either method of provocation. Two of these patients, however, showed nasal congestion and rhinitis after the oral challenge, and one of them also showed nasal symptoms after the inhalation challenge. These two patients were consequently also considered as ASA-sensitive. Thus, of the 22 patients challenged by both routes, 10 exhibited aspirin-asthma, 8 were negative and four responded with nasal symptoms, but no bronchoconstriction. The oral provocation was more prone to trigger extrapulmonary reactions.

Influence of L-ASA on airway function in aspirin-insensitive asthmatics

As a control group, 19 patients were carefully selected to comprise a group of asthmatics with the same variation of disease severity as the ten asthmatics with documented aspirin-sensitivity in the airways. Thus, their percentages of predicted FEV₁ ranged from 43–109%,

with a mean value of 80%. The inhalation of L-ASA caused insignificant changes of FEV₁ (mean±SD: 99±6% of baseline) in the control group.

Characteristics of the ten aspirin-sensitive asthmatics (table 2)

The group comprised 3 women and 7 men, aged 20–67 yrs with a mean age of 49 yrs. Their asthma was of different severity (the percent of predicted FEV₁ ranged from 52–104, mean 73%) and duration (range 1–17 yrs, mean 8 yrs). Eight patients had a history of nasal symptoms. Interestingly, three of the ten patients were unaware of their sensitivity to ASA prior to this investigation.

Airway response

The degree of obstruction in the ten patients during oral and bronchial provocation is shown in figure 1. Baseline FEV₁ values did not differ significantly between the two test sessions (means±SD for FEV₁ were 2.3±0.6

Table 2. - Characteristics of patients subjected to both per oral and bronchial provocations with ASA

Patient no.	Age yrs	Sex	History of yrs			Current medication	FEV ₁ %pred
			ASA -sensitivity	Asthma	Nasal symptoms		
1	47	m	no	1	18	IB,OB,IS	85
2	66	m	1	8	no	IB,OB,OT,IS,OS	66
3	39	f	5	5	16	IB,OT	97
4	20	m	no	4	4	IB,OB,OT,IS	58
5	61	m	17	17	21	IB,IS	52
6	50	m	no	6	3	IB,OB,OT,IS,DSCG	65
7	67	m	16	2	11	IB,OB,IS	59
8	31	f	6	8	8	IB,IS	104
9	57	f	5	16	no	IB,OB,OT,IS	90
10	49	m	9	9	19	IB,OB,OT,IS,OS	53

IB: inhaled β -agonists; OB: oral β -agonists; OT: oral theophylline; IS: inhaled steroid; OS: oral steroid; DSCG: inhaled cromoglycate; m: male; f: female; FEV₁: forced expiratory volume in one second.

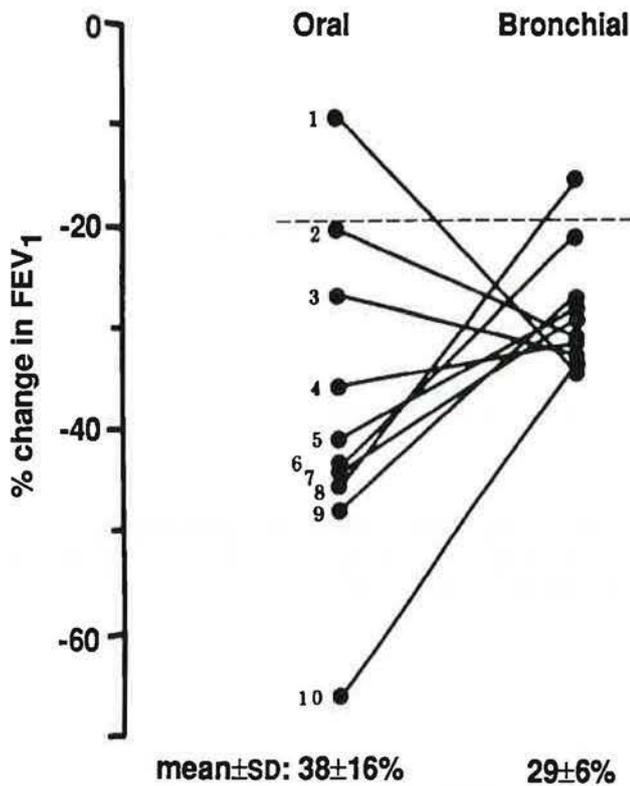


Fig. 1. - Airways response in 10 aspirin-sensitive asthmatics after oral and bronchial provocations with ASA. The values of each patient are connected with a solid line. The dotted line represents a 20% decrease in FEV₁ from baseline (the criterium used for a positive diagnosis). Note the wider distribution as well as the occurrence of more severe responses after the oral challenge.

and 2.6 ± 0.5 for the oral and the bronchial provocations, respectively).

The airway responses were on the whole of significantly smaller magnitude after the bronchial provocations than after the oral provocations (fig. 1). For example, none of the patients had a decrease in FEV₁

below 35% during the bronchial provocation, whereas in six patients FEV₁ fell by more than 40% during the oral provocation. Furthermore, the airway responses were more widely scattered after the oral provocations, with peak drops in FEV₁ ranging from 68–9%, as compared with 35–15% during the bronchial provocations. Moreover, during the oral provocations, two of the patients (subjects no. 9 and 10) developed very severe reactions which necessitated hospital treatment overnight. The time course of the airway response to oral challenge with ASA in one of those patients (subject no. 9) is shown in figure 2. This severe reaction was reversed by the next day after further treatment with hydrocortisone and theophylline systemically as well as inhalation of salbutamol from a jet-nebulizer.

In contrast, the airway response appeared more promptly during the bronchial provocations as exemplified in figure 3. For the whole group, the mean time from provocative dose (the last dose given before the reaction evolved) to a $\geq 20\%$ decrease in FEV₁ was less than 20 min in the bronchial test sessions as compared with one hour during the oral provocations (fig. 4).

One patient, subject no. 1, did not react with airway constriction during the oral provocation, although he exhibited nasal congestion and gastro-intestinal distress including vomiting. However, during the bronchial provocation he showed a prompt and typical decrease in FEV₁ (fig. 3). On the other hand, in subject no. 8, the oral provocation produced a 46% decrease in FEV₁ whereas this patient exhibited a nonsignificant decrease in FEV₁ (15%) during the bronchial provocation.

The cumulated doses of aspirin given during the oral provocations ranged from 11–410 mg, whereas the estimated doses administered during the bronchial provocations varied from 1–25 mg. However, under the conditions used, there was no apparent correlation between the amount of inhaled and ingested ASA needed to provoke a positive reaction in a sensitive individual.

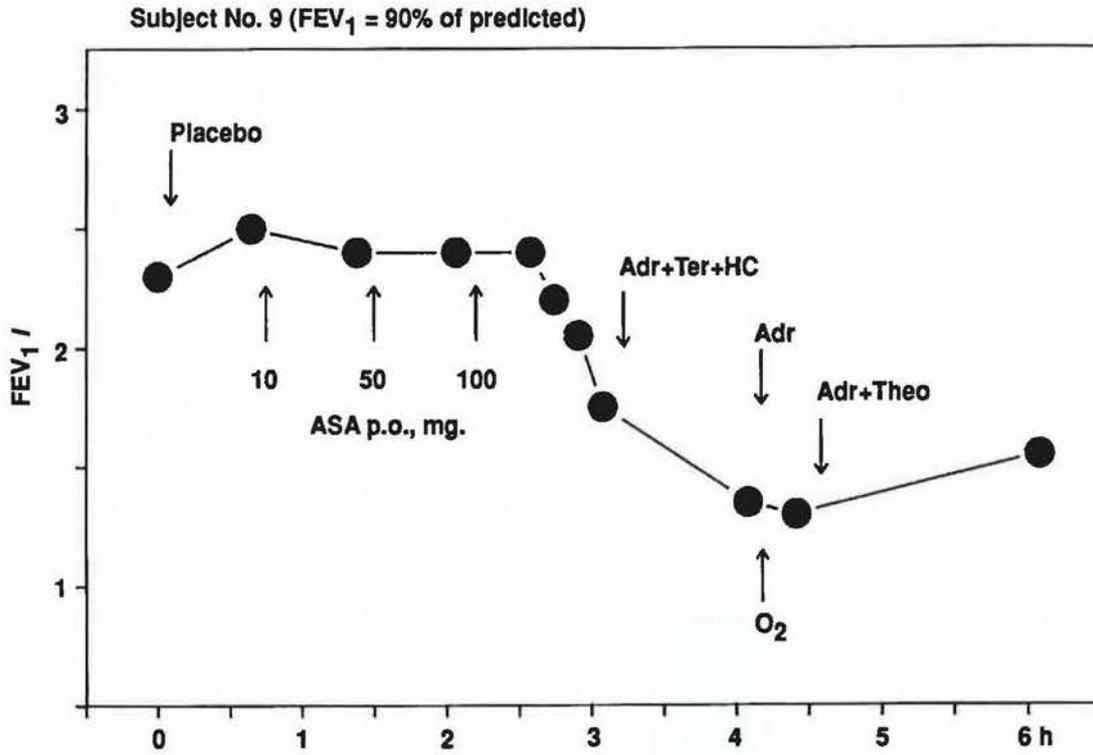


Fig. 2. - Oral challenge with ASA in patient no. 9. FEV₁ values were monitored initially, after placebo (P), after each dose of ASA and during the resulting airway response. Still 30 min after the last dose no symptoms had occurred. However, within, another half an hour a very rapid and severe reaction evolved. Systemic treatment with adrenaline, theophylline and corticosteroids eventually made the reaction vanish the next day.

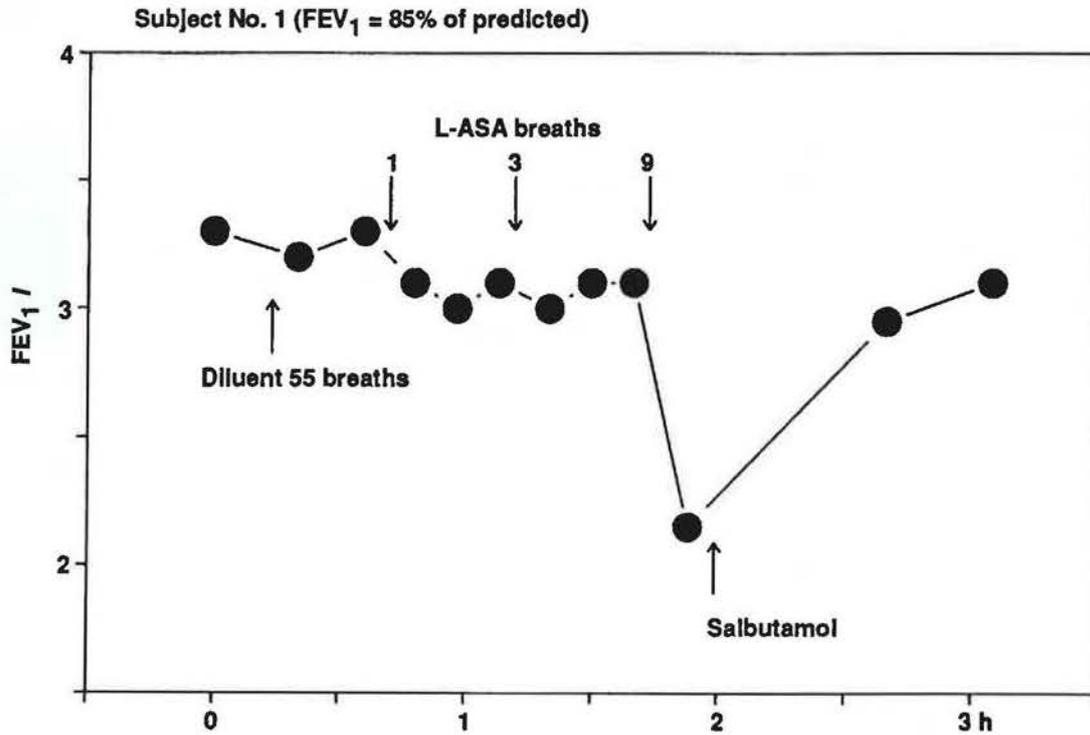


Fig. 3. - Bronchial provocation in patient no. 1. After inhalation of the diluent the patient inhales an increasing number of breaths of the L-ASA solution. (50 mg·ml⁻¹). The response evolves quickly and is easily reversed by inhalation of salbutamol.

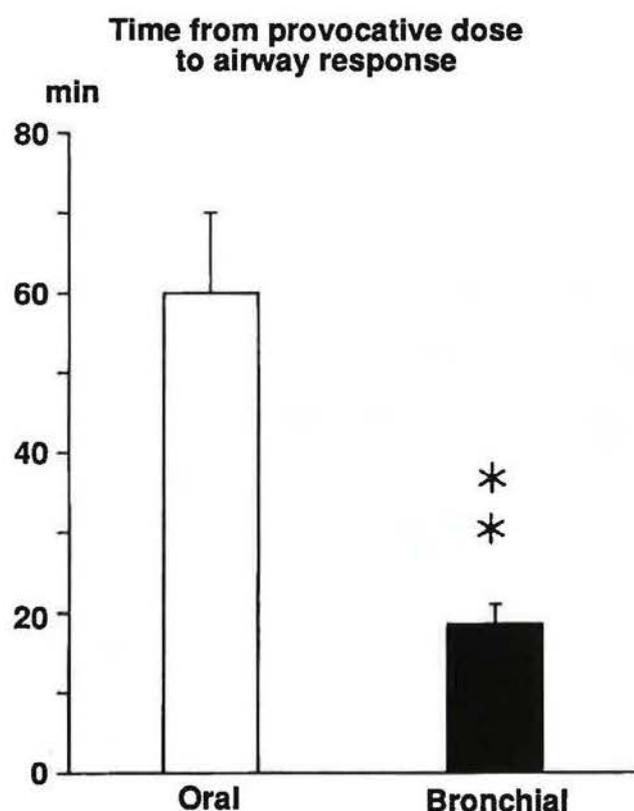


Fig. 4. — The time from provocative dose to airway response was 60 ± 10 min (mean \pm SEM) during the oral provocation and 17 ± 3 min during the bronchial provocation.

Extra-pulmonary symptoms

The symptoms elicited during the bronchial provocations were restricted to the airways. Apart from bronchoconstriction, one patient experienced slight nasal stuffiness.

In contrast, during the oral provocations, eight of the ten patients reported a feeling of general distress and showed symptoms from one or several extrapulmonary sites. Nasal congestion and/or rhinitis occurred in five patients, flushing and injection of conjunctivae was seen in four patients, Quincke's oedema occurred in one patient and sickness and vomiting in two patients.

Reversibility

Table 3 shows the total amount of drugs required to achieve a reversal of the evoked bronchoconstriction after each method of provocation. Thus, inhalation of a β_2 -stimulant (salbutamol) was sufficient to achieve reversibility after the bronchial challenge with L-ASA, whereas after the oral provocations additional treatment with theophylline, adrenaline and hydrocortisone was required in 7 out of the 10 cases.

Furthermore, the bronchial provocations were as a whole significantly less time consuming than the oral challenges. The average time for the test session (from the very start until the patient left hospital) was four hours for the bronchial provocations whereas the mean duration of the oral provocations was eight hours (fig. 5). Even if the two patients who were hospitalized overnight were omitted from this comparison, there was still a significant difference (3.8 ± 0.7 h vs 4.9 ± 1.0 h; $p \leq 0.01$).

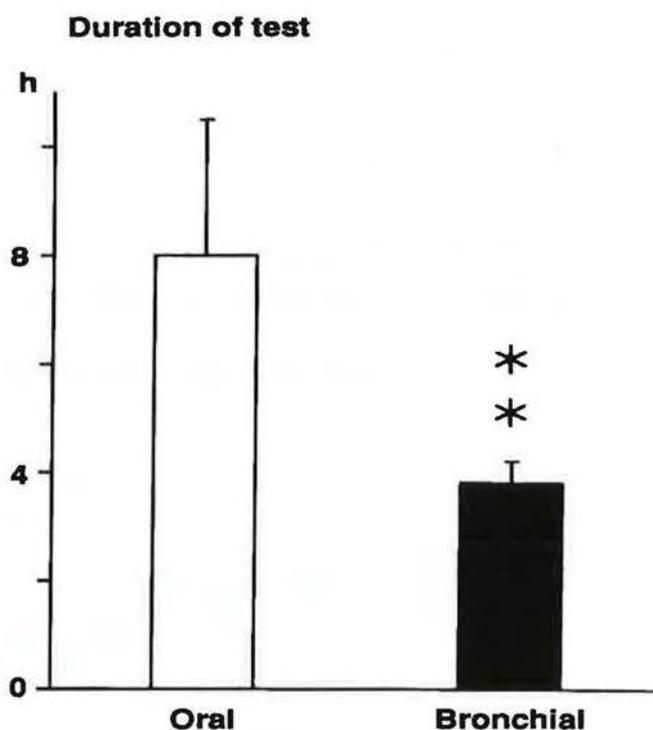


Fig. 5. — Comparison of total time-consumption (from the start of the test session until the patient left hospital) between oral and bronchial provocations. Thus, the oral test took 8 ± 2.5 h (mean \pm SEM) to perform, in contrast to 4 ± 0.25 h (mean \pm SEM) for the bronchial provocations.

Table 3. — Drug treatment required for reversal of bronchoconstriction after provocation of aspirin-sensitive asthmatics with aspirin by the oral or bronchial route

Drug	Oral provocation	Bronchial provocation
Salbutamol inhalation	55 mg	35 mg
Adrenaline sc.	4.4 mg	0
Theophylline iv.	1238 mg	0
Hydrocortisone iv.	1466 mg	0

Expressed as cumulated amount used for all ten patients at each occasion.

Discussion

The overall aim of this study was to evaluate whether or not bronchial provocations with ASA were suitable for use in our out-patient practice. We wanted to adopt a challenge procedure which could be used on large groups of patients without compromising necessary requirements for specificity and safety. Previous to this investigation, we have for many years used a protocol for oral provocations involving dose increments at approximately every 45 min. Therefore, it was decided to compare this oral test procedure and bronchial provocations with L-ASA in a group of consecutive patients being investigated on an out-patient basis to establish the diagnosis of ASA-intolerance.

The main objective of each provocation was to detect ASA-elicited asthma, as this is a potentially dangerous feature in asthmatics [7, 11]. Since asthmatics with ASA-sensitivity constitute a population with a high frequency of severe asthma [3, 15, 20], we felt that it was important to include such patients in the study. Consequently, it was sometimes necessary to allow for some flexibility in the challenge procedure, but the same basic protocol was always employed. As a corollary, however, the present study was not designed to compare dose-response relationships between the two methods.

The overall results of the oral provocations in this study of 22 patients (table 1) conforms well to our earlier experiences with this particular oral test procedure [13], as well as oral challenges performed with other protocols [21]. Thus, 9 patients reacted with an airway obstruction of $\geq 20\%$ drop in FEV_1 , 1 patient had a 10% drop in FEV_1 in combination with extrapulmonary symptoms and 4 patients had only extrapulmonary symptoms, whereas five patients were entirely negative at the time of this study.

It is also well known that the sensitivity to ASA varies with time in the patients. For example, in a study where a similar oral protocol was used, 10–15% of the patients reacted differently on two separate occasions [22], and using a three-day oral protocol the variations in airways response to ASA has been described to be as high as 39% [21]. It is therefore altogether acceptable that in the present study of 10 ASA-sensitive asthmatics, 8 patients showed sensitivity in the airways during both the oral and the bronchial provocations.

However, one major difference between the two provocation methods was that the inhalation method did not cause ASA-reactions extraneous to the respiratory tract. Out of a maximum dose of 25 mg of ASA inhaled, the portion of drug that finally reached the airways was presumably too small to elicit any remote effects as opposed to the maximum dose of 300 mg of ASA given during the oral provocations. Thus, the sensitivity of the two methods was the same in detecting adverse reactions in the airways (9/10), whereas the oral method was more sensitive in detecting extrapulmonary symptoms.

The specificity of the bronchial challenge was validated by the absence of airway response in a control group of asthmatics. Using different methods for bronchial challenge, others have also reached the same

conclusion [17, 19]. In addition, a recent study found no correlation between unspecific bronchial hyperresponsiveness (tested with histamine) and the dose of L-ASA required to produce a 20% decrease in FEV_1 among ASA-asthmatics [23].

In the further evaluation of the usefulness of the bronchial test some advantages were evident. First, although being performed during a comparatively short time-period (2–4 h) no severe bronchoconstrictions were seen. This in spite of 6 of the 10 ASA-sensitive patients suffering from rather severe asthma. In fact, the milder reactions during the bronchial provocation were presumably related to the shorter time required for a given dose of aspirin to elicit a clearly detectable bronchoconstriction. The short time course also facilitates the interpretation of the challenge. Thus, the longer the provocation procedure, the more difficult is it to decide whether a slight airway response is due to a developing reaction towards aspirin or unrelated variations.

Moreover, the bronchial provocations could be performed strictly according to the predetermined protocol in all of the asthmatics, whereas the oral protocol sometimes had to be adapted to the course of events. Therefore, the bronchial provocation method may be more suitable for studies of the influence of pharmacological agents on the asthmatic response. In addition, since bronchial provocations are widely used in asthma research, the use of bronchial provocations with ASA in ASA-sensitive individuals may facilitate comparative studies between different subsets of asthmatics.

In conclusion, we found the same sensitivity with respect to detection of airway obstruction for oral and bronchial provocations with ASA in ASA-sensitive asthmatics. On average, the oral provocation was more difficult to control, and it sometimes caused very pronounced airway responses. The bronchial provocation method was easier to perform and it caused on the whole milder reactions. Furthermore, after bronchial provocations, the reactions were limited to the airways, whereas the oral provocation induced a significant degree of symptoms at extrapulmonary locations. Therefore, we consider the bronchial provocation method very suitable for use on an out-patient basis. In fact, our experiences show that the bronchial provocation is very specific. It may also be safer than the oral method. Finally, it is possible that the bronchial provocation represents a first hand choice for many types of scientific investigations as well. On the other hand, the per oral provocation is required to diagnose and investigate extrapulmonary manifestations of ASA-sensitivity.

Acknowledgements: We thank Ms H. Johansson and Ms M. Mohlin for expert technical assistance, and Dr G.C. Folco, Milan, for help in obtaining initial samples of L-ASA.

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- Comparaison des provocations bronchiques et perorales à l'aspirine chez les asthmatiques sensibles à l'aspirine. B. Dahlén, O. Zetterström.*
- RÉSUMÉ: Une provocation perorale à l'acide acétylsalicylique (ASA) a été comparée à l'inhalation de lysine-acide acétylsalicylique (L-ASA) pour le diagnostic de l'idiosyncrasie des voies aériennes à l'égard de l'aspirine. Les deux voies ont été utilisées chez 22 patients consécutifs chez lesquels le diagnostic avait été porté sur la base de l'anamnèse et/ou des données cliniques (asthme, rhinorrhée, polyposé nasale). Deux d'entre eux ont développé une bronchoconstriction significative (chute du VEMS $\geq 20\%$) pendant les 2 provocations, la sensibilité absolue des deux tests étant la même (9/10). Pendant les provocations bronchiques, les réactions se sont développées plus rapidement (20 min vs 1 h après la dose de provocation) et se sont limitées aux voies aériennes. Par contre, les réactions dues à la provocation per os sont souvent plus prononcées, et de plus longue durée, et s'accompagnent plus régulièrement de symptômes systémiques. Par conséquent, les tests oraux nécessitent un traitement plus important pour obtenir la résolution, alors que les seuls bronchodilatateurs suffisaient toujours pour les provocations bronchiques. Celle-ci permet donc de raccourcir la durée du test (4 h vs 8 h). La spécificité du test bronchique est démontrée par le fait que dans un groupe contrôle de 19 asthmatiques dont la maladie était d'une gravité égale, la L-ASA ne provoquait pas de bronchoconstriction. En conclusion, la méthode bronchique de provocation est aisée à interpréter et à contrôler, même dans l'asthme grave. En conséquence, la provocation bronchique au L-ASA s'avère particulièrement utile dans les consultations externes ou pour la recherche sur les réponses des voies aériennes à l'ASA chez les asthmatiques sensibles à ce produit.
- Eur Respir J.*, 1990, 3, 527–534.