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

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ABSTRACT: Oral challenge with acetylsalicylic acid was compared with inhalation of L-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 (%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 astmatic 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.

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 ß2-stimulant in the morning of the day of provocation. However, the prechallenge medication taken by these patients was generally 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 (Dr 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 glyicine. Salbutamol (Ventolin®, Glaxo), adrenaline (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 (Alios), 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 μm (Malvern particle- and dropletsizer-meter type S.T. 200, Volvo Flygmotor AB, Trollhätta). 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 ≥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 means±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 (≥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

<table>
<thead>
<tr>
<th>Group</th>
<th>Asthmatics with suspected ASA-intolerance (n=17)</th>
<th>Non-asthmatics with rhinosinusitis and suspected ASA-intolerance (n=5)</th>
<th>Asthmatics without ASA-intolerance (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>Bronchial</td>
<td>Oral</td>
</tr>
<tr>
<td>Positive reactions</td>
<td>12</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Bronchial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only naso-ocular</td>
<td>9*</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>GI-tract and naso-ocular</td>
<td>2</td>
<td></td>
<td>1**</td>
</tr>
<tr>
<td>Negative reactions</td>
<td>5</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>History of yrs ASA-sensitivity</th>
<th>Current medication</th>
<th>FEV\textsubscript{1} %pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>m</td>
<td>no</td>
<td>IB,OB,IS</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>m</td>
<td>1</td>
<td>IB,OB,OT,IS,OS</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>f</td>
<td>5</td>
<td>IB,OB,IS</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>m</td>
<td>no</td>
<td>IB,OB,OT,IS,OS</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>m</td>
<td>17</td>
<td>IB,OB,IS</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>m</td>
<td>no</td>
<td>IB,OB,OT,IS,OS,DSCG</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>f</td>
<td>16</td>
<td>IB,OB,IS</td>
<td>59</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>f</td>
<td>6</td>
<td>IB,OB,OT,IS</td>
<td>104</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>f</td>
<td>5</td>
<td>IB,OB,OT,IS</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>m</td>
<td>9</td>
<td>IB,OB,OT,IS,OS</td>
<td>53</td>
</tr>
</tbody>
</table>

IB: inhaled β-agonists; OB: oral β-agonists; OT: oral theophylline; IS: inhaled steroid; OS: oral steroid; DSCG: inhaled cromoglycate; m: male; f: female; FEV\textsubscript{1}: 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 FEV\textsubscript{1} 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.

Fig. 2. Airways response in one of the patients (subject no. 9) during the oral provocation with ASA. The 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.

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.
Subject No. 9 (FEV₁ = 90% of predicted)

![Graph showing FEV₁ values over time with placebo, ASA, Adrenaline (Adr), Theophylline (Theo), and Corticosteroids (HC).]

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.

Subject No. 1 (FEV₁ = 85% of predicted)

![Graph showing FEV₁ values over time with diluent, L-ASA breaths, and Salbutamol.]

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.
The time from provocative dose to airway response was 60±10 min (mean±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 β₂-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<0.01).

**Duration of test**

![Duration of test](image)

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral provocation</th>
<th>Bronchial provocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salbutamol inhalation</td>
<td>55 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>4.4 mg</td>
<td>0</td>
</tr>
<tr>
<td>Theophylline iv.</td>
<td>1238 mg</td>
<td>0</td>
</tr>
<tr>
<td>Hydrocortisone iv.</td>
<td>1466 mg</td>
<td>0</td>
</tr>
</tbody>
</table>

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 ≥20% drop in FEV₁, 1 patient had a 10% drop in FEV₁, 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 FEV₁ among ASA-asthmatics [23].

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.

References
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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, polypose nasale). Deux d'entre eux ont développé une bronchoconstriction significative (chute du VEMS >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 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.