

The incidence of analgesics intolerance in asthmatic children detected by history and inhalation challenge with lysine acetylsalicylate

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Summary

To determine the incidence of adverse reactions to analgesics in unselected asthmatic children, histories were obtained from 486 children, using questionnaires and interviews. Mean age was $11,4 \pm 2,3$ (± 1 SD) years (range 6–17 years), and mean duration of disease was $7,6 \pm 3,6$ (1–15) years. The majority of 21 children gave an equivocal history, and only 7 (1,4%) of all children had a reliable history of adverse reactions to various analgesics.

Inhalation challenge with increasing doses of lysine acetylsalicylate (LASA) was performed in 75 randomly selected asymptomatic children. Two boys of these (2,7%) had a positive test, defined as a 25% or more decrease of FEV1 and/or a 50% or more increase of the oscillatory airway resistance, compared with base line values. Both children had a mild airway obstruction, and had no personal or family history of analgesics intolerance. Further 27 children with suspected positive personal or family histories were also challenged. One girl of these manifested a mild urticaria; her pulmonary function remained unchanged.

The incidence of analgesics intolerance in unselected asthmatic children is much lower than that of 12,5% to 28% reported in severe chronic asthma. The inhalation challenge with LASA proved simple, safe, effective and time saving, and thus, it offers an alternative method to the oral challenge in suspected children.

Die Häufigkeit der Analgetika-Intoleranz bei asthmatischen Kindern, ermittelt durch Anamnese und inhalative Provokation mit Lysin-Azetilsalizylat

Gezielte Anamnese mittels Fragebogen wurde bei 486 nicht selektierten asthmatischen Kindern erhoben, um die Häufigkeit der Analgetika-Intoleranz zu ermitteln. Das Alter betrug im Mittel $11,4 \pm 2,3$ (6–17) Jahre und die Asthma-Dauer $7,6 \pm 3,6$ (1–15) Jahre. 21 Kinder machten meist fragliche Angaben über adverse Reaktionen auf verschiedene Analgetika, die bei nur 7 (1,4%) von diesen annehmbar waren.

Inhalative Provokation mit steigenden Dosen von Lysin-Azetilsalizylat (LASA) wurde bei 75 zufällig gewählten, asymptomatischen Kindern durchgeführt. Zwei Jungen (2,7%) reagierten mit einer bronchialen Obstruktion, definiert als einen Abfall von FEV1 um mehr als 25% und/oder einen Anstieg des oszillatorischen Atemwegswiderstandes um mehr als 50%, im Vergleich zu den Ausgangswerten. Beide Kinder hatten keine eigene oder familiäre Anamnese einer Analgetika-Intoleranz. Weitere 27 Kinder mit fraglicher eigener oder familiärer Anamnese wurden getestet. Ein Mädchen von diesen reagierte mit einer leichten Urticaria ohne bronchiale Obstruktion.

Die Häufigkeit der Analgetika-Intoleranz bei nicht selektierten asthmatischen Kindern ist viel kleiner als die bei Kindern mit schwerem chronischem Asthma mit 12,5% bis 28% berichtet worden war. Die inhalative Provokation mit LASA erwies sich als einfach, sicher, effektiv und zeitsparend; sie stellt somit eine bessere Alternative zur oralen Provokation.

Introduction

Most peripheral analgesics cause in some asthmatics airway obstruction, nasal congestion and urticaria. These symptoms may appear separately or in combinations and urticaria may also be caused in nonasthmatics. The patients have typically a severe chronic asthma, chronic sinusitis and nasal polyps (14, 15). The underly-

ing mechanisms of these adverse reactions are not completely understood: In sensitive asthmatics, the inhibition of the cyclooxygenase activity by analgesics results in a decreased synthesis of bronchodilating prostaglandins (16); this leads directly or indirectly to an increasing production of bronchoconstrictive leukotrienes (8).

Analgesics intolerance is common in adult asthmatics and it has been reported in 8 to 20% of unselected patients (14, 15). In most studies in children (5, 6, 11, 13, 18, 19), small numbers of selected patients with severe chronic asthma have been investigated and the reported incidence, detected by history (5, 19) or by oral challenge with aspirin (6, 11, 13, 18, 19) varied considerably from zero in unselected patients (13) to 28% in selected ones (11) (table 1). The purpose of this study was, therefore, to determine by history and by inhalation challenge the incidence of analgesics intolerance in a sufficient sample of unselected asthmatic children. The inhalation challenge with lysine acetylsalicylate (LASA) (3) was used, because this method has proved effective and safe and lesser time-consuming than the oral challenge (3, 12), and therefore it has been recommended as the method of choice for challenging suspected patients (12, 14).

Patients and methods

Patients: All asthmatic children, aged 6 to 17 years, who were admitted for a long-term care in the hospital from May to November 1986, were entered in the study. All parents received a questionnaire, and about

a quarter of them were also interviewed, to obtain information whether their child, or other first-degree relatives, had suffered from wheezing, skin rash, itching, nasal discharge and faintness following ingestion of a drug against fever, aches, cold or rheumatism. The brand name and the dosage of the drug should also be stated. Parents and children were informed of the purpose of the study and of possible risks of the inhalation challenge and a written consent was requested.

Two thirds of the children had elevated IgE-values and/or had positive prick- and RAST-tests for common airborne allergens. Disease severity was graded according to the number and severity of asthmatic attacks in the last year: Grade I=less than 5 attacks; grade II=6-10; grade III=11-20; grade IV=more than 20, or severe attacks requiring an intensive care in a hospital. 65% inhaled regularly dinatrium chromoglycate (DNCG) and a half of these inhaled a β_2 -adrenergic drug and/or received an oral aminophylline; 6% received inhaled steroids in addition. The remaining children received β_2 -adrenergics as required. None received oral steroids regularly.

Children born at the 1st to the 9th of a month were selected as a random sample for the inhalation challenge. Children with a suspected personal or family history, who were not included in the random sample, were separately challenged.

Tab. 1 The incidence of analgesics intolerance in asthmatic children - A review of the literature

Authors	Selection criteria	Methods	Patients Nr.	Incidence %
Falliers 1973 (5)*	Severe persistent asthma	History	1298	1.9
Rachelefsky et al. 1975 (11)	Intractable allergic asthma; no history of A.I. +)	Double-blind o. ch. +); placebo, 300 mg ASA +)	50	28.0
Vedanthan et al. 1977 (19)	Severe chronic asthma (60% required oral steroids)	History; double-blind o. ch.; placebo, 300 or 600 mg ASA	56	12.5
Schuhl & Pereyra 1979 (13)	No selection	o. ch. 500 mg ASA	32	0
Fischer et al. 1983 (6)	Chronic asthma; no history of A.I.	Double-blind o. ch.; placebo, 600 mg ASA 600 mg acetaminophen	25	16 8
Towns & Mellis 1984 (18)	Moderate-to-severe chronic asthma (28/29 required inhaled, and 10/29 oral steroids)	Single-blind o. ch.; placebo, 30-150 mg ASA	29	20.7
Bahemann & Debelic 1986 (1)	No selection; severity not specified; no history of A.I.	Single-blind o. ch.; placebo, 500 mg ASA (n=48) Inhalation challenge (n=12)	60	1.7

*) Figures refer to references

+) A.I. = Analgesics intolerance; o. ch. = Oral challenge; ASA = Acetylsalicyl acid

All challenged children were actually asymptomatic and complete pulmonary function test (PFT), performed during a week prior to the challenge were within normal range, except for moderate hyperinflation in a few. DNCG and Ketotifen were stopped three days prior to the challenge, since some authors reported on a protective effect of these drugs against analgesics intolerance (21). All other antiasthmatic drugs were stopped at least 12 hours prior to the test.

Challenge procedure: The study was designed as a single blind placebo controlled procedure. All challenges were performed in the morning. Base line values for forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and oscillatory airway resistance (R_{os}) were measured (Spirognost FD 10 S and FD 5, Siemens, Erlangen, FRG) and values were expressed in percent of predicted for height (2, 23). PFTs were repeated following inhalation of one ml saline as placebo and then at 0,15 and 30 minutes following inhalation of ten breaths from a LASA-solution diluted in saline to obtain 25 mg ASA in one ml (Aspisol®, Bayer, Leverkusen, FRG). The number of breaths required to inhale one ml saline was recorded. When the challenge was negative, the procedure was repeated with 20 breaths, a.s.o. (12). In children with a suspected history of analgesics intolerance, the challenge was started with 5 breaths LASA. An inspiration-triggered nebulizer (Chemomat WE, Weinmann, FRG) was used to minimize substance losts during pauses. The challenge was considered positive, when FEV1 decreased at least 25% and/or when R_{os} increased at least 50%, from the values obtained following inhalation of saline. PFTs were performed three times and the best values were considered.

The threshold dose was calculated as follows (12):

$$\text{Threshold dose (mg ASA)} = \frac{\text{Nr. breaths of LASA}}{\text{Nr. breaths pro 1 ml saline}} \times 25$$

The cumulative threshold dose is the total amount of inhaled ASA in repeated Challenges, being maximally 25 mg.

Results

Adequately filled questionnaires were obtained from 486 (89,7%) of the 542 children originally entered in the study. 105 (21,6%) of these refused to participate in the challenge tests. From the remaining 381 children, 75 (19,7%) were randomly selected for the inhalation challenge and other 27 with a suspected history were also tested. The children, who were and who were not tested, showed no differences in respect to age, duration and severity of disease, except for a male predominance in those who refused to participate in the test (table 2).

History: 21 children (4,3%) had a personal history and three of them had also a family history of adverse reactions to various drugs containing analgesics (table 3). The associations between the adverse reactions and the drugs were described as uncertain in most cases, since other drugs were ingested simultaneously and the responsible drugs were uncertain in 11 cases (table 3). The ingested dose and the interval between ingestion and adverse reaction were not remembered by any case. Thus, history was equivocal in most cases and it could be con-

Tab. 2 Study population

	Total	Challenged patients		
		Random sample	Suspected history	Refused challenge
Nr. of patients	486	75	27	105
Males/Females (Ratio)	285/201 (1,4:1)	42/33 (1,3:1)	14/13 (1,1:1)	81/24 (3,4:1)
Age (years)*)	11,4±2,3 (6-17)	11,8±2,5	11,2±2,6	11,8±2,7
Disease duration*) (years)	7,6±3,6 (1-15)	7,4±3,4	6,1±4,0	7,7±3,5
Disease severity grade*)	2,5±0,9 (1-4)	2,4±1,0	2,5±1,0	2,4±0,8

*) Figures are mean ± SD (range)

Tab. 3 Suspected drugs and the reported adverse reactions in 21 asthmatic children

Nr. patients	Drug	Adverse reactions (in some more than one)
3	Aspirin	Rash, itching
5	Gelonida®-syrup ^{a)}	Wheezing, itching, enanthem, nasal discharge
2	Treupel-supp.® ^{b)}	Wheezing, itching, nasal discharge
3	Antipyretic-supp. (?)	Wheezing, rash, nasal discharge
7	Drugs against cold (?)	Nasal discharge, rash
1	Unknown drug	Itching and nasal discharge

^{a)} 5 ml syrup contains: 125 mg sodium salicylate, 125 mg phenacetin, 4,8 mg codeine phosphate

^{b)} One suppository contains: 62,5 mg acetylsalicylic acid, 125 mg phenacetin, 4,8 mg codeine phosphate

Tab. 4 Children with a positive inhalation challenge with lysine acetylsalicylate

Age (years)	Sex	Threshold (mg ASA)	Cumulative threshold (mg ASA)	Latent period	%-FEV1 decrease	%-R _{os} increase
15	male	7.5	11.3	15'	35	80
12	male	12.5	18.7	15'	45	110
9	female	10.0	17.5	3 h (only urticaria)	10	20

sidered realible only in a third of the 21 cases, resulting in an incidence of 1,4%. Other 18 children had a family history alone, which was also uncertain in all cases.

Inhalation challenge: Base line values of FEV1 ($89 \pm 8\%$ predicted) and of R_{os} ($103 \pm 13\%$ predicted) were within the reference ranges (2, 23) in all cases and the values changed less than 5% following inhalation of saline or LASA, except for those with a positive challenge.

Two boys of the 75 tested children (2,7%) showed a moderate airway obstruction following inhalation of 7,5 and 12,5 mg ASA, respectively (table 4). PFTs returned to base line values following inhalation of 2,5 mg salbutamol. Both children had no personal or family history of analgesics intolerance.

Of the 39 children with a suspected personal or family history, 6 refused the test and other 6 were tested in the random group. From the remaining 27 children, only one girl manifested a mild urticaria three hours following inhalation of 10 mg ASA; her PFTs remained unchanged (table 4). She had a history of urticaria following administration of an unspecified antipyretic suppository.

All three children with a positive challenge test had a moderate mixed asthma and none was steroid-dependent or had a chronic rhinosinusitis or nasal polyps.

The results are summarized in table 5.

Tab. 5 Incidence of analgesics intolerance in asthmatic children

	Absolute	Percent
Positive history (roughly)	7/486	1.4
Positive inhalation challenge with Lysine acetylsalicylate	3/102	2.9
a) Random sample	2/75	2.7
b) Suspected history	1/33	3.0

Discussion

The details on personal and family history of adverse reactions to analgesics, obtained by questionnaires and by interviews, were insufficient and were difficult to evaluate. Similar difficulties have been reported by others (4, 5, 18). The estimated incidence of 1,4% is similar to the 1,9% reported by *Falliers* (5) among 1298 chronic asthmatic children, but it is higher than the 0,55% incidence of analgesics-induced urticaria found among 1632 children attending an allergy clinic (4).

Most of the reported adverse reactions might been caused by the intercurrent disease, for which the antipyretic drugs were taken, such as nasal discharge and wheezing following a viral infection. Moreover, other drugs, such as antibiotics may cause rash, urticaria and itching. Urticaria and angioedema may occur as isolated adverse reactions to analgesics in asthmatic (1, 14-16) and in nonasthmatic (1, 4) patients. This was the case in an asthmatic girl, who manifested an isolated mild urticaria, by history and on inhalation challenge (table 4).

A familial occurrence of analgesics intolerance has been reported in a few cases (5, 9) and recently, an association with HLA-DQw2 was found, with a relative risk of 4,06 (10). In the present study, family histories were much less precise than the personal ones and could not be evaluated. None of the children with a suspected family history had a positive challenge test. The frequencies of positive challenge tests were identical in children with and without a personal or a family history, indicating a low predictive value of an equivocal history in unselected, moderately severe asthmatic children. In contrast, in 56 children with severe asthma, 60% of whom requiring oral steroids, *Vedanthan* et al. (19) found among five children with a positive oral challenge only one child with a negative history. Generally, history remains uncertain in most cases and needs confirmation by a provocation challenge. The inhalation challenge with LASA offers considerable advantages compared with the oral challenge with ASA: 1. The administered ASA-doses are lower and the dose increments are smoother, making the procedure safer and easier to control. 2. The test is much less time consuming and needs only one to two hours, compared with two to three days for the oral test (15). However, the inhalation method can not be applied in cases with suspected adverse reactions to acetaminophen and other analgesics, since appropriate solutions for inhalation are commercially unavailable; such cases must be orally challenged (1, 6).

The incidence of 3% of analgesics intolerance detected by inhalation challenge with LASA is considerably lower than that of 9% to 28% reported by others using oral challenge (6, 11, 18, 19). These different results may be explained mainly by differences in the severity of asthma in the studied children: Severe chronic asthma is more frequently associated with an intolerance to analgesics than mild to moderate asthma (5, 14, 15). In the present study, patients were unselected and had predominantly a mild to moderate asthma, as expected in unselected asthmatic children (20); in the other studies (6, 11, 18, 19), in contrast, children were highly selected and had predominantly a severe chronic asthma and thus, they were at a higher risk to manifest an analgesics intolerance than our children. The different challenge methods seem unlikely to account for the above mentioned different results, since our results are in keeping with those of *Schuhl* and *Pereyra* (13), who performed an oral challenge with 500 mg ASA in 32 unselected asthmatic children, as in our study population, and none of these had a positive challenge test; our results compare also favourably with those of *Bahemann & Debelic* (1), who found a positive oral challenge in only one child among 60 unselected, 10–25 years old asthmatics, of whom 48 have been tested orally with 500 mg ASA and 12 by inhalation challenge with 25–50 mg ASA (Table 1). On the other hand, the inhalation challenge test has proved effective in adults and in children with a clear-cut history of analgesics intolerance (1, 3, 12, 14). The incidence of clinically apparent severe adverse reactions to analgesics is probably much lower than that of 3%, detected by inhalation challenge, since only a few such cases have been reported (1, 4, 7, 17, 22). Among 4532 in-patient asthmatic children seen in our clinic during four years, we found only four cases with an unequivocal history of severe analgesics-intolerance (7).

The threshold doses (table 4) are higher than those detected by the same challenge procedure in 32 adult asthmatics (5.94 ± 5.14 mg ASA), aged 16 to 53 years (12) and they are considerably higher than the doses of 1.31 to 2.62 mg ASA in adults (3), detected by a somewhat differing procedure of the inhalation challenge. All these patients (3, 12) had a sure history of aspirin-asthma. The different threshold doses may be explained in part by differences in the test procedures and in the nebulizing techniques and above all by differences in the disease severity and thus in the drug sensitivity of the tested patients. In most studies using an oral challenge (4, 6, 11, 13, 18, 19), threshold doses were not reported and the administered oral doses were often much higher than the inhalative ones, used by us and by others.

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