

Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation

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ABSTRACT: The records of 92 asthmatics who underwent mechanical ventilation were reviewed. In seven patients (8%) the severe attack was precipitated by a non-steroidal anti-inflammatory drug (NSAID); one of these patients died. Five of the cases had a history of asthmatic attacks provoked by NSAIDs; whilst in two the severe attack requiring mechanical ventilation was the first manifestation of NSAID-intolerance. In two patients the NSAID had been prescribed by their physicians. Another aspirin-intolerant patient, a general practitioner, self-administered a NSAID. The sudden attack in another patient was precipitated by a preparation which contains aspirin and is usually recommended for indigestion. In the fatal case the attack was provoked by a capsule containing aspirin, which had been given by a herbalist. Unlike other reports, we found that NSAID-intolerance is a frequent provoking factor in severe acute asthma requiring mechanical ventilation. Inadequate investigation of precipitating factors in asthmatics with severe sudden attacks is a possible reason why this phenomenon is underreported.

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Intolerance to acetylsalicylic acid (ASA) (aspirin) and other non-steroidal anti-inflammatory drugs (NSAIDs) is relatively frequent in bronchial asthma. Although asthmatic attacks precipitated by aspirin are usually severe, only a few cases requiring mechanical ventilation have been reported [1-4]. In a previous study we found that ASA or NSAIDs were responsible for a severe exacerbation of asthma (SEA) requiring mechanical ventilation in 3 out of 26 patients [5]; whereas, in similar studies, other authors found that none of the SEA cases needing artificial ventilation were related to NSAIDs [6, 7].

The present study analyses the prevalence of ASA-intolerance as a precipitating factor in life-threatening acute severe asthma. We also reviewed the circumstances related to severe attacks provoked by ASA or NSAIDs.

Patients and methods

The records of 92 asthmatics who underwent mechanical ventilation between 1977 and 1986, were reviewed. A diagnosis of asthma was accepted if clinically reversible signs of wheezing, shortness of breath and/or recurrent cough, unrelated to other diseases were observed. A history of positive or negative aspirin or NSAID-intolerance was specifically mentioned in the clinical records of 81 patients, whereas no such mention was made in the clinical notes of the remaining eleven patients. A diagnosis of ASA-intolerance was based on history; challenge tests were not used to confirm diagnosis.

The clinical records of the 26 previously reported asthmatics, who underwent mechanical ventilation between 1977 and 1981 [5], were included in the group of 92 patients.

Clinical characteristics of these patients are shown in table 1. Sixty two percent of patients were intubated immediately on arrival at the emergency room, 35% and 3% were intubated in the intensive care unit and ward, respectively, because of progressive clinical and arterial

Table 1. - Clinical characteristics of the 92 patients

Age yrs	46.7±17	range, 13-79
Sex		
Female	57 (62%)	
Male	35 (38%)	
Age of onset of asthma yrs	30.5±18.4	range, 1-76
Duration of asthma yrs	16.2±15.3	range, 1-58
NSAID-intolerance by clinical history	14%	
Place where endotracheal intubation was carried out	emergency room	62%
	intensive care unit	35%
	wards	3%

Values are expressed as mean±SD. NSAID: non-steroidal anti-inflammatory drug.

blood gases deterioration in spite of being treated with steroids and bronchodilators.

Results

Thirteen patients (14%) had experienced bronchospastic reactions to ASA or NSAIDs. In seven patients (8%) the severe attack necessitating mechanical ventilation was precipitated by ingestion of a NSAID. Characteristics of all seven patients (5 males and 2 females, aged 25–63 yrs) are depicted in table 2.

Table 2. – Clinical characteristics of patients with a severe attack of asthma precipitated by NSAIDs

Case n	Sex	Age yrs	Duration of asthma yrs	Oral steroid treatment	Nasal polyps
1	M	51	10	continuous	yes
2	M	60	14	continuous	yes
3	F	63	15	intermittent	no
4	M	25	2	intermittent	no
5	M	47	3	intermittent	no
6	M	27	7	intermittent	no
7	F	43	3	intermittent	no

Five patients (cases 1–3, 5 and 6) had a history of asthmatic attacks provoked by ASA or NSAIDs; one of these patients (case 5) had required mechanical ventilation owing to causes other than ASA-intolerance. In cases 4 and 7 the severe attack requiring mechanical ventilation was the first manifestation of ASA-intolerance. In cases 1–3 the attack was precipitated by NSAIDs other than ASA. Two of these patients (cases 1 and 2) were treated with dipirone and indomethacin for chest (costal fracture) and back pain (discal hernia), respectively, even though their physicians had been warned that they were ASA-intolerant. Case 6, a general practitioner, who knew he was ASA-intolerant self-administered sulindac for a headache. In case 5 the sudden attack came immediately after ingesting a preparation usually recommended for indigestion containing 230 mg of ASA (AlkaSeltzer). Patient 7 was a tense woman who had been suffering from asthma for three years. She required continuous bronchodilator and beclomethasone treatment with short courses of oral steroids. In an attempt at freeing herself of steroid dependence, the patient consulted a herbalist who treated her with a "special capsule". She developed a severe attack 20 min after taking the capsule. The patient was intubated immediately on arrival at the emergency room but she died several days later as a consequence of anoxic encephalopathy. The capsule contained 500 mg of ASA.

Prior to the onset of asthma, all patients had suffered from a perennial rhinitis for 2–7 yrs. Two patients received continuous bronchodilator and steroid treatment (prednisone and beclomethasone); the remaining five were on continuous treatment with beta-adrenergic agents and beclomethasone and had received short cycles of steroids during exacerbations.

Discussion

In aspirin-sensitive asthmatics asthma attacks may also be precipitated by other non-steroidal anti-inflammatory drugs with different chemical structures. Since all these drugs are inhibitors of the cyclo-oxygenase enzyme a pharmacological mechanism has been proposed to explain this finding [8]. Recently a hypothesis has been presented suggesting that aspirin-induced asthma results from a chronic viral infection [9].

In contrast to other studies, we found that NSAID-intolerance is a relatively frequent precipitating factor in cases of life-threatening acute severe asthma requiring mechanical ventilation. Nonetheless, these cases are probably under reported for several reasons: 1) inadequate investigation of precipitating factors; 2) absence from the reports based on records from intensive care units because some ASA-induced attacks are, at times, of a brief duration and treated with artificial ventilation for only a few hours in emergency rooms; and 3) reluctance to report mistakes in the selection of analgesic drugs.

ASA-intolerance must be suspected when suffocation occurs, in a stable asthmatic, within a few minutes after ingestion. Many physicians and surgeons are not well-informed about cross-reactivity between ASA and NSAIDs. The ASA-intolerant family physician, reported in this paper, who provoked a SEA by taking a NSAID is a striking example of this ignorance and the need to strictly avoid all kinds of cyclo-oxygenase inhibitors in ASA-sensitive patients.

To date challenge test is the only method available to determine if an asthmatic is sensitive to ASA, other than a known history of respiratory reaction to an NSAID [10]. Unfortunately, as we saw in two of our patients, the first adverse reaction can be severe enough to provoke a SEA requiring mechanical ventilation. Aspirin and the related NSAIDs can be found in many manufactured multiple-drug preparations, such as AlkaSeltzer, which is an over-the-counter medicament recommended for indigestion. As we observed ASA can even be found in an apparently "innocent" capsule prepared by a herbalist, which caused the death of one of our patients.

ASA-intolerance is usually discovered when a bronchospastic reaction occurs immediately after having taken an aspirin or NSAID [10, 11]. However, in many patients the first asthma attack is not recognized as the precipitating factor; and thus, several bronchospastic episodes often occur before the patient is alerted to his or her ASA-sensitivity.

Clinical histories of patients with ASA-intolerance are very specific. However, they have shown to be only moderately sensitive [12]; some asthmatics who have denied being ASA-intolerant have subsequently had a positive ASA challenge test [12, 13]. This finding might explain why surveys based on challenge testing [12–14] almost always indicate higher prevalence of ASA-intolerance than those based on clinical history [11, 15, 16]. In fact, challenge testing is currently considered to be the most reliable method available for confirming the clinical diagnosis of ASA-intolerant asthma [10]. However, only a few centres have the trained personnel

and/or adequately equipped laboratories to carry out challenge testing with aspirin.

In the light of these limitations it would be advisable to avoid administering all NSAIDs to asthmatic patients [17]. Although isolated cases of intolerance to paracetamol have been described [13, 18], this drug is usually safely consumed by NSAID-intolerant patients and thus, it is the analgesic generally recommended for asthmatics [10]. If the patient has an equivocal history of paracetamol intolerance, a challenge test with this compound should be performed. When the test for paracetamol is positive, dextropropoxyphene, salicylamine, benzydamine, guaiacolic ester, salicylamide and chloroquine are safe alternatives [17]. ASA-sensitive patients requiring a potent analgesic or anti-inflammatory treatment, can be easily desensitized by administering increased oral doses of aspirin [19, 20]. Desensitization can be indefinitely maintained by daily doses of ASA; however, in some cases desensitization could not be sustained during long-term therapy [21].

Most patients with life-threatening attacks of asthma necessitating artificial ventilation are admitted to intensive care units. However, in some cases remission is quick and patients can be extubated within a few hours. Some of these patients are treated in the emergency room and subsequently transferred to the ward. Although asthma attacks precipitated by ASA are sudden, recovery from such attacks usually requires several hours. Only one of our patients was briefly intubated in the emergency room for 5 h; the remaining six were admitted to the intensive care unit where 18–46 h of mechanical ventilation was required. These brief intubations might account for a small number of cases of SEA precipitated by ASA, which we suspect are under reported in series based on records gathered from intensive care units.

Finally, we suspect that under reporting of ASA reactions in bronchial asthma might be partly due to an understandable tendency to focus on clinical achievements rather than mistakes.

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Intolérance à l'Aspirine comme facteur précipitant de crises asthmatiques gravissimes nécessitant la ventilation mécanique. C. Picado, J.A. Castillo, J.M. Montserrat, A. Agusti-Vidal.

RÉSUMÉ: Nous avons revu les observations de 92 asthmatiques qui avaient subi une ventilation mécanique. Chez sept d'entre eux (8%), la crise d'asthme grave avait été précipitée par une drogue anti-inflammatoire non stéroïdienne; un de ces patients est décédé. Cinq de ces cas avaient des antécédents de crises d'asthme provoquées par les anti-inflammatoires non stéroïdiennes, alors que chez deux d'entre eux la crise d'asthme grave nécessitant la ventilation mécanique était la première manifestation d'intolérance aux AINS. Chez deux patients, les AINS avaient été prescrits par leurs médecins. Un autre sujet intolérant à l'Aspirine, médecin généraliste, s'était administré lui-même un AINS. La crise subite, survenue chez un autre patient, avait été précipitée par une préparation contenant de l'Aspirine, et qui est généralement recommandée pour les indigestions. Dans le cas mortel, la crise avait été provoquée par une capsule contenant de l'Aspirine, qui avait été donnée par un herboriste. A l'opposé d'autres études, nous avons trouvé que l'intolérance aux AINS est un facteur de provocation fréquent dans l'asthme grave aigu nécessitant une ventilation mécanique. Une investigation inadéquate des facteurs précipitants chez les asthmatiques avec des crises sévères et soudaines pourrait être une des raisons possibles pour lesquelles ce phénomène est sous-estimé.

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