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Oral Provocation Test in the Diagnosis of Anaphylactoid Reactions to 'Mild' Analgesic Preparations

Key Words

Oral provocation test
Analgesics
Acetylsalicylic acid
Aspirin
Anaphylactoid reactions
Nonsteroidal anti-inflammatory drugs

Abstract

'Mild' analgesic preparations (MAPs) are well known elicitors of anaphylactoid reactions (ARs). The identification of the causative agent is often difficult since reliable skin tests or in vitro methods are not available. In 128 patients (32 males, 96 females) with a history of ARs to MAPs containing only one single analgesic compound, placebo-controlled oral provocation tests (OPTs) were performed. Among 100 of them undergoing the OPT with the suspected drug, there was a concordance between the patient's history and the OPT in 44 patients. Concomitant ARs to other mild analgesics (without a history of previous incompatibility) were observed in 113 of 413 OPTs, but in almost all cases one or more alternative analgesics were tolerated in the OPT. Our results confirm that the OPT remains at present the most reliable diagnostic procedure alongside a comprehensive history in patients with ARs to MAPs. Because many of the patients showed concomitant ARs to unsuspicious analgesics OPTs should include a standard battery of different analgesics. The simple recommendation of one single preparation, such as acetaminophen, as a 'safe' substitute without an OPT is not recommended.

Introduction

Mild analgesic preparations (MAPs) contain as main active agents, salicylates (e.g. aspirin/ASA), para-aminophenol derivatives (e.g. acetaminophen/paracetamol) and pyrazolones (e.g. propyphenazone, dipyron) alone or in combination. They often contain in addition other compounds such as codeine, caffeine, sedatives or vitamins as well as additives such as dyes, and are widely used in the general population [1]. MAPs exert their pharmacological effects by interference with prostaglandin synthesis [2] and are well known elicitors of anaphylactoid reactions (ARs) [1, 3–5].

ARs may be elicited immunologically (that is by an allergy), or they are due to nonimmunological idiosyncrasy (pseudo-allergy) [1, 3–6]. The spectrum of clinical symptoms of ARs ranges from acute urticaria, angioedema, minor respiratory distress, and gastrointestinal or cardiovascular symptoms to full shock as a possible life-threatening event (table 1) [7].

In the diagnosis of ARs to analgesics, the identification of the causative agent is often difficult since reliable skin tests or in vitro techniques are not available [1, 3, 8]. Therefore, we examined the diagnostic value of the oral provocation test (OPT) in patients with ARs to MAPs.

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Table 1. Severity Grading of Anaphylactoid Reactions [from reference 7].

Severity grade	Skin	Gastro-intestinal tract	Respiratory tract	Cardiovascular system
I	itching flush urticaria angioedema	—	—	—
II	as grade I*	nausea colic	rhinorrhea hoarseness dyspnea	tachycardia ($\Delta > 20/\text{min}$) hypotension ($\Delta > 20 \text{ mm Hg}$) arrhythmia
III	as grade I*	vomiting defecation	larynx edema asthma cyanosis	shock
IV	as grade I*	as grade III*	respiratory arrest	cardiac arrest

*not obligatory.

Material and Methods

For 371 patients (86 males, 285 females; age: 6–83 years) with a history of an AR to MAPs, a comprehensive and detailed history, skin tests as well as OPTs with a standard battery of analgesics were performed. 128 of them (32 males, 96 females) had reported an AR to MAPs containing one single analgesic compound.

OPTs were performed single blind and placebo controlled under emergency conditions in the hospital. Each day, incremental amounts of one single analgesic were given in gelatine capsules (ASA: 50/250/500/1,000 mg, in patients with bronchial asthma an initial dose of 1 or 5 mg; propyphenazone: 5/20/100/200 mg; dipyrone, acetaminophen, diflunisal: 50/250/500 mg; tramadol 5/25/50 mg) with a time interval of at least 2 h between each application.

Patients were challenged at a time when their symptoms were in remission. They were observed for subjective and objective symptoms of ARs and the severity was graded according to the classification of Ring and Messmer [7] (table 1). Contraindications for the OPT were intercurrent infections, usage of β -blockers, adrenaline contraindications, actual asthmatic complaints, poor general health and poor patient compliance.

The patient was instructed to report immediately any symptoms appearing after challenge. They were supervised continuously and ARs were treated immediately and appropriately until all symptoms subsided.

Following positive reactions, an interval of at least 72 h elapsed before the next challenge in order to avoid false-negative results during a possible refractory period [9–12]. Criteria for positive reactions were defined as reproduction of the patient's symptoms, other symptoms of anaphylaxis and change of vital signs (e.g. changes in blood pressure, pulse rate and/or peak flow).

Results

Case Histories

The analysis of the case histories of the 128 patients with ARs to MAPs containing only one single analgesic compound yielded as most frequent elicitors ASA ($n = 51$), propyphenazone ($n = 37$), and dipyrone ($n = 26$). 13 patients reported an AR to acetaminophen and 1 patient to tramadol. The mode of application of the analgesic was predominantly oral. 7 patients reacted after rectal application and 7 after parenteral injection of the drug.

Most ARs developed within 30 min after application of the MAP, especially after dipyrone and propyphenazone, and a delayed AR ($> 120 \text{ min}$) occurred predominantly after ASA and acetaminophen.

The severity of the AR was in most cases mild (severity grade I: $n = 60$) to moderate (grade II: $n = 48$), but 11 patients reported severe reactions [grade III: $n = 10$ (3 to ASA, propyphenazone and dipyrone, 1 to acetaminophen); grade IV: $n = 1$ (dipyrone)].

OPTs

Clear-cut positive reactions occurred in 157 of a total of 513 OPTs (30.6%): propyphenazone 39/99, tramadol 19/50 [11 of the 19 reactions to tramadol may be due to an increased sensitivity towards a specific pharmacological effect of the drug (intolerance)], dipyrone 37/101, diflunisal 9/48 and acetaminophen 18/110.

The severity of these ARs was predominantly mild (grade I: n = 123) to moderate (grade II: n = 30), only 2 patients developed a grade III reaction. The majority of ARs occurred within 2 h after oral application of an analgesic (e.g. ASA 15/25, propyphenazone 25/32, dipyron 19/29).

Among 100 patients undergoing OPTs with the suspected drug, there was a concordance between the patient's history and the OPT in 44 patients (table 2). In 113 of 413 OPTs patients reacted to analgesics not previously suspected.

(27.3% previously suspected)

Discussion

Patients with immediate-type reactions (idiosyncrasy or allergy) to analgesics/nonsteroidal anti-inflammatory drugs (NSAIDs) can probably be classified into different categories according to predominant symptomatology: (1) bronchial asthma and/or chronic eosinophilic rhinosinuitis (with or without nasal polyps) [3, 10, 13–17]; (2) chronic urticaria (with or without associated angioedema) [13, 18, 19]; (3) anaphylactoid reactions without either underlying asthma or chronic urticaria [1, 3, 4].

Much research has been focussed on the importance of ASA idiosyncrasy in the first two groups of patients but little is known about the special population with ARs to analgesics/NSAIDs. Therefore, we analyzed the data of the allergological examination in 128 patients with a history of ARs to MAPs with one single analgesic compound.

Our results confirm that, at present, the OPT is the most reliable diagnostic procedure to evaluate ARs to MAP [1,

Table 2. Confirmation of the history of ARs to MAPs with one single compound in the OPT

	Positive/tested	%
ASA	16/41	39.0
Propyphenazone	15/32	46.9
Dipyron	10/20	50.0
Acetaminophen	2/6	33.3
Tramadol	1/1	100
Total	44/100	44.0

(58%)

13], although in more than 50% of the cases, the OPT with the culprit drug remained negative. This may be the result of many different factors, e.g. the history is not necessarily absolutely reliable, a long time interval elapses between the AR and the OPT, other causes of ARs such as additives [20] or food allergy, failure to imitate the circumstances of the AR such as a concomitant infection, exercise and stress.

Because many of the patients showed concomitant ARs to other analgesics in the OPT, this diagnostic procedure has to include a battery of different analgesics including acetaminophen [1, 21]. The simple recommendation of one single preparation such as acetaminophen as a 'safe' substitute without an OPT cannot be supported by our data because each patient seems to show an individual specific reaction pattern to one or more analgesic(s)/NSAIDs.

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