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Aspirin challenge/desensitisation before coronary stenting in subjects with history of hypersensitivity. A pragmatic approach

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Summary

Background. *Aspirin hypersensitivity may represent a major problem in patients with ischemic coronary disease who need a stenting procedure. In those patients, clinically unsettled, reasonably quick desensitisation procedures are needed. In our study we attempted to select the most suitable procedure on the basis of characteristics and severity of ASA hypersensitivity. Methods Thirty patients with a history of mild reactions to anti-inflammatory doses of aspirin (> 325 mg) were considered at low risk and underwent a tolerance test in 5 steps. Thirty-one patients, with a history of severe reactions to anti-platelet doses of aspirin (100 mg) underwent a slow desensitisation in 12 steps, reaching a cumulative dose of 150mg ASA in 220 minutes.* ***Results.*** *In the first group, 29 patients tolerated the challenge. One developed urticaria, thus underwent challenge/desensitisation and achieved tolerance. In the second group, 3 patients did not tolerate the procedure and had to discontinue.* ***Conclusion.*** *Our approach to aspirin hypersensitivity in patients needing coronary stenting, based on a severity stratification, allowed to achieve an effective tolerance to aspirin in the majority of subject in a reasonable short time.*

Introduction

In clinical practice, most cases of acetylsalycilic acid (ASA, aspirin) intolerance are easily managed using alternative drugs, such as nimesulide or selective COX-2 inhibitors (1). In selected cases, when alternative drugs are not suitable, ASA desensitisation can be performed, but the procedure carries some risks, and patients must continue to take the drug in order to maintain an effective tolerance status. On the other hand, ASA desensitisation becomes mandatory for patients with ischaemic heart disease who require coronary stenting (2), as they should receive a double anti-platelet therapy up to 12 months with ticlopidine or clopidogrel plus ASA after intervention (3). In such cases, the only alternative approach remains coronary surgery (by-pass), which is more hazardous and needs a more prolonged hospitalization with subsequent discomfort for patients. The literature about ASA desensitisation in aspirin-exacerbated respiratory disease is relatively abundant (4, 5) and homogeneous. In particular, it is accepted that the dose to maintain an effective desensitisation is 325 mg, which has anti-aggregant and anti-inflammatory effects. On the other hand, there are fewer data on ASA desensitisation in patients with non respira-

tory diseases (e.g. urticaria/angioedema), which represent a not negligible proportion of ASA-sensitive subjects (6). This assumes a greater relevance in those patients needing a stenting procedure for coronary diseases (2), and who would require ASA only at anti-aggregant doses (75-160 mg). Desensitisation procedures for these patients, are less standardized, case series are small, and therapeutic failures have been reported. These patients are clinically unsettled, when an urgent coronarography is needed, and a quick desensitisation is, therefore, required. In such patients, a diagnostic challenge cannot be done and the diagnosis must be based only on clinical history, despite it is not fully reliable (7). Of note, we do not exactly know if our procedures represent a true desensitisation which needs a regular administration to maintain tolerance or a simple up-dosing challenge, to ascertain a pre-existing tolerance to the drug. This latter seems to be the case in those patients with clinical history of reactions to aspirin at doses equal to or greater than 325 mg.

In this study we wanted to assess, in clinical emergency situations, the types of patients suitable for a tolerance test compared to those who would need a more conservative but reasonably rapid desensitisation procedure.

Methods

At our department, patients with a consistent history of ASA hypersensitivty and waiting for a stenting intervention underwent two different procedures, according to their clinical characteristics. A solution of commercial ASA (Cardirene®) at the concentration of 10 mg/mL was prepared and used for all procedures.

In those patients with a history of mild symptoms of urticaria-angioedema (without asthma, laryngeal oedema, or hypotension, and not needing systemic emergency treatment) due to ASA at doses equal to or greater than 325 mg, a challenge test with increasing does was carried out. This involved 5 administrations (10 mg, 25 mg, 25 mg, 50 mg, 50 mg) at 45 minute intervals, so that a cumulative dose of 160 mg was achieved in 3 hours. Those patients with severe symptoms of urticaria/angioedema or asthma or laryngeal oedema at antiaggregant or anti-inflammatory doses underwent immediately a 12-step challenge/desensitisation procedure. The doses administered were 0.1, 1, 1.5, 2, 3, 4, 5, 10, 15, 25, 35 and 50 mg every 20 minutes, for a total duration of 200 minutes and a cumulative dose of about 150 mg (Tab. 1). All the patients were kept under observation for 3 hours after the procedure.

Results

The first group included 30 patients (14 female, 16 male, mean age 67.1 years). Of them, 18 had had urticaria and 12 urticaria-angioedema due to ASA and other antinflammatory agents. Asthma and nasal polyposis was present in 2 patients. In this group, 29 patients fully tolerated the incremental dose tolerance test. One patient developed nasal obstruction and shortness of breath 1 hour after the last dose. Symptoms resolved rapidly after inhaled salbutamol. This patient subsequently underwent the challenge/desensitization procedure and achieved full tolerance. The second group involved 31 patients (14 female, 17 male, mean age 66.4 years). All of them had urticaria-angioedema requiring systemic corticosteroids and/or antihistamines (11 in emergency department), and in 3 patients also fixed drug eruption, asthma and hypotension, respectively, had occurred. Of them, 11 had had symptoms with antiaggregant doses of ASA, and 20 with doses of 325 mg or greater. The procedure was successful in 28 patients, although in three cases the procedure was prudentially slowed by 1 hour for the onset of pruritus. The procedure proved ineffective in three subjects, none of which underwent coronary angioplasty. One had maculopapular rash and was treated only with clopidopgrel, one had urticaria-angioedema and received ticlopidine only.

Table 1 - The 12-step ASA challenge/desensitization A 10 mg/mL ASA solution was used

Minute (mg)	ML	Dose (mg)	Cumulative dose
0	0.0 1	0.1	0.1
20	0.1	1	1.1
40	0.15	1.5	2.6
60	0. 2	2	4.6
80	0.3	3	7.6
100	0.4	4	11.6
120	0.5	5	16.6
140	1	10	26.6
160	1,5	15	41.6
180	2,5	25	66.6
200	3,5	35	101.6
220	5	50	151.6

The third one had fixed drug eruption, and the cardiologist recommended indobufen and surgical by-pass after coronarography.

Discussion

ASA desensitisation in patients with coronaric disease is extremely important, and usually a rapid procedure is needed. Looking at the available literature, desensitisation procedures for aspirin intolerance vary widely among authors (8). For instance, Wong (9), in 11 patients and with antihistamine pre-medication, started with 0.1 mg to reach a cumulative dosage of 640 mg in about 300 minutes. In this study 2 therapeutic failures, at 160 mg ASA, were reported. Rossini (10) started with 1 mg and reached the cumulative dose of 176 mg with 6 progressive increases every 30-120 minutes. In this work 3 therapeutic failures were reported. Silberman (11) treated 16 patients using 2 different protocols: a 5 step challenge with 5 increasing doses in 2.5 hours to reach 150 mg, and a challenge/desensitisation with 8 doses every 3.5 hours, starting with 1 mg and reaching 100 mg. He reported one therapeutic failure.

As compared to the previously reported approaches, the protocol herein described seems to be an acceptable and reasonable compromise in term of time, effectiveness and safety. In addition, a simple preliminary clinical evaluation allowed to choose the more appropriate procedure. In fact, according to our data, in patients with only mild reactions the tolerance test seems to be an adequate first approach, whereas for patients with previous severe reactions the desensitisation procedure should be applied at first instance. We acknowledge that, challenge test is the gold standard for diagnosing ASA hypersensitivity and should have preceded our protocol, but this is not always feasible or practical in patients needing a prompt management, and for this reason we attempted to simplify the procedure, on the basis of a clinical evaluation. Our protocol was safe in the majority of subjects and allowed to reach tolerance in a reasonably short time, that is crucial for such patients.

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