

## Original Research

## Rapid Desensitisation of Patients with Aspirin Allergy Who Undergo Coronary Angioplasty

APOSTOLOS CHRISTOU, NIKOLAOS KAFKAS, ATHANASIOS MARINAKOS, SPYRIDON KATSANOS, KIMON PAPANIKITAS, SOTIRIOS PATSILINAKOS

Cardiology Department, Konstantopoulou General Hospital, Nea Ionia, Athens, Greece

Key words: **Aspirin allergy, angioplasty, desensitisation.**

**Introduction:** Although aspirin is the cornerstone of medication in patients with coronary artery disease, a minority of these patients have aspirin sensitivity. The aim of this study was to evaluate the efficacy and safety of an aspirin desensitisation protocol in patients scheduled for coronary angioplasty and stenting.

**Methods:** We used a challenge-desensitisation protocol in 11 patients (6 men, mean age  $56 \pm 9.6$  years) who reported allergy to aspirin and were to undergo percutaneous coronary intervention with stent implantation. Eight had a history of cutaneous sensitivity, 1 had rhinitis, 1 reported urticaria and rhinitis, while another patient showed a respiratory response in the form of an asthma attack after taking aspirin in the past. Eight successive doses of aspirin were given (0.1, 0.3, 10, 30, 40, 81, 162, 325 mg) at intervals of 15-25 min over a total period of 2 h 15 min.

**Results:** All patients with aspirin sensitivity completed the desensitisation therapy successfully, without adverse effects, and subsequently underwent angioplasty and stenting. During follow up, the patients continued to take aspirin over 6-19 months without any problems.

**Conclusions:** Rapid aspirin desensitisation is an effective and safe procedure for patients with aspirin allergy who are to undergo coronary angioplasty and stenting, allowing them to receive the optimum treatment.

Manuscript received:  
April 27, 2010;  
Accepted:  
May 11, 2010.

Address:  
Apostolos Christou

20 Argyroupoleos St.  
142 31 N. Ionia  
Athens, Greece  
e-mail: [christouapostolos@yahoo.com](mailto:christouapostolos@yahoo.com)

**L**ong-term treatment with aspirin reduces mortality in patients with coronary artery disease after an initial coronary event, while it significantly reduces cardiovascular events after coronary artery interventions.<sup>1,2</sup> Despite the abundance of clinical data concerning the effectiveness of aspirin therapy in patients with cardiovascular diseases, its use in daily clinical practice continues to be less than would be expected.<sup>3,4</sup> Most of the adverse effects of aspirin, such as gastrointestinal intolerance, are usually predictable and are associated with the patients themselves and the dosage of the drug.<sup>5</sup> However, aspirin may also cause hypersensitivity reactions, known variously over time as aspirin intolerance, aspirin idiosyncrasy, pseudo-allergic reactions, and aspirin sensitivity.<sup>6</sup>

Aspirin-exacerbated respiratory disease is a triad that includes asthma, aspirin sensitivity, and rhinitis or nasal polyps.<sup>7</sup> Cutaneous reactions to non-steroidal anti-inflammatory drugs include urticaria, which may occur separately from or concurrently with angioedema. Cutaneous reactions also have a tendency to appear more often in adult life, in young women, in atopic individuals, and in patients with chronic idiopathic urticaria.<sup>8-10</sup> Anaphylactoid reactions occur within minutes of taking aspirin and are characterised by hypotension, laryngeal oedema, generalised itching, tachypnoea, and consciousness disorders.<sup>11</sup> In the general population the incidence of aspirin sensitivity ranges from 0.07% to 0.2% for cutaneous hypersensitivity,<sup>12</sup> while hypersensitivity of the respiratory system is the cause in 10-15% of all

cases of asthma.<sup>13</sup> In patients with cardiovascular diseases the incidence is unknown.

Apart from the substitution of another category of antiplatelet agents, such as thienopyridines, aspirin desensitisation is an alternative option for patients who are allergic to aspirin and need long-term therapy for cardiovascular diseases.<sup>6</sup> Given that many of them (e.g. acute coronary syndromes, stenting) have an immediate need to take combined antiplatelet treatment (aspirin and thienopyridine), the desensitisation procedure needs to be carried out within a short period of time.

## Methods

In our department we used the challenge-desensitisation protocol of Wong et al<sup>14</sup> (Table 1) in 11 patients (6 men, 5 women, mean age  $56 \pm 9.6$  years) who reported an allergy to aspirin and were to undergo percutaneous coronary intervention with stenting. Five had stable coronary artery disease and the others had unstable coronary syndromes (3 unstable angina, 2 non-ST elevation myocardial infarction and 1 ST-elevation infarction). As regards the aspirin allergy, 8 had a history of cutaneous sensitivity (urticaria or angioedema), 1 patient had rhinitis, 1 reported urticaria and rhinitis, while another patient had a respiratory response in the form of an asthma attack after taking aspirin in the past. No patient had a history of anaphylactoid reactions. The patients' clinical characteristics are shown in Table 2.

The medication used for desensitisation was acetylsalicylic lysine powder 288 mg, corresponding to 160 mg acetylsalicylic acid, which was dissolved in 160 ml water (1 mg/ml) and administered orally in a total of 8 successive doses, starting with 0.1 mg and continuing at intervals of 15-25 min (Table 1). The total duration of the procedure was 2 h 15 min, during which the patients remained in the Cardiology De-

**Table 1.** Protocol for rapid aspirin desensitisation in patients with aspirin hypersensitivity (Wong et al<sup>14</sup>).

Time (min)	Aspirin dose (mg)
0	0.1
15	0.3
30	10
45	30
60	40
85	81
110	162
135	325

**Table 2.** Clinical characteristics of 11 patients who underwent aspirin desensitisation.

Age (years)	56 $\pm$ 9.6
Men	6 (54.5%)
History of aspirin allergy:	
Urticaria	6 (54.5%)
Angioedema	2 (18.2%)
Rhinitis	1 (9.1%)
Urticaria and rhinitis	1 (9.1%)
Asthma	1 (9.1%)
Clinical syndrome:	
Stable angina	5 (45.4%)
Unstable angina	3 (27.3%)
Non ST-elevation myocardial infarction	2 (18.2%)
ST-elevation myocardial infarction	1 (9.1%)

partment. Checks for clinical indications of hypersensitivity reactions (itching, rash, dyspnoea, rhinorrhoea, wheezing) and measurements of blood pressure, arterial pulse, and arterial blood O<sub>2</sub> saturation were performed every 30 min during the procedure and for 4 hours afterwards. None of the patients had taken antihistamine or corticosteroid medication before the procedure.

## Results

None of the patients showed any cutaneous, respiratory or systemic hypersensitivity reactions during the challenge procedure; thus, all of them received the maximum dose of 325 mg. The 3 patients with myocardial infarction were referred to the haemodynamics laboratory the next day, and the others within the following week, during which time they received 325 mg aspirin per day. All patients underwent angioplasty and drug-eluting stent implantation and continued to take aspirin daily (325 mg for 1 month and then 100 mg) while also taking 75 mg clopidogrel. All patients continued to take aspirin in this dosage for a period of 6-19 months, without exhibiting any delayed hypersensitivity reactions or other adverse effects.

## Discussion

The only way of distinguishing patients who have hypersensitivity to aspirin is by using various challenge-desensitisation tests, administering aspirin orally, bronchially or nasally. There are no available *in vitro* techniques, while skin tests have failed to give consistent and reliable wheal and flare responses.<sup>11</sup> Although a number of successful desensitisation protocols are available, involving oral administration and

challenge with dosage intervals up to 24 hours, they have not become widely established in clinical practice.<sup>11</sup> Aspirin challenge should not be used exclusively for diagnostic purposes, since some of the reactions can be quite severe. In patients with acute coronary syndromes and/or recent stent implantation, it is necessary to develop protocols that will allow aspirin to be administered with safety within a few hours.<sup>14,15</sup>

Szczeklik and Stevenson described a strategy for the desensitisation of patients who have respiratory disease exacerbated by aspirin.<sup>13</sup> This protocol, which is also known as the “Scripps Clinical Protocol”, includes small oral doses of aspirin that are administered over 2 to 3 days, up to 400-650 mg. Aspirin desensitisation, followed by daily aspirin treatment, can be considered as a therapeutic option in patients with aspirin-exacerbated respiratory disease who suffer from chronic coronary artery disease.

Wong et al carried out challenge-desensitisation tests in 11 patients (9 with coronary artery disease) who had a history of urticaria or angioedema in response to aspirin or non-steroid anti-inflammatory drugs.<sup>14</sup> Nine of the 11 patients tolerated the procedure without adverse effects and continued the aspirin treatment for 1 to 24 months, without exhibiting urticaria or angioedema. This protocol (Table 1) is particularly useful in patients with unstable coronary syndromes, since it can be completed within a few hours, thus permitting rapid desensitisation. The short duration (<3 hours), the low starting doses, the few adverse effects and the high efficacy were the basic reasons why this protocol was selected for our series of patients.<sup>16</sup> Although the protocol was only applied in a small number of patients, it succeeded in desensitising all of them without causing any adverse effects.

More recently, Rossini et al used a different protocol for rapid desensitisation in 26 patients with a history of hypersensitivity to aspirin who were to undergo a coronary intervention with stent implantation and had shown aspirin sensitivity in the past, with respiratory or cutaneous reactions.<sup>15</sup> The procedure included the administration of 6 progressively increasing doses of aspirin (1, 5, 10, 20, 40 and 100 mg) over 5.5 hours. Of the 23 patients who were desensitised successfully, 22 received stents and took aspirin for 1 year without showing any adverse effects, apart from 1 who discontinued the treatment because of a peptic ulcer.

There are no published protocols for aspirin desensitisation in individuals who are known to have an anaphylactoid response to the drug. In such cases it

is probably more practical to use an alternative antiplatelet agent such as a thienopyridine.<sup>6</sup>

The current recommendations of the American College of Cardiology and the American Heart Association regarding aspirin sensitivity in cardiovascular patients are that, if there is a real allergy to aspirin, other antiplatelet agents, such as dipyridamole, ticlopidine, or clopidogrel, should be substituted. This practice cannot be applied in patients who need percutaneous coronary intervention with stent implantation. The European Society of Cardiology, in its guidelines for acute myocardial infarction, mentions that aspirin desensitisation may be used as an alternative solution in patients with myocardial infarction.<sup>17</sup>

Because of the frequent need for stents during coronary artery interventions, the patients who have an indication for dual antiplatelet therapy with a combination of aspirin and thienopyridine (clopidogrel, prasugrel) have multiplied. Especially with the newest drug-eluting stents, dual antiplatelet treatment must be continued for a long period of time, probably more than 1 year.<sup>18</sup> In patients who have a history of aspirin allergy, the symptoms of aspirin hypersensitivity may develop during the period following stent implantation, when discontinuing aspirin runs the risk of catastrophic stent thrombosis.<sup>19</sup> A rapid challenge-desensitisation procedure could allow the introduction of aspirin in therapeutic doses within a few hours in such cases.<sup>15,20</sup> Since this procedure has been proved effective and safe, a history of aspirin allergy should not be an obstacle to stent implantation and the patients should not be excluded from optimal therapeutic management.

## Conclusions

Avoiding aspirin in patients with a reported allergy is a significant drawback in the majority of patients with acute coronary syndromes and/or a need for stent implantation. The correct classification of patients with “aspirin allergy” and their prompt referral for desensitisation is a safe option and allows the use of appropriate therapy in these patients.

## References

1. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med.* 1998; 339: 1665-1671.
2. Schwartz L, Bourassa MG, Lespérance J, et al. Aspirin and dipyridamole in the prevention of restenosis after percutaneous

- ous transluminal coronary angioplasty. *N Engl J Med.* 1988; 318: 1714-1719.
3. Hoekstra JW, Pollack CV, Roe MT, et al. Improving the care of patients with non-ST-elevation acute coronary syndromes in the emergency department: the CRUSADE initiative. *Acad Emerg Med.* 2002; 9: 1146-1155.
  4. Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 15 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. *J Am Coll Cardiol.* 2000; 36: 2056-2063.
  5. Julius S. Long-term potential of angiotensin receptor blockade for cardiovascular protection in hypertension: the VAL-UE trial. Valsartan Antihypertensive Long-term Use Evaluation. *Cardiology.* 1999; 91 Suppl 1: 8-13.
  6. Namazy JA, Simon RA. Sensitivity to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol.* 2002; 89: 542-550.
  7. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol.* 2003; 111: 180-186.
  8. Settipane GA. Aspirin sensitivity and allergy. *Biomed Pharmacother.* 1988; 42: 493-498.
  9. Strom BL, Carson JL, Morse ML, West SL, Soper KA. The effect of indication on hypersensitivity reactions associated with zomepirac sodium and other nonsteroidal antiinflammatory drugs. *Arthritis Rheum.* 1987; 30: 1142-1148.
  10. Sánchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol.* 2000; 84: 101-106.
  11. Ramanuja S, Breall JA, Kalaria VG. Approach to "aspirin allergy" in cardiovascular patients. *Circulation.* 2004; 110: e1-4.
  12. Gollapudi RR, Teirstein PS, Stevenson DD, Simon RA. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA.* 2004; 292: 3017-3023.
  13. Szezeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. *J Allergy Clin Immunol.* 1999; 104: 5-13.
  14. Wong JT, Nagy CS, Krinzman SJ, Maclean JA, Bloch KJ. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. *J Allergy Clin Immunol.* 2000; 105: 997-1001.
  15. Rossini R, Angiolillo DJ, Musumeci G, et al. Aspirin desensitization in patients undergoing percutaneous coronary interventions with stent implantation. *Am J Cardiol.* 2008; 101: 786-789.
  16. Page NA, Schroeder WS. Rapid desensitization protocols for patients with cardiovascular disease and aspirin hypersensitivity in an era of dual antiplatelet therapy. *Ann Pharmacother.* 2007; 41: 61-67.
  17. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J.* 2007; 28: 1598-1660.
  18. Pyrgakis VN, Goudevenos JA. Clopidogrel and cardiovascular diseases: recommendations for its correct use. *Hellenic J Cardiol.* 2009; 51: 83-86.
  19. Patane S, Marte F, Di Bella G. Catastrophic early drug eluting stents thrombosis and aspirin hypersensitivity. *Int J Cardiol.* 2008 17; 131: 25-27.
  20. Silberman S, Neukirch-Stoop C, Steg PG. Rapid desensitization procedure for patients with aspirin hypersensitivity undergoing coronary stenting. *Am J Cardiol.* 2005; 95: 509-510.