

Aspirin Desensitization in Patients Undergoing Percutaneous Coronary Interventions With Stent Implantation

Roberta Rossini, MD, PhD^{a,*}, Dominick J. Angiolillo, MD, PhD^b, Giuseppe Musumeci, MD^a, PierMario Scuri, MD^a, Paolo Invernizzi, MD^a, Theodore A. Bass, MD^b, Laurian Mihalcsik, MD^a, and Antonello Gavazzi, MD^a

The aim of this study was to test the safety and efficacy of a novel rapid desensitization procedure in patients with acetylsalicylic acid sensitivity and coronary artery disease who underwent cardiac catheterization and coronary stent implantation. Aspirin plays a key role in the secondary prevention of atherothrombotic events and thrombotic complications after stent implantation. Aspirin sensitivity not only limits patients to benefit from the long-term use of this antiplatelet agent but is also often an impediment to the implantation of bare-metal and drug-eluting coronary stents. Of 1,014 patients admitted for cardiac catheterization, 26 (2.6%) had histories of aspirin sensitivity characterized by respiratory or cutaneous manifestations (none had previous anaphylactic reactions); of these, 61.5% presented with acute coronary syndromes. All patients underwent a novel rapid desensitization challenge procedure before cardiac catheterization, except for those presenting with ST-elevation myocardial infarctions ($n = 4$), who underwent desensitization before hospital discharge. The desensitization procedure involved the oral administration of 6 sequential doses of aspirin (1, 5, 10, 20, 40, and 100 mg) over 5.5 hours without the use of corticosteroids or antihistamines. Patients were followed for 1 year to assess compliance with aspirin therapy and adverse events. The desensitization procedure was successful in 23 patients (88.5%). Percutaneous coronary intervention with stent implantation was performed in 22 patients (1.8 stents/patient). Drug-eluting stents were used in all patients except those who underwent primary percutaneous coronary intervention ($n = 3$), in whom bare-metal stents were used. Multivessel percutaneous coronary intervention was performed in 30.7% of patients. At follow-up, all patients who successfully responded to the desensitization procedure tolerated aspirin well, without developing allergic reactions. Aspirin was withdrawn in only 1 patient, because of a peptic ulcer. In conclusion, rapid desensitization is safe and highly effective in patients with aspirin sensitivity and coronary artery disease who undergo coronary stent implantation, including those who receive drug-eluting stents. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101:786–789)

Acetylsalicylic acid desensitization therapy might be an option for aspirin-allergic patients who require coronary stent implantation, in particular when drug-eluting stents (DES) are used.^{1,2} Acetylsalicylic acid desensitization therapy involves slowly increasing exposure to oral acetylsalicylic acid to reduce and/or eliminate pharmacologic and presumed immunologic reactions.³ Several desensitization protocols have been described.^{4,5} However, there is very limited experience with acetylsalicylic acid desensitization in patients with coronary artery disease (CAD), in particular those who undergo coronary stenting. Of note, many desensitization protocols use dosing intervals of up to 24 hours and thus are not practical for patients requiring early invasive management in whom the prompt administration of aspirin is required. Therefore, rapid and safe desensitization protocols are warranted for patients with CAD requiring

early invasive strategies with stent implantation. We report the safety and efficacy of a novel rapid acetylsalicylic acid desensitization protocol for patients with aspirin sensitivity who undergo early percutaneous coronary intervention (PCI) with stent implantation.

Methods and Results

From October 2005 to September 2006, 1,014 consecutive patients were admitted to our department for cardiac catheterization. Of these, 26 (2.6%) had histories of aspirin sensitivity. Aspirin sensitivity presented with respiratory ($n = 10$; asthma and/or rhinitis) and cutaneous ($n = 16$; urticaria and/or angioedema) manifestations. None of the cases involved previous anaphylactic reactions.

After providing informed written consent, patients with aspirin sensitivity underwent a novel desensitization challenge procedure. Patients underwent the desensitization procedure in the general cardiology ward. The oral desensitization challenge was performed with 6 sequential doses of aspirin, with a starting dose of 1 mg. Doses were increased every 30 to 120 minutes, with the overall procedure lasting 5.5 hours (Table 1). Per protocol, none of the patients were pretreated with antihistamines or corticosteroids. Blood pressure, pulse, and saturation were measured every 30

^aDivisione di Cardiologia, Dipartimento Cardiovascolare, Ospedali Riuniti di Bergamo, Bergamo, Italy; and ^bUniversity of Florida College of Medicine-Shands Jacksonville, Jacksonville, Florida. Manuscript received August 29, 2007; revised manuscript received and accepted October 21, 2007.

*Corresponding author: Tel: 39-035-269345; fax: 39-035-400491.

E-mail address: roberta_rossini@yahoo.it (R. Rossini).

Table 1
Aspirin desensitization protocol

Time (min)	Aspirin Dose (mg)
0	1
30	5
60	10
90	20
210	40
330	100

minutes, and cutaneous, naso-ocular, and pulmonary reactions were monitored closely until 4 hours after coronary intervention. Aspirin administration was immediately discontinued if cutaneous, respiratory, or systemic signs of sensitivity occurred. Coronary interventions were performed per local practice. Clopidogrel was used for 12 months in patients treated with DES and for 1 month in patients treated with bare-metal stents. All patients were followed for ≥ 12 months to monitor the incidence of major adverse events and compliance with aspirin therapy.

The baseline demographics of the study population are listed in Table 2. There was a prevalence of men and patients with acute coronary syndromes (61.5%) in our study. The desensitization procedure was performed before cardiac catheterization in all patients, except in those with ST-elevation myocardial infarctions in whom immediate reperfusion was required. In the latter group, the desensitization procedure was performed before hospital discharge. The desensitization procedure was immediately successful in 23 patients (88.5%). Nonserious adverse reactions occurred in the 3 patients in whom the procedure failed. Two of these patients had histories of chronic idiopathic urticaria and had experienced urticaria after taking aspirin. They were admitted for stable angina, and the desensitization procedure was attempted before performing coronary angiography. The 2 patients developed cutaneous reactions, 1 patient after the administration of 40 mg and the other < 12 hours after the administration of the last dose. The symptoms subsided after treatment with corticosteroids. The third patient in whom the desensitization protocol was unsuccessful had chronic obstructive pulmonary disease and had experienced the precipitation of asthma after the ingestion of aspirin several years earlier. She was admitted for an anterior non-ST-elevation myocardial infarction, during an acute attack of asthma with severe hypercapnia that had required mechanical ventilation. The patient was already receiving therapy with corticosteroids and inhaled salbutamol when aspirin desensitization was attempted. After the administration of the first dose (1 mg), she had a severe precipitation of asthma, with shortness of breath and bronchospasm. The symptoms resolved immediately after treatment with inhaled salbutamol. In none of these patients was rechallenge attempted.

PCI was performed in 22 patients (84.6%) and was uneventful in all cases. A total of 1.8 stents/patient were used; the mean stent length was 31.8 ± 19.6 mm. Multivessel PCI was performed in 8 patients (30.8%). All patients who underwent coronary intervention underwent stent implantation. DES were used in all patients ($n = 3$ sirolimus, $n = 16$ paclitaxel) except in those who underwent primary

Table 2
Baseline demographics

Characteristic	Value
Age (yrs)	61.8 ± 8.6
Men	20 (77%)
Diabetes	5 (19.2%)
Systemic hypertension	18 (69.2%)
Hypercholesterolemia*	20 (77%)
Current smokers	5 (19.2%)
Previous myocardial infarction	6 (23%)
Previous stroke	1 (3.8%)
Previous PCI	4 (15.3%)
Previous coronary bypass	1 (3.8%)
Clinical presentation	
Stable angina pectoris	10 (38.4%)
Unstable angina pectoris	5 (19.2%)
Non-ST-elevation myocardial infarction	7 (26.9%)
ST-elevation myocardial infarction	4 (15.5%)
Medical therapy	
Nitrates	19 (73%)
Angiotensin-converting enzyme inhibitors	12 (46.1%)
Angiotensin II receptor blockers	3 (11.5%)
Calcium antagonists	6 (23%)
β blockers	18 (69.2%)
Thienopyridine	15 (57.6%)
Statins	17 (65.3%)
Diuretics	8 (30.7%)
Multivessel coronary disease	18 (69.2%)
Left ventricular ejection fraction	$51.7 \pm 7.9\%$

* Defined as history or recent cholesterol level ≥ 90 th percentile for age and gender.

PCI ($n = 3$) for ST-elevation myocardial infarctions, who were treated with bare-metal stents (Table 3); 1 patient with an ST-elevation myocardial infarction did not undergo PCI, because of a lesion in small distal vessel not amenable to revascularization. In patients treated with DES and in those with acute coronary syndromes, combined therapy with aspirin and clopidogrel was continued for 12 months.

All patients were followed for ≥ 12 months. In all 23 patients who successfully responded to the desensitization protocol during hospitalization, long-term treatment with aspirin 100 mg was maintained and well tolerated. Aspirin was withdrawn in only 1 patient, because of the development of a peptic ulcer 1 month after cardiac catheterization. During follow-up, 2 patients were hospitalized 4 and 11 months after discharge because of the development of new ischemic symptoms. The 2 patients were still receiving treatment with aspirin and were referred to cardiac catheterization. One patient underwent PCI with DES implantation in the left anterior descending artery, and the other underwent coronary artery bypass grafting (Table 3). Major adverse cardiac events did not occur in the remaining patients or in the 3 patients in whom the desensitization protocol was unsuccessful.

Discussion

Aspirin, in addition to a thienopyridine, is the treatment of choice for the secondary prevention of atherothrombotic events in patients with CAD, particular those who undergo PCI with stent implantation.⁶ The present study is the large-

Table 3
Patient characteristics

Patient	Age (yrs)	Gender	Aspirin Hypersensitivity–Related Symptoms	Clinical Presentation	PCI	Stent Type	Stent Length (mm)	No. of Lesions Treated With PCI	No. of Vessels Treated With PCI	Pre-PCI Desensitization	Successful Desensitization	Aspirin Use at Follow-Up	Adverse Events at Follow-Up
1	58	M	Asthma	NSTEMI	0	—	—	0	0	+	+	+	0
2	61	M	Urticaria	SA	0	—	—	0	0	+	0	0	0
3	62	F	Asthma	SA	0	—	—	0	0	+	+	0	0
4	74	F	Urticaria	STEMI	0	—	—	0	0	0	+	+	0
5	42	M	Urticaria	STEMI	+	BMS	16	1	1	0	+	+	0
6	48	M	Asthma	STEMI	+	BMS	20	1	1	0	+	+	0
7	62	M	Urticaria	STEMI	+	BMS	20	1	1	0	+	+	CABG
8	46	M	Angioedema	SA	+	DES	20	1	1	+	+	+	0
9	54	F	Urticaria	NSTEMI	+	DES	24	1	1	+	+	+	0
10	58	M	Asthma	NSTEMI	+	DES	44	3	3	+	+	+	0
11	58	M	Urticaria	NSTEMI	+	DES	20	2	1	+	+	+	0
12	59	M	Urticaria	UA	+	DES	36	2	2	+	+	+	0
13	59	M	Urticaria	SA	+	DES	28	2	2	+	+	+	0
14	60	M	Urticaria	SA	+	DES	16	1	1	+	+	+	0
15	60	M	Asthma	SA	+	DES	70	2	1	+	+	+	0
16	61	F	Urticaria	SA	+	DES	15	2	2	+	0	0	0
17	63	M	Asthma	UA	+	DES	60	2	2	+	+	+	0
18	63	M	Angioedema	UA	+	DES	44	2	2	+	+	+	0
19	64	M	Angioedema	UA	+	DES	24	2	2	+	+	+	0
20	64	M	Asthma	NSTEMI	+	DES	32	2	2	+	+	+	0
21	67	M	Asthma	SA	+	DES	20	1	1	+	+	+	0
22	70	M	Angioedema	SA	+	DES	12	1	1	+	+	+	0
23	70	F	Asthma	NSTEMI	+	DES	12	1	1	+	0	0	0
24	70	M	Urticaria	SA	+	DES	32	2	1	+	+	+	0
25	72	M	Angioedema	UA	+	DES	60	3	1	+	+	+	Repeat PCI
26	82	F	Asthma	NSTEMI	+	DES	76	2	1	+	+	+	0

BMS = bare-metal stent; CABG = coronary artery bypass grafting; NSTEMI = non-ST-elevation myocardial infarction; SA = stable angina; STEMI = ST-elevation myocardial infarction; UA = unstable angina.

est to explore aspirin desensitization in patients with CAD and is the first performed in patients who underwent DES implantation. In this investigation, we used a novel desensitization protocol that, compared with others previously described, is more rapid and does not require the use of antihistamines or corticosteroids. This was shown to be safe and efficacious, with approximately 90% patients responding to the desensitization procedure, all of whom maintained treatment with aspirin without developing allergic reactions. Importantly, it allowed us to perform complex percutaneous revascularization procedures with the implantation of DES without increasing periprocedural events; many of these patients were also at high risk, because they had presented with acute coronary events.

Three types of aspirin sensitivity have been described: respiratory sensitivity (asthma and/or rhinitis), cutaneous sensitivity (urticaria and/or angioedema), and systemic sensitivity (anaphylactic reaction).⁷ The prevalence of aspirin-exacerbated respiratory tract disease is approximately 10%, and for aspirin-induced urticaria, the prevalence varies from 0.07% to 0.2% in the general population.^{3,8} In the present study, 2 of the 3 patients in whom the desensitization protocol was unsuccessful had chronic urticaria independent of the intake of aspirin. This is consistent with previous data, which showed that the desensitization challenge is more likely to be unsuccessful in patients who have continuing urticaria independent of aspirin.⁶ Close surveillance of such patients is warranted if a desensitization challenge is attempted, and the high risk for desensitization failure has to be taken into account before proceeding to revascularization. The third patient in whom desensitization was unsuccessful had recently had a severe asthma attack, and by the time the protocol was started, it was probably not completely resolved.

Most aspirin desensitization protocols reported are time consuming and may take several days to perform.^{4,9,10} In addition, dedicated protocols have been developed for patients with specific types of aspirin hypersensitivity. Szczeklik and Stevenson¹¹ described a strategy for desensitizing patients with respiratory manifestations. This protocol, also referred to as the "Scripps Clinic protocol," involves small incremental oral doses of aspirin administered over the course of 2 to 3 days, until 400 to 650 mg is tolerated. Although a long interval between doses can guarantee the safety of the procedure, as symptoms can be detected at each given dose, the entire procedure requires several days to be completed. Such protocols, however, are not practical in patients with acute coronary syndromes or those who undergo stent implantation who require the immediate administration of aspirin. In addition, a protocol applicable for patients with different manifestations of aspirin sensitivity, as in this study, is more practical. Indeed, the simplified protocol of Silberman et al¹² required only 2.5 hours. However, because of the greater risk of our population, we lowered the starting dose from 5 to 1 mg, which added 3

hours to the protocol. This enables the detection of potential late reactions, which can occur after 2 to 4 hours, and enhances the safety profile of our strategy.

To date, few data exist on aspirin desensitization in patients with CAD, particularly in patients with acute coronary syndromes. This is of note because hypersensitivity symptoms may be dramatic and can rapidly worsen the clinical conditions of patients with acute coronary syndromes. Wong et al⁶ performed desensitization challenge studies in 11 patients with histories of aspirin-induced or nonsteroidal anti-inflammatory drug-induced urticaria or angioedema; of these, 9 had CAD. Nine of 11 patients tolerated the procedure without adverse effects and continued aspirin therapy from 1 to 24 months without developing urticaria or angioedema. However, these patients were pretreated with either antihistamines or corticosteroids before the administration of aspirin. In the present study, only patients with CAD were studied, many of whom had acute coronary syndromes and were treated with DES, for which per protocol, patients were not pretreated with antihistamines or corticosteroids.

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