ORIGINAL ARTICLE

Aspirin desensitisation for Chinese patients with coronary artery disease

CME

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Objective To assess the efficacy and safety of aspirin desensitisation in Chinese patients with coronary artery disease.

Design Case series.

Setting A regional hospital in Hong Kong.

Patients Chinese patients with coronary artery disease and a history of a hypersensitivity reaction to aspirin or non-steroidal anti-inflammatory drug, who underwent aspirin desensitisation between February 2008 and July 2012.

Results There were 24 Chinese patients with coronary artery disease who were admitted to our unit for aspirin desensitisation during this period. The majority (79%) were clinical admissions for desensitisation; eight (33%) of them developed a hypersensitivity reaction during desensitisation. Half of the latter had only limited cutaneous reactions and were able to complete the desensitisation protocol and developed aspirin tolerance. Overall, 20 (83%) of the patients were successfully desensitised at the initial attempt. No serious adverse reactions occurred in the cohort. Twelve of the patients had significant coronary artery disease revealed by coronary angiography and received a percutaneous coronary intervention, nine of whom received drug-eluting stents while three received bare metal stents due to financial constraints. All 11 successfully desensitised patients received aspirin and clopidogrel as double antiplatelet therapy after percutaneous coronary intervention. The remaining patient had a bare metal stent implant due to failed aspirin desensitisation.

Conclusion Given the potentially different genetic basis of aspirin hypersensitivity in different ethnicities, recourse to desensitisation in the Chinese population has not previously been addressed. This study demonstrated that aspirin desensitisation using a rapid protocol can be performed effectively and safely in Chinese patients. Our results were comparable to those in other reported studies involving other ethnicities. Successful aspirin desensitisation permits patients to pursue long-term double antiplatelet therapy that includes aspirin after percutaneous coronary intervention, and thus allows the use of drug-eluting stents as a feasible option.

Key words
Anti-inflammatory agents, non-steroidal; Aspirin; Coronary artery disease; Desensitization, immunologic

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New knowledge added by this study

- This study demonstrated that a protocol entailing rapid desensitisation to aspirin can be performed effectively and safely in Chinese patients. The results were comparable to those reported in other ethnicities.

Implications for clinical practice or policy

- Successful desensitisation of patients to aspirin permits long-term double antiplatelet therapy that includes aspirin after percutaneous coronary intervention, and thus allows the use of drug-eluting stents as a feasible option.

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Introduction

Aspirin is one of the most commonly prescribed drugs worldwide, with its pain-relieving, anti-inflammatory, and antiplatelet indications. However, some patients suffer from hypersensitivity reactions to aspirin and/or non-steroidal anti-inflammatory drugs

為冠狀動脈病華籍患者進行阿司匹林脫敏療法

目的 探討阿司匹林脫敏療法對於冠狀動脈病華籍患者的療效和安全性。

設計 病例系列。

安排 香港一所分區醫院。

患者 對阿司匹林和非類固醇類抗炎藥有過敏反應，並於2008年2月至2012年7月期間接受阿司匹林脫敏療法的冠狀動脈病華籍患者。

結果 研究期間共24名冠狀動脈病華籍患者入院接受阿司匹林脫敏療法。大部份患者（79%）在非緊急情況下入院接受脫敏療法；8人（33%）在接受脫敏療法的過程中出現過敏性反應，其中一半出現有限度的皮膚過敏，但仍能完成脫敏療程，並產生阿司匹林耐受性。總體而言，20名（83%）患者初次成功脫敏；患者均無嚴重不良反應。12名患者經冠脈造影證實有明顯的冠狀動脈病，遂接受經皮冠狀動脈介入治療；其中9人植入藥物洗脫支架，另3人因經濟困難而植入裸金屬支架。經皮冠狀動脈介入治療後，11名患者接受阿司匹林和氯吡格雷的雙重抗血小板治療，其餘1人由於阿司匹林脫敏失敗而須植入裸金屬支架。

結論 由於遺傳基因的差異，阿司匹林過敏反應在不同種族中也有不同。過往亦未有檢視華籍人口中脫敏療法的情況。本研究顯示使用阿司匹林快速脫敏療法可以在冠狀動脈病華籍患者中有效及安全地進行。本研究的結果與其他牽涉不同種族的研究報告相近。阿司匹林脫敏療法讓冠狀動脈病患者能接受長期的雙重抗血小板治療，包括經皮冠狀動脈介入治療後的阿司匹林，而藥物洗脫支架亦成為一種可行的選擇。

(NSAIDs). Among asthmatics, the reported prevalence of aspirin-exacerbated respiratory symptoms ranged from 8 to 20%.[1-3] Cutaneous reactions to NSAIDs occur in 0.1 to 3% of patients consuming these drugs.[4] Specific cyclo-oxygenase (COX)–2 inhibitors or other classes of drugs, such as paracetamol, can be used as alternative pain killers.[5,6] However, in the subgroup of patients with coronary artery disease (CAD), the use of aspirin as secondary prophylaxis appears more compelling.[7-9] A thienopyridine, namely clopidogrel, has been used as an alternative in these patients, although the cost-effectiveness of this approach has not been validated.[10] For patients receiving percutaneous coronary intervention (PCI) and for acute coronary syndrome (ACS), the indications of double antiplatelet have expanded in the past decade.[11-14] Aspirin desensitisation, which permits aspirin-hypersensitive patients with CAD to pursue long-term aspirin treatment, therefore becomes an attractive treatment strategy and has been incorporated in major international guidelines.[15]

Different genetic markers have been associated with aspirin-intolerant asthma and aspirin-intolerant urticaria,[16-18] yet the association of some single nucleotide polymorphisms of these genes and their phenotypes differs depending on ethnicity. For example, the -444C allele in the gene promoter region of the leukotriene C4 synthase (*LTC4S*) gene is associated with the development of aspirin-intolerant asthma in Polish people.[19] Such correlation with phenotypes was not found in the Japanese and people from the United States.[20,21] The presence of this variant allele in patients with aspirin-intolerant asthma in the Japanese population is less frequently found than in those of East European descent. Therefore, it is believed that the genetic basis of aspirin hypersensitivity differs in different ethnic groups, and the response to aspirin desensitisation in different ethnicities may be variable. Although the success of aspirin desensitisation has been demonstrated in several studies,[22-27] to our knowledge this issue has not been addressed in the Chinese. In this study, we investigated the efficacy and safety of aspirin desensitisation in a cohort of Chinese patients who suffered from aspirin hypersensitivity and CAD, for whom cardiac catheterization and PCI were indicated. In these patients, therefore, continuation of aspirin as part of double antiplatelet therapy was desirable.

Methods

We embraced the rapid desensitising protocol developed by Silberman et al,[27] except that we used aspirin 80 mg as the final dose instead of Silberman's 75 mg dose, as the 80 mg oral preparation was more readily available in our locality. Before the procedure took place, patients were instructed to withhold antihistamine and steroid medications for 3 days, as these drugs can mask the early signs of anaphylaxis, which can be fatal. Beta-blockers were omitted for 1 day prior to starting desensitisation. Desensitisation was performed in the coronary care unit to ensure close monitoring. A 5 mg per mL aspirin solution was used to administer five sequential escalating doses every 30 minutes (Table 1). Baseline blood pressure, respiratory rate, oxygen saturation, and peak flow rate (based on bedside spirometry) were closely monitored every 15 to 30 minutes during the process of desensitisation, followed by a 3-hour monitoring period after the final aspirin dose. Patients who developed a hypersensitivity reaction during desensitisation were managed according to its severity with chlorpheniramine, steroids, adrenaline, volume resuscitation and/or early termination of desensitisation. After successful desensitisation, the patient was advised to continue taking aspirin without interruption in order to maintain aspirin tolerance.

TABLE 1. Aspirin desensitisation protocol

Time (mins)	Dosage	Cumulative dosage
0	5 mg (1 mL)	5 mg
30	10 mg (2 mL)	15 mg
60	20 mg (4 mL)	35 mg
90	40 mg (8 mL)	75 mg
120	80 mg (16 mL) or 80 mg tablet	155 mg

In this study, aspirin desensitisation was performed in patients of Chinese ethnicity with CAD under consideration for PCI, who had reported a history of, or had a clearly documented hypersensitivity reaction to aspirin or an NSAID. The data of consecutive patients admitted to our centre for aspirin desensitisation from February 2008 to July 2012 were collected retrospectively. The demographic data, CAD status, indications, and details of aspirin desensitisation were reviewed. The success rate of desensitisation and adverse events were analysed. Categorical variables were analysed as frequencies and percentages, whereas for continuous variables we used means.

Results

From February 2008 to July 2012 (54 months), 24 Chinese patients were admitted to our centre for aspirin desensitisation (Table 2). The majority (92%) had cutaneous symptoms such as rash, urticaria, or angioedema as the initial hypersensitivity manifestation. One patient had anaphylaxis after ingestion of diclofenac. Among patients with a cutaneous presentation only, one with chronic idiopathic urticaria (CIU) developed recurrent exacerbations of urticaria since starting aspirin and several other cardiac drugs after an ACS event. More than half of the patients (54%) had an ACS as the primary presentation of CAD. The majority of the patients (79%) attended through clinical admissions for desensitisation, whereas the rest received desensitisation during the index admissions for ACS. Concerning the indications for undergoing the desensitisation procedure, 21 (88%) procedures served as preparation for elective cardiac catheterization with or without PCI. Two patients received desensitisation after PCI. One suffered an ST-segment elevation myocardial infarction (STEMI) with failed fibrinolysis and received rescue PCI with a drug-eluting stent on the second day of hospitalisation. This patient received prasugrel as single antiplatelet therapy after PCI and underwent successful desensitisation on day 4 as an emergency. The other patient had PCI with a drug-eluting stent during the index hospitalisation after successful fibrinolytic therapy for STEMI and was started on

TABLE 2. Patient demographic data, clinical features, and desensitisation outcomes

Characteristics and outcomes of desensitisation*	No. (%)†
Age (mean ± standard deviation) [years]	64 ± 13
Gender (male)	16 (67)
Initial presentation of aspirin/NSAIDs allergy	
Respiratory symptoms	0 (0)
Cutaneous symptoms	22 (92)
Respiratory + cutaneous symptoms	1 (4)
Anaphylaxis	1 (4)
Drugs causing allergy	
Aspirin	16 (67)
NSAIDs other than aspirin	2 (8)
Aspirin and NSAIDs	6 (25)
Presentation of CAD	
ACS	13 (54)
Stable CAD	11 (46)
Indication of desensitisation	
Urgent desensitisation after ACS	1 (4)
Elective desensitisation to prepare cardiac catheterization ± PCI	21 (88)
Urgent desensitisation after PCI	1 (4)
Elective desensitisation after PCI	1 (4)
Admission type for desensitisation	
Clinical admission	19 (79)
During index admission for ACS	5 (21)
Immediate allergic reaction during desensitisation	
Skin rash	5 (21)
Urticaria	2 (8)
Angioedema	1 (4)
No immediate allergic reaction	16 (67)
Treatment given for immediate allergic reaction‡	
No treatment	4 (50)
Antihistamine	3 (38)
Stop desensitisation	1 (13)
Immediate desensitisation success	20 (83)
Revascularisation outcome after desensitisation	
PCI after successful desensitisation	9 (38)
PCI despite failed desensitisation	1 (4)
Successful desensitisation after PCI	2 (8)
CABG	1 (4)
No PCI due to mild CAD	10 (42)
No revascularisation due to other reason	1 (4)
Stent use in PCI§	
Bare metal stent	3 (25)
Drug eluting stent	9 (75)
Mean (range) No. of stents implanted	1.8 (1-6)
Mean (range) period of aspirin treatment to latest follow-up (months)	16 (1-53)

* NSAIDs denotes non-steroidal anti-inflammatory drugs, CAD coronary artery disease, ACS acute coronary syndrome, PCI percutaneous coronary intervention, and CABG coronary artery bypass graft

† Unless otherwise indicated

‡ Among the eight patients who developed immediate allergic reactions

§ Among the 12 patients having PCI

prasugrel and cilostazol (a phosphodiesterase inhibitor that inhibits platelet aggregation). He was desensitised to aspirin successfully during an elective readmission 22 days after the initial ACS event. Prasugrel and aspirin were continued as post-PCI double antiplatelet therapy. Desensitisation was performed semi-urgently in one patient on the second day of hospitalisation for non-STEMI event, in order to prepare for a semi-urgent PCI. This patient failed aspirin desensitisation and received PCI with a bare metal stent during the index admission. A 4-week course of prasugrel and cilostazol was used instead as the post–coronary stenting antiplatelet regimen.

The patients had not received pretreatment before desensitisation with the exception of one with CIU, in whom the usual dose of maintenance antihistamine was continued throughout the desensitisation procedure. During the desensitisation process, eight (33%) of the patients experienced immediate hypersensitivity symptoms—five developed a skin rash, two had urticaria, and one had angioedema. Among the five patients who experienced a skin rash, in four it was limited. The latter were able to complete the desensitisation procedure and acquire tolerance, one of whom temporarily received oral antihistamine treatment to alleviate symptoms. The remaining patient's rash became worse the day after desensitisation and was considered as having failed to develop tolerance. The remaining three patients (with urticaria and angioedema) also failed desensitisation (Table 3). None of these patients had any life-threatening adverse event or any severe adverse reaction for which intravenous steroids were given. Immediate success, as defined by developing tolerance permitting maintenance aspirin treatment, was achieved in 20 (83%) patients. In one woman who failed initial desensitisation, a second attempt at desensitisation was successfully performed 2.5 years later. One patient with mild CAD developed a skin rash 7 months after the initial successful desensitisation, for whom aspirin was replaced by clopidogrel. Up to the latest follow-up (mean period of 15.6 months), 20 patients who underwent desensitisation were able to continue maintenance aspirin.

In the whole cohort, 12 patients had significant CAD revealed by coronary angiography and underwent PCI (after successful desensitisation in 9 patients and failed desensitisation in 1, and 2 underwent successful desensitisation after PCI). Nine of the 11 successfully desensitised, who underwent revascularisation, received drug-eluting stents. Bare metal stents were used in the three others due to financial constraints. In one of these three patients, failure of desensitisation also contributed to the decision to use bare metal stents.

Discussion

Aspirin desensitisation involves the use of gradually increasing dosages of aspirin at intervals to enable development of tolerance. Long-term administration of aspirin after successful desensitisation is mandatory to maintain tolerance. Aspirin desensitisation has been shown to be successful in patients with either aspirin-exacerbated respiratory disease or aspirin-induced cutaneous

TABLE 3. Details of the four patients who failed initial aspirin desensitisation*

Patient No.	Age (years)/ gender	Presentation of aspirin/NSAIDs allergy	Presentation of CAD	Presentation of allergic reaction during desensitisation and treatment	Outcome
1	39/M	Aspirin-induced angioedema	ACS	Desensitisation on day 2 of NSTEMI. Periorbital oedema 1.5 hours after the last dose of aspirin. Antihistamine was given for symptom relief.	PCI with BMS was performed during index hospitalisation. 4-Week course of prasugrel and cilostazol were used as post-PCI antiplatelet regimen.
2	55/F	Aspirin-induced rash	Stable CAD	Mild erythema over the neck and back after the second aspirin dose. The patient was able to complete the whole desensitisation protocol without treatment for symptom relief. However the rash worsened on the same day and the patient was not able to continue maintenance aspirin.	Cardiac catheterization showed mild CAD.
3	64/F	Aspirin and mefenamic acid–induced rash	Stable CAD	Urticaria over the chin after 40 mg aspirin dose. Desensitisation was terminated.	Cardiac catheterization showed mild CAD.
4	75/F	Aspirin and diclofenac–induced rash	Stable CAD	Urticaria over the back 1 hour after the last aspirin dose. Antihistamine was given for symptom relief.	Cardiac catheterization showed mild CAD. Successful desensitisation in the second attempt 2.5 years later to prepare for cardiac catheterization for recurrent chest pain.

* ACS denotes acute coronary syndrome, BMS bare metal stent, CAD coronary artery disease, NSAIDs non-steroidal anti-inflammatory drugs, NSTEMI non–ST-segment elevation myocardial infarction, and PCI percutaneous coronary intervention

presentations.[22-27] In aspirin-intolerant patients suffering from severe rhinosinusitis and nasal polyps, aspirin desensitisation has even been used as a therapeutic measure to ameliorate the nasal symptoms. Different aspirin desensitisation protocols have been developed and yield promising results. The traditional desensitisation protocols adopt long intervals of up to 24 hours between aspirin doses and take several days to complete.[22-25] The latter approach is theoretically safer as early signs of anaphylaxis can be picked up during the long observation intervals between drug challenges. Protocols for rapid desensitisation involving shorter intervals between drug doses evolved subsequently and have been shown to be effective and safe.[26,27] Such protocols allow the desensitisation process to be completed in just a few hours. The rapid development of tolerance is especially important in the situation of an ACS, in which the antiplatelet effect of aspirin is needed quickly. In our study in Chinese subjects, the success rate of desensitisation was comparable to that in published series conducted in the United States and some European countries. The rapid protocol was also considered safe, as no serious adverse reaction was encountered in our cohort. Although hypersensitivity reactions are fairly common during the desensitisation process (33%), half of such reactions are mild and self-limiting, which allows the patients to complete the procedure and develop aspirin tolerance.

Stevenson et al[6,28] developed a classification of aspirin and NSAID hypersensitivity based on the symptomatology and the underlying pathogenic mechanisms (Table 4). Two pathological processes have been described.[5] One entails the pseudo-allergic reaction due to COX-1 inhibition, in which hypersensitivity develops once the patient is exposed to any drugs with COX-1 inhibition properties, including aspirin and other NSAIDs. Another entails a true immunoglobulin E (IgE)–mediated allergic reaction, in which patient develops an allergic reaction during re-exposure to aspirin or another specific NSAID but not to others with structural dissimilarity. Owing to these different pathogenic mechanisms, the development of aspirin tolerance during desensitisation should also be considered as having different mechanisms.[5,29] Nevertheless, precise categorisation of aspirin hypersensitivity has not been made in subjects involved in previous desensitisation studies because classifying patients as having pseudo-allergy or true allergy is sometimes difficult based on symptoms and drug exposure history alone. Thus, individuals are often instructed to avoid aspirin and all other NSAIDs once a hypersensitivity reaction ensues. The results of desensitisation studies nevertheless suggest that both types of hypersensitivity reactions can be successfully treated, with the possible exception of those involving CIU. Despite the potentially different genetic basis of aspirin hypersensitivity in different ethnic groups, the comparable success rate of desensitisation in Chinese subjects in this and other case series[26,27] suggests that the immunogenic mechanisms for developing tolerance may be similar.

It has been reported that 21 to 30% of patients with CIU have aspirin hypersensitivity.[30] In several case series, the failure rate of aspirin desensitisation has been reported to be high, although successful desensitisation has been reported with a 3-day protocol.[26,27,31-34] Therefore perhaps in them, aspirin desensitisation utilising long observation (dosing) interval protocols should be considered and individualised, and only in patients for whom such treatment is strongly indicated. At the same time, the high chance of desensitisation failure should also be considered when deciding on the treatment strategy. Our patient with CIU was successfully desensitised with the rapid protocol. However, we are not certain whether aspirin was the only cause of his hypersensitivity reaction. After the initial STEMI event, the patient was started on aspirin, along with other cardiac medications (clopidogrel, carvedilol and perindopril). Despite an abstinence period from all medications, the patient repeatedly developed cutaneous flares that did not show any temporal relation to carvedilol and perindopril

TABLE 4. Classification of aspirin/NSAIDs hypersensitivity* [6,28]

Type	Description of reactions	Underlying disease	Mechanism	Reaction at first exposure	Cross-reactions with other COX-1 inhibitors
I	Multiple NSAIDs–induced rhinitis and asthma	Asthma/nasal polyps/sinusitis	COX-1 inhibition	Yes	Yes
II	Multiple NSAIDs–induced urticaria/ angioedema	Chronic idiopathic urticaria	COX-1 inhibition	Yes	Yes
III	Multiple drug–induced urticaria/angioedema	None	COX-1 inhibition	Yes	Yes
IV	Single drug or multiple NSAIDs–induced blended reaction	Asthma, rhinitis, urticaria, or none	COX-1 inhibition	Yes or no	Yes or no
V	Single drug–induced urticaria/angioedema	None	IgE-mediated	No	No
VI	Single drug–induced anaphylaxis	None	IgE-mediated	No	No

* NSAIDs denotes non-steroidal anti-inflammatory drugs, COX cyclo-oxygenase, and IgE immunoglobulin E

rechallenges. Therefore, we inferred that either aspirin or clopidogrel was responsible for his initial hypersensitivity reaction, although we did not attempt rechallenging him with either of these drugs. After prolonged antihistamine and oral steroid treatment, his chronic urticaria was brought under control. Eventually, the patient again underwent uneventful aspirin desensitisation followed by clopidogrel desensitisation.

In our study, two patients reported hypersensitivity reaction to NSAIDs without previous exposure to aspirin or any other structurally different NSAID. As mentioned earlier, it is usually difficult to assess cross-sensitivity and to classify hypersensitivity reactions by symptoms and drug history alone. There was also no in-vitro test or specific IgE assay to help determine underlying pathogenic mechanisms. The aspirin challenge test has been proposed in this situation.[35] Lack of aspirin cross-reactivity with other COX-1 inhibitors may suggest an IgE-mediated true allergic reaction. Such a patient may be considered eligible for taking aspirin or a structurally different NSAID. This differentiation is essential in patients requiring intermittent use of NSAIDs, such as patients with recurrent arthritis. However, the challenge test has the potential to induce severe allergic reactions and therefore close clinical monitoring during drug challenge is always necessary. As these various procedures involve similar manpower resources, for patients with CAD we prefer proceeding directly to desensitisation rather than challenge tests. Unlike patients who need NSAIDs intermittently, for those with CAD who mostly require long-term aspirin treatment, establishing tolerance to aspirin is probably more important than knowing whether they have cross-sensitivity.

In our cohort, as well as in previous case series,[26,27] most of the subjects received elective desensitisation. Successful desensitisation permitted them to receive long-term aspirin and therefore drug-eluting stents became a reasonable option during PCI. In emergent situations like STEMI, the role of aspirin desensitisation is uncertain. A recent case series reported the success of urgent desensitisation by rapid protocols in patients admitted for ACS.[31] Some of the procedures were initiated just after urgent PCI, or even carried out in the cardiac catheterization laboratory during urgent PCI. Such an urgent desensitisation approach requires validation through further studies. For unstable patients undergoing urgent PCI without prior aspirin tolerance being established, several treatment strategies may be considered. To get through such urgent situations, Gollapudi et al[36] proposed using bare metal stents and alternative perioperative medications such as glycoprotein IIb/IIIa inhibitors, direct thrombin inhibitors, and subsequently thienopyridines and warfarin. The use of ticlopidine as a single antiplatelet agent has also been described after coronary artery stenting without leading to more adverse events.[37] In this situation, the role of novel P2Y12 inhibitors, including prasugrel and ticagrelor, has not yet been addressed in any trial. In our study, we adopted a post-coronary stenting antiplatelet regimen involving prasugrel and cilostazol in two patients, one of whom had failed aspirin desensitisation and received a bare metal stent. The other patient had PCI with a drug-eluting stent, after successful fibrinolysis for STEMI and was successfully desensitised 22 days after the procedure. The Genous bioengineered stent (OrbusNeich; Hong Kong SAR, China), with its endothelial progenitor cell-capturing property, also appears to be an attractive option to minimise the risk of stent thrombosis in patients not eligible for aspirin.[38]

One limitation of this study was its retrospective nature. Another was that the status of aspirin or NSAID hypersensitivity was based on a self-reported history or a history of allergy as documented in the medical records. Challenge tests for the purpose of confirming or refuting hypersensitivity or to classify the allergy type were not carried out.

Conclusion

The success of aspirin desensitisation has been established in several case series. Given the potentially different genetic basis of aspirin hypersensitivity in different ethnic groups, its use in the Chinese has not been previously addressed. In our study, the efficacy and safety of aspirin desensitisation in a group of Chinese patients were demonstrated and the results were comparable to those of other reported studies of patients in other ethnic groups. Successful aspirin desensitisation permits patients with CAD to pursue long-term use of aspirin, and makes the use of drug-eluting stents a feasible option.

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