

RAPID ASPIRIN DESENSITISATION TO AID USE IN CORONARY ARTERY DISEASE: ILLUSTRATIVE CASE SERIES OF LOCAL PRACTICE

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SUMMARY

Several international cardiac units have found rapid aspirin desensitisation to be safe and effective. The management of acute coronary syndromes requires dual anti-platelet therapy post percutaneous coronary intervention. For patients with aspirin hypersensitivity this poses a problem. The Groote Schuur Allergy Unit in collaboration with the Cardiology service implemented a rapid aspirin desensitisation protocol at C27 Coronary Care Unit in 2016. The following case demonstrates how the protocol was adjusted to make the procedure even safer. Summative data are also provided of the other cases desensitised successfully to date despite the variation in the clinical presentation of their aspirin hypersensitivity.

Keywords: aspirin, rapid desensitisation, coronary artery disease

ILLUSTRATIVE CASE

CARDIAC NEED

A 54-year-old male British immigrant from Simon's Town was admitted to the coronary care unit in Groote Schuur Hospital (GSH) with a non-ST segment elevation myocardial infarction (NSTEMI) and left ventricular failure. He was known with Type 2 diabetes mellitus, a previous myocardial infarction in 2017, is an ex-smoker and had experienced worsening asthma and atopic dermatitis over the past eight months, which prompted increased topical corticosteroids and medium-dose ICS/LABA. He had a history of anaphylaxis within minutes after aspirin ingestion. He presented initially at Victoria Hospital with chest pain, diaphoresis and shortness of breath that worsened on exertion. Current medications included: simvastatin, enalapril, bisoprolol, clopidogrel and actraphane insulin. ECG changes were: T wave inversion in leads V4–V6, Troponin I level of 439 ng/mL and initial diagnosis was made of NSTEMI. One day later, however, the patient developed ST elevation in leads V1–V3, Q waves in leads V2 and V3 and the diagnosis was made of ST segment elevation MI (STEMI). The patient was transferred to cardiology at GSH for intervention; angiography showed

100%, 90% and 50% occlusion of the left anterior descending artery, left circumflex and right coronary arteries respectively. The patient underwent successful percutaneous stenting. However, in order to maintain stent patency dual anti-platelet therapy was required (clopidogrel and aspirin). Our allergy team was consulted to assess the patient for aspirin desensitisation.

ALLERGY ASSESSMENT

The patient was atopic, with a history of moderate persistent childhood asthma, including hospitalisation, but no ventilation. During the past eight months, his allergic rhinitis (AR) and asthma had recurred, with several episodes of chest tightness with wheezing, for which he was prescribed medium-dose ICS/LABA combination therapy by his general practitioner. However, he defaulted on this treatment.

He reported a severe reaction to aspirin for the first time two years previously after he took aspirin without water in a fish-and-chips shop. Prior to this episode, he had tolerated both aspirin and ibuprofen (other NSAIDs). He experienced a tingling of his tongue and a feeling of impending doom soon after and alerted the person behind the counter that he was having an

allergic reaction. His chest became extremely tight and he subsequently had cardiovascular collapse with cardiac arrest. Fortunately, a trained nurse was the first responder and he made it to the ICU and survived. He was told that he was allergic to aspirin. General examination found tachypnea (RR 20/min) and tachycardia (101 bpm), with bilateral weeping eczema in the cubital fossae. Nasal examination showed erythematous and swollen turbinates, but no easily visible polyps. Chest examination revealed a bilateral wheeze, with prolonged expiration. Allergy testing included a negative CAST for Lys-aspirin (24 pg/mL, cut-point for positive > 90 pg/mL). Available specific IgE measurements for inhalant allergens were positive for both dog and cat dander as well as for *dermatophagoides pteronyssinus* and *farinae*. Since this initial severe aspirin reaction, he had been avoiding all COX-1 NSAIDs.

Differential diagnosis included aspirin-exacerbated respiratory disease (AERD), with poorly controlled asthma; single NSAID IgE-mediated aspirin allergy; and co-morbid left ventricular failure.

MANAGEMENT

The absolute and urgent need for dual platelet therapy, including aspirin, meant that we proceeded to desensitisation in the Cardiac ICU without challenge, using a modified protocol to improve safety due to the patient's history of anaphylaxis and recent poor asthma control. In addition, we waited until the patient had received 24 hours of antibiotics for cellulitis of his arm. The standard pre-proceed practice was followed, which included:

- beta-blockers were stopped for 24 hours;
- informed consent was taken;
- IVI access was secured and 0.5 mL of 1 : 1 000 adrenaline was drawn up;
- montelukast 10 mg was given 30 minutes prior to commencement; and

- baseline vitals measurement of blood pressure (BP), heart rate and peak expiratory flow rate (PEFR) were done. A mixture of 300 mg aspirin in 150 mL water for a concentration of 2 mg/mL; the starting dose of 2 mL (4 mg) was given. The patient was observed for cutaneous, vocal cord, nasal and respiratory symptoms. The first and second doses of 4 mg and 10 mg were repeated at 30-minute intervals during the first two hours; thereafter, the dose was doubled every 30 minutes to the therapeutic dose of 150 mg.

The procedure was completed in four hours and 30 minutes without any adverse reaction. Should any reaction have occurred, the procedure would have been stopped and the patient treated for the particular reaction, that is, with adrenaline, nebulised B-agonists and given oral or IV antihistamines and prednisone, depending on the severity of the reaction. The absolute necessity to take daily aspirin was stressed to the patient both in order to maintain tolerance and well as for the cardiac benefits.

DISCUSSION

ASPIRIN IN ISCHAEMIC HEART DISEASE

Aspirin irreversibly inhibits cyclo-oxygenase 1 (COX-1), which limits thromboxane A₂ production, a potent stimulator of platelet aggregation. Aspirin is the most commonly used anti-platelet medication for both primary and secondary prevention in ischaemic heart disease (IHD). An estimated 1.5% of cardiac patients have aspirin hypersensitivity.¹ Alternative agents, such as P2Y₁₂ receptor or phosphodiesterase (PDE) inhibitors, are effective alternatives in situations requiring only single anti-platelet therapy; however, in several clinical settings of acute coronary syndromes and percutaneous coronary intervention (PCI), dual anti-platelet therapy is needed.² For example, dual anti-platelet therapy prevents stent blockage and myocardial infarction post-PCI and angioplasty. These evidenced-based

TABLE 1: CURRENT CLASSIFICATION OF NSAID HYPERSENSITIVITY PHENOTYPES WITH EXAMPLE DRUGS (ADAPTED FROM REFERENCES^{3,4,6})

Cat	Group	Mechanism	Entities	Drug involvement
CI	NERD	Inhibition PG-LEK pathways	Rhinitis Asthma Rhinosinusitis Nasal polyposis	NSAIDs
CI	NECD	Unknown	CSU-aggravated or -reactivated NSAIDs	NSAIDs
CI	NIUA	Unknown	Anaphylaxis, urticaria and/or angioedema, rhinitis, anaphylaxis, mixed reactions	NSAIDs
SR	SNIUAA	IgEab/others	Anaphylaxis, urticaria and/or angioedema, rhinitis, anaphylaxis, mixed reactions	Aryl-propionics
SR	SNIDHR	T cells	Cutaneous adverse drug reactions	NSAIDs, Cox2 inhibitors
SR	Organ specific	T cells/ toxicologic/both	Hepatitis, bile-duct syndrome, meningitis	Diclofenac, ibuprofen
SR	Skin systems, in some instances systemic manifestations	Unknown	Vasculitis	Naproxen, ibuprofen

CI – Cross intolerant; CSU – Chronic spontaneous urticaria; CD – Contact dermatitis; NERD – NSAID-exacerbated respiratory disease; NECD – NSAID-exacerbated cutaneous disease; NIUA – NSAID-induced urticaria and angioedema or anaphylaxis; SNIUAA – Single NSAID-induced delayed hypersensitivity reaction; SNIDHR – single NSAID-induced delayed hypersensitivity reaction; SR – selective responders.

clinical benefits of dual anti-platelet therapy have created the need for rapid aspirin desensitisation for patients with the comorbidity of ischaemic heart disease and aspirin hypersensitivity, such as in our illustrative case.

ASPIRIN AND NSAID HYPERSENSITIVITY

Non-steroidal anti-inflammatory drugs (NSAIDs) are the commonest group of drugs causing hypersensitivity reactions, with just under 2% of the general adult population affected.³ Table I shows the current consensus classification of NSAID hypersensitivity; it is adapted from a recent review of NSAID hypersensitivity classification.⁴ The key distinction for a patient giving a history of a reaction to aspirin is to distinguish cross-intolerance from single reactions to specific NSAIDs, including aspirin – either IgE- or non-IgE-mediated (Table I). An important consideration in our presented case, especially given the adult-onset worsening of asthma and new onset of aspirin hypersensitivity, is whether his diagnosis is of NSAID-exacerbated respiratory disease with cross-intolerance. The history was most suggestive of this phenotype and therefore the patient had been managed appropriately to the point of his admission and need for aspirin anti-platelet therapy. Putative mechanisms for the different phenotypes have been discussed in our previous Current Allergy Review article on NSAID hypersensitivity.³

The clinical reaction history and drug provocation testing are the mainstays of hypersensitivity diagnosis for both aspirin and other NSAIDs.^{3,4} NSAIDs, including aspirin, are irritant to the skin and these limit the use of skin and intradermal testing. Basophil activation testing (BAT) can aid diagnosis: in our case, it took the form of a cellular antigen stimulation assay measuring sulpholeucotrienes in the supernatant of patient-stimulated basophils. BAT for NSAID has good specificity but low sensitivity when compared to drug-provocation testing.⁵ A negative CAST test, as in our illustrative case, therefore, does not rule out aspirin hypersensitivity.

RAPID ASPIRIN DESENSITISATION IN ISCHAEMIC HEART DISEASE

Aspirin desensitisation in the context of coronary artery disease (CAD) is fast, safe and effective. Several small case series have been published and have recently been combined into a patient-level meta-analysis.² Data from 691 patients with CAD and aspirin hypersensitivity were included. The mean age was 67.1 years and 66% were male patients; 480 patients were classified as acute coronary syndrome – ST-segment elevated myocardial infarction (STEMI, 25%) or unstable angina/non-ST-segment elevated myocardial infarction (NSTEMI, 75%). The majority of aspirin hypersensitivity was cutaneous (74%), with only 8% giving a history of systemic reactions. The mean time and number of steps in the desensitisation protocols were 3.3 hours and 7.1 dose escalation respectively. The success rate was 98.3% (463/480 patients); protocols with > 6 doses were associated with higher success rates. Long-term follow-up between one and 46 months showed no adverse events or discontinuations associated with aspirin hypersensitivity, with doses of between 75 mg and 325 mg per day used.

Table II provides summative data on our local GSH allergy clinic experience for the past 24 months. Data were available for seven patients, with isolated bronchospasm and angioedema being the two main clinical phenotypes of prior aspirin reaction. Two patients developed symptoms during desensitisation but all successfully completed the protocol and were discharged on daily aspirin therapy. Table III shows the routine and modified protocols for rapid aspirin desensitisation with 7 and 9 steps (dose escalations) respectively. Clinicians should be aware of the suggested pre-procedure steps with cessation of beta-blockers for 24 hours prior to the start of the procedure; the performance within a coronary high-care or intensive-care setting; and pre-medication with montelukast 10 mg at least one hour prior to commencing the procedure.

TABLE II CHARACTERISTICS AND OUTCOMES OF GSH IHD PATIENTS DESENSITISED BY OUR ALLERGY CLINIC

	AGE	SEX	NSAID CAUSING HYPERSENSITIVITY	TYPE OF PREVIOUS ASPIRIN-RELATED REACTION	ASTHMATIC	CLINICAL PRESENTATION	REACTION TYPE DURING PROCEDURE	SUCCESSFUL COMPLETION OF PROTOCOL
1.	54	M	Aspirin	Anaphylaxis	Yes	NSTEMI	None	Yes
2.	49	F	Aspirin	Isolated bronchospasm	No	NSTEMI	None	Yes
3.	72	F	Aspirin	Facial angioedema	No	STEMI	None	Yes
4.	42	F	Aspirin and ibuprofen	Isolated bronchospasm	Yes	IHD	Persistent sneezing	Yes
5.	50	M	Aspirin	Anaphylaxis	No	STEMI	None	Yes
6.	56	F	Aspirin	Facial angioedema and bronchospasm	Yes	Unstable angina	None	Yes
7.	53	M	Aspirin	Isolated bronchospasm	Yes	Unstable angina	Bronchospasm	Yes

TABLE III: RAPID ASPIRIN DESENSITISATION PROTOCOLS IN USE AT GSH ALLERGY CLINIC**PRE-PROCEDURE PREPARATIONS:**

- Informed consent
- Admit to ICU
- Stop beta-blocker for 24 hours
- Montelukast 10 mg OD
- IV access
- Mix 300 mg aspirin in 150 mL water (2 mg/mL concentration)
- Check BP, pulse and PEFR prior to commencement

STANDARD PROTOCOL

1. First dose administered 2 mL (4 mg).
2. Observe for 30 minutes, check any cutaneous, nasal or lung symptoms.
3. 30 minutes later, check for any cutaneous, nasal or lung symptoms.
4. If above normal, proceed with next dose of 5 mL (10 mg).
5. For 30 minutes, check for any cutaneous, nasal or lung symptoms.
6. Repeat vitals and after further 30 mins.
7. If above normal, proceed with next dose of
8. 10 mL (20 mg). Repeat steps 5 and 6 after further 30 mins;
9. If above normal, proceed with next dose of 20 mL (40 mg).
10. Repeat steps 5 and 6 after further 30 mins;
11. If above normal, proceed with next dose of 40 mL (80 mg).
12. Repeat steps 5 and 6 after further 30 mins;
13. If above normal, proceed with next dose of 50 mL (100 mg).
14. Repeat steps 5 and 6 after further 30 mins;
15. If above normal, proceed with next dose of 75 mL (150 mg).
16. Observe for a further 3 hours in CCU for reactions.

MODIFIED EXTENDED PROTOCOL

1. First dose administered 2 mL (4 mg).
2. Observe for 30 minutes, check any cutaneous, nasal or lung symptoms.
3. 30 minutes later, check for any cutaneous, nasal or lung symptoms.
4. If above normal, proceed with a repeat dose of 2 mL (4 mg).
5. For 30 minutes later, check any cutaneous, nasal or lung symptoms.
6. Check PEFR, BP and PR.
7. If above normal, proceed with next dose of 5 mL (10 mg).
8. Repeat steps 5 and 6 after further 30 mins;
9. If above normal, proceed with a repeat dose of 5 mL (10 mg).
10. Repeat steps 5 and 6 after further 30 mins;
11. If above normal, proceed with next dose of 10 mL (20 mg).
12. Repeat steps 5 and 6 after further 30 mins;
13. If above normal, proceed with next dose of 20 mL (40 mg).
14. Repeat steps 5 and 6 after further 30 mins;
15. If above normal, proceed with next dose of 40 mL (80 mg).
16. Repeat steps 5 and 6 after further 30 mins;
17. If above normal, proceed with next dose of 50 mL (100 mg).
18. Repeat steps 5 and 6 after further 30 mins;
19. If above normal, proceed with next dose of 75 mL (150 mg);
20. Observe for a further 3 hours in CCU for reactions.

CONCLUSION

Aspirin is a life-saving medication for primary and secondary prevention in IHD. But aspirin hypersensitivity is common. We are adamant that where dual anti-platelet therapy necessitates aspirin use in allergic patients, desensitisation should be performed. Our own local data support the international literature that the procedure is safe and effective. We would encourage

other South Africa coronary-care centres to make this aspirin desensitisation routine available in their clinical settings.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest. No funding was required for folder review.

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