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# Aspirin desensitization in patients undergoing percutaneous coronary intervention: A survey of current practice

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## Abstract

**Background:** *Aspirin remains the mainstay of anti-platelet therapy in cardiac patients. However, if a patient is allergic to aspirin and dual anti-platelet therapy is indicated — such as with percutaneous coronary intervention (PCI), then there is no clear guidance. One possibility is aspirin desensitization. A variety of protocols exist for the rapid desensitization of patients with aspirin allergy. The aim of this survey was to assess current knowledge and practice regarding aspirin desensitization in the UK.*

**Methods and results:** *We conducted a UK wide survey of all UK 116 PCI centers and obtained complete responses from 40 (35.4%) centers. Of these, just 7 (17.5%) centers had previously desensitised patients; 29 (87.9%) centers suggested a lack of a local protocol prevented them from desensitizing, with 10 (30.3%) unsure of how to conduct desensitization. Only 5 (12.5%) centers had a local policy for aspirin desensitization although 25 (64.1%) units had a clinical strategy for dealing with aspirin allergy; the majority (72%) giving higher doses of thienopyridine class drugs.*

**Conclusions:** *In the UK, there appears to be no consistent approach to patients with aspirin allergy. Patients undergoing PCI benefit from dual anti-platelet therapy (including aspirin), and aspirin desensitization in those with known allergy may facilitate this. Sustained effort should be placed on encouraging UK centers to use desensitization as a treatment modality prior to PCI rather than avoiding aspirin altogether.* (Cardiol J 2013; 20, 2: 134–138)

**Key words: aspirin, allergy, desensitization, percutaneous coronary intervention**

## Introduction

Aspirin or acetylsalicylic acid (ASA) is widely used in cardiology patients, however, up to 20% are intolerant, with true allergy affecting 0.5–2.4% of patients [1, 2]. ASA acts primarily through irreversible inhibition of cyclooxygenase-1 (COX-1), preventing conversion of arachidonic acid to thromboxane ($TxA_2$) and thus inhibiting platelet aggregation. The production of $TxA_2$ can be completely inhibited through 75 mg/day dosing of aspirin [3].

In patients undergoing percutaneous coronary intervention (PCI), dual anti-platelet therapy with aspirin, and an ADP-receptor antagonist (such as clopidogrel) has been shown to reduce the incidence of thrombotic events compared to aspirin alone [3–5]. The therapeutic goal is to reduce ischemic events and minimise bleeding complications. Despite the

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development of newer agents such as prasugrel and ticagrelor, aspirin remains the first antiplatelet of choice. Where patients are intolerant, non-aspirin based dual anti-platelet combinations may be utilised, but there is only a limited evidence base for this [6].

## Aspirin allergy

Allergy to aspirin may be broadly categorized into having either a pharmacological or immunological basis. The pharmacologic 'allergy' is the direct, symptomatic result of COX-1 inhibition, whereas a true immunological allergic response is due to production of aspirin-antigen specific immunoglobulin E (IgE). Allergy to aspirin may manifest as aspirin--exacerbated respiratory disease (AERD), cutaneous, mixed or systemic reactions.

AERD is a triad of asthma, aspirin sensitivity and rhinitis with or without nasal polyps, and may also be known as aspirin intolerant asthma. Respiratory reactions to asthma typically occur within the first few hours of ingestion, with wheeze and shortness of breath accompanied by rhinitis, conjunctival irritation and facial flushing. The majority of AERD patients may be successfully desensitized [7].

Cutaneous reactions to asthma are comprized of urticaria and angioedema. Patients are more likely to react to aspirin when urticaria is active. 21––30% of those with chronic idiopathic urticaria will experience heightened urticaria when exposed to aspirin [8–10]. Patients with a specific diagnosis of chronic idiopathic urticaria are not thought to be appropriate for desensitisation, however, patients with urticaria as part of a cutaneous reaction may be considered for desensitization [10]. One mechanism of preventing angioedema or urticarial symptoms as a result of non-steroidal anti-inflammatory drugs (NSAIDs) administration is the use of leukotriene receptor antagonists. When angioedema occurs alongside hypotension this should be considered a systemic not cutaneous insult.

The systemic reactions to aspirin administration tend to be most severe. They occur within minutes of administration and include classical features of anaphylaxis such as hypotension, laryngeal edema, pruritis, tachypnoea and may evolve to cause loss of consciousness. There is no consensus within the literature as to whether systemic reactions should be desensitized [10–12]. Generally, given the potential for a life-threatening event, such patients are not desensitized.

It is vital to obtain a complete drug history from patients considered to be 'allergic' to aspirin. If a reaction occurred on first exposure to the drug, this is likely to represent a pharmacological anaphylactoid response. Whereas, if a reaction occurred on second exposure it is more likely that this is IgE mediated and hence a true anaphylactic episode. Adverse reactions to other NSAIDs should be documented as cross-reactivity is known to occur.

## Aspirin desensitization

Desensitization can be described as the temporary induction of a tolerance to a drug antigen. In the case of aspirin, the mechanisms are poorly understood. It is thought that desensitization occurs as a result of decreased leukotriene production, down-regulation of cystienyl leukotriene receptors and hence a decrease in histamine and tryptase release from mast cells [10–13].

Aspirin desensitization has been shown to be both safe and effective when carried out under controlled conditions. There are several published protocols which have established safe procedures to desensitize patients with known aspirin allergy [9, 13, 14], but no single guideline has been internationally adopted (Table 1). In principle, a patient is 'challenged' with incremental dose increases over fixed time periods, until a positive reaction to aspirin is noted, characterized typically by a reduction in FEV1 of > 20%, combined with naso-ocular symptoms [13]. Symptomatic treatment is initiated at this stage, with the dose repeated until the patient becomes tolerant. Provided a desensitized patient does not interrupt regular aspirin dosing, the desensitized state will persist [7]. The dose at which desensitization is commenced is dependent on risk stratifying given their history.

It is recommended that beta-blockers are stopped 24 h prior to an aspirin challenge as a precautionary measure [15] as it is thought that they may increase sensitivity to allergens, and hence provoke a more significant immune response [16––20]. In addition, beta-blockers can decrease the response to adrenaline — first line treatment for anaphylaxis [15, 16, 19]. In those taking angiotensin converting enzyme (ACE) inhibitors undergoing desensitization, a higher rate of systemic reactions have been observed and hence it is suggested that these are also omitted [19, 21].

# Methods

We conducted a UK based survey of all 116 PCI centers as identified in the British Cardiovascular Intervention Society audit database (www.BCIS.org). A brief eight point questionnaire was designed

**Table 1.** Available protocols for aspirin desensitisation.

| | Indications | Doses of aspirin [mg] | Dose interval | Monitoring intervals[1] | Duration |
|---|---|---|---|---|---|
| Silberman et al. [14] | Acute CAD and hypersensitivity | 5, 10, 20, 40, 75 | 30 min | 30 min | 2.5 h |
| Szczeklik, Stevenson [22] | High risk patients challenge protocol | Day 1: placebo/ /placebo/placebo Day 2: 30/60/120 Day 3: 150/325/650 | 3 hourly (over 3 days) | 1 hourly[2] | 72 h |
| Wong et al. [23] | Cutaneous reactions | 0.1, 0.3, 10, 30 40, 81, 162, 325 | First 4 doses × 15 min Subsequent doses × 25 min | 1 hourly[2] | 2.25 h |
| Schafer, Gore [9] | Cutaneous reactions | Placebo/placebo, placebo/150 mg, placebo/325 mg, 325 mg/ /325 mg, placebo/placebo | 1 h | 1 h | 6 h |
| Stevenson, Simon 'Scripps Clinic' [24] | AERD | 20.25, 40.5, 60, 75, 81, 101.25, 162.5, 325 | 3 h | 1 hourly[2] | 48 h |
| Hope et al. [25] | AERD | 30, 45, 60, 100, 150, 325, 650 | 3 h | 1 hourly[2] | 48/72 h |

[1] Typically involves HDU monitoring, and pulse/BP/FEV1 at pre-determined intervals; [2]or when symptomatic; CAD — coronary artery disease; AERD — aspirin exacerbated respiratory disease

and tested for face validity by an expert panel before being posted to the lead cardiologist of each unit (Table 2). After 4 weeks the questionnaire was resent to departments which had not responded. Participants were notified of our intention to publish results to guide future practice via a covering letter, and implied consent was taken with all responses. We excluded any incomplete responses.

## Results

Of 116 units posted a questionnaire, we received 41 (35.5%) responses. There was 1 exclusion as the center no longer performed PCI, leaving 40 questionnaires for analysis. Responses were obtained from centers in Scotland (5/8), England (33/101), Northern Ireland (2/4) and Wales (1/3). Complete results are displayed in Table 2.

## Discussion

This survey has demonstrated wide variation in clinical practice. A minority of cardiac units had conducted aspirin desensitization in the past year, and even in those units who did, only a very small number of patients underwent desensitization. Those units that have not conducted desensitization seem to suggest that primarily this is down to a lack of a local protocol (29 centers, 87.9%), in addition to a lack of understanding (10 centers, 30.3%). Only a small number of units had concerns regarding the safety of desensitization.

The majority of units had no local protocol for desensitizing patients with a known aspirin allergy, and most of these were unsure of which particular responses they would consider desensitizing. Of interest, 12 units (30%) would consider desensitizing those with a previous systemic reaction. Those who had previously desensitized patients gave thorough responses when asked about particular patient responses, with one center rapidly desensitizing patients with AERD or previously documented anaphylaxis on an intensive care unit.

In patients with known aspirin allergy, most units (whilst not able to desensitize) will attempt to compensate for the lack of aspirin through the use of other agents, primarily use of higher doses of ADP-receptor antagonists such as clopidogrel (10/41), prasugrel (7/41) or ticagrelor (1/41). One unit responded by mentioning GP IIb/IIIa receptor antagonists such as tirofiban. Whilst increased doses of these drugs may increase the likelihood of suppressing thrombotic events, this area has not been extensively studied when compared to known benefits of dual anti-platelet therapy, and there is only limited data on patient outcomes with this approach.

Whilst the majority of units would consider desensitizing either elective PCI (7 units, 17.9%)

**Table 2.** Results from questionnaire based survey of 40 percutaneous coronary intervention (PCI) units.

| | |
|---|---|
| Has your unit administered an aspirin desensitization regimen before? | 40 (100%) |
| Yes | 7 (17.5%) |
| If yes, how many patients per year? | 40 (100%) |
| 1 | 4 (10%) |
| 2–6 | 3 (7.5%) |
| 7–12 | 0 (0%) |
| > 12 | 0 (0%) |
| If no, is this due to: | 33(100%) |
| No local desensitization protocol? | 29 (87.9%) |
| Unsure of how to complete desensitization? | 10 (30.3%) |
| Concerns regarding the safety of desensitization? | 3 (9%) |
| Not clinically indicated? | 4 (12.1%) |
| Other (specified) | 0 (0%) |
| Does your unit have a desensitization policy for patients with aspirin allergy? | 40 (100%) |
| Yes | 5 (12.5%) |
| Which allergies would you consider desensitizing? | 40 (100%) |
| None | 11 (27.5%) |
| Cutaneous | 11 (27.5%) |
| Aspirin exacerbated respiratory disease | 8 (20%) |
| Systemic reactions | 12 (30%) |
| Mixed reactions | 7 (17.5%) |
| Unsure | 17 (42.5%) |
| Does your unit have a clinical strategy for patients requiring PCI with an aspirin allergy? | 39 (100%) |
| Yes | 25 (64.1%) |
| If yes, what strategy? | 25(100%) |
| ADP-receptor antagonist monotherapy (e.g. clopidogrel) | 18 (72%) |
| GP IIb/IIIa receptor antagonists (e.g. tirofiban) | 1 (4%) |
| Aspirin desensitization if scheduled procedure | 1 (4%) |
| No information given | 5 (20%) |
| Would you consider elective desensitization in the following patients? | 39 (100%) |
| Elective PCI only | 7 (17.9%) |
| Post-myocardial infarction PCI only | 0 (0%) |
| All PCI | 18 (46.1%) |
| Neither | 16 (41%) |
| If you answered post-myocardial infarction PCI or both, would you stop beta-blockers or ACE inhibitors? | 18 (100%) |
| Yes | 6 (33.3%) |
| No | 7 (33.3%) |
| Unsure | 4 (22%) |

or both elective and post-myocardial infarction (18 units, 46.1%), 16 (41%) units would not consider desensitising any patients. When asked about omitting beta-blockers or ACE inhibitors, a wide variety of responses were given and knowledge in this area would appear inconsistent. This has obvious implications to cardiac patients, particularly in the context of a recent myocardial infarction. Those that stated they would hold beta-blockers or ACE inhibitors did so in the context of patients with preserved left ventricular function, a lack of ongoing ischemia, patients with asthma or previous anaphylaxis who were considered to be high risk, or for those having elective PCI.

We have found a wide variety of current practice throughout the UK, and further to this there seems to be a lack of a consistent approach to the management of patients with aspirin allergy who are

to undergo PCI. This may in part be due to limited knowledge of this specialized area.

## Limitations of the study

This was a self-reported survey and therefore there is a risk that the responses did not accurately reflect local practices, however, this is unlikely as questionnaires were sent to the clinical lead for the cardiac catheterization lab in each center. Whilst the response rate was low, responses were received from all areas in the UK. Furthermore, it is likely that additional responses would just add to the variation in clinical practice that has been demonstrated and would not greatly affect the outcomes of this study.

## Conclusions

Based on the data presented, the use of aspirin desensitization in the UK appears to be low. There appears to be a need to address this apparent lack of awareness regarding aspirin desensitization as a therapeutic modality, and thereby increase its availability to patients currently unable to tolerate and potentially benefit from conventional and evidence based dual anti-platelet therapy.

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