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## Rapid and sequential desensitization to both aspirin and clopidogrel

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### Abstract

Hypersensitivity reactions to aspirin and clopidogrel are 2.5% and 1%, respectively. Dual anti-platelet therapy with these drugs is effective in preventing thrombosis following deployment of stents for cerebrovascular and cardiovascular syndromes. Desensitization therapy with both aspirin and clopidogrel may be required for patients undergoing stent implantation that have experienced hypersensitivity to these agents. We report the case of a 58-year-old woman who developed urticaria and angioedema following aspirin therapy for ischaemic cerebrovascular disease. She developed an identical reaction after clopidogrel was subsequently administered. Investigations revealed the presence of an internal carotid artery aneurysm that required deployment of a stent. Rapid desensitization to aspirin over 5.5 h followed 3 days later by rapid desensitization to clopidogrel over 2.5 h was successfully performed prior to stenting. After 4 months she has tolerated this dual anti-platelet therapy without any adverse reaction. Rapid and sequential desensitization to both aspirin and clopidogrel can be successfully performed for patients who require stent deployment but have hypersensitivity to both these anti-platelet agents.

Adverse reactions to aspirin and clopidogrel are common. The incidence of reactions to both these agents in a single individual is unknown. However, a proportion of individuals requiring dual anti-platelet therapy with these agents when stenting is deployed for coronary or cerebrovascular syndromes may have a history of adverse reactions to both these drugs. Rapid and sequential desensitization to both these agents may therefore be necessary to enable optimal prevention of stent occlusion. We describe a case of successful rapid and sequential desensitization to aspirin and clopidogrel in a 58-year-old woman prior to stenting and coiling of her right internal carotid artery.

A 58-year-old woman with a 2-month history of headaches and numbness of the right side of the body, including the right side of the face, was initially treated presumptively for ischaemic cerebrovascular disease with aspirin 100 mg daily. After 7 days of treatment, she developed generalized urticaria and angioedema. She subsequently developed an identical reaction after 7 days of clopidogrel therapy. She had the vascular risk factors of hypertension, hypercholesterolaemia, heavy smoking and a strong family history of ischaemic stroke. Her magnetic resonance imaging of the brain and transoesophageal echocardiogram were normal, but her magnetic resonance angiography revealed an incidental finding of

**Table 1** Aspirin desensitization protocol (adapted from Rossini *et al.*<sup>1</sup>)

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

a 1 cm aneurysm in the right internal carotid artery in the intra-petrous region. A cerebral single photon emission computed tomography study demonstrated a perfusion defect and balloon occlusion in the right posterior frontal region that was not seen in the baseline study. Stent-assisted coiling of the right internal carotid artery was planned with prior desensitization to both aspirin and clopidogrel.

A 5.5-h aspirin desensitization was successfully completed to a dose of 100 mg daily (Table 1).<sup>1</sup>

After 3 days of ingesting aspirin 100 mg daily without adverse reaction, she was successfully desensitized to clopidogrel over 2.5 h to a therapeutic dose of 75 mg daily (Table 2).<sup>2</sup>

Desensitization was performed under strict medical supervision in a monitored ward after intravenous access was obtained with adrenaline, intravenous fluids, hydrocortisone and loratadine available at the patient's bedside. Stent-assisted coiling of her right internal carotid artery was then performed without complication and she has had no adverse reaction to her dual anti-platelet therapy after 4 months.

The benefit of aspirin in the treatment of coronary and cerebrovascular disease is well established, but its exposure results in hypersensitivity reactions in up to 2.5% of the general population and up to 11% of adult

asthmatics.<sup>3</sup> These reactions manifest most commonly as either asthma or urticaria/angioedema although anaphylaxis has also been described.<sup>4</sup> Aspirin-exacerbated reactive airways disease (AERD) and many cases of aspirin-induced urticaria and angioedema are mediated by inhibition of COX-1 and is typified by cross-reactivity with non-steroidal anti-inflammatory drugs (NSAIDs).<sup>5</sup> Aspirin-induced anaphylaxis and some cases of urticaria and angioedema, are mediated by anti-aspirin immunoglobulin E (IgE) antibodies and there is an absence of cross-reactivity with other NSAIDs.<sup>6</sup> COX-1 is necessary for the synthesis of prostaglandin E<sub>2</sub>, which in turn inhibits 5-lipoxygenase, an enzyme responsible for leukotriene production that mediates mast cell degranulation and release of histamine and cytokines. COX-1 inhibition by aspirin therefore results in excessive lipoxygenase activity and release of mast cell mediators.<sup>7</sup>

Aspirin sensitivity is confirmed with nasal or oral challenge given the lack of availability of a commercial preparation of aspirin polylysine for skin testing for IgE mediation.<sup>8</sup> Such challenges are generally performed to clarify spurious reactions given the risk of severe adverse events. Selective COX-2 inhibitors, such as celecoxib, may not always be safe in patients with aspirin hypersensitivity<sup>9</sup> and may even increase the risk of cardiovascular disease.<sup>10</sup> Desensitization therapy involves the incremental administration of aspirin until a therapeutic dose is reached and has proved successful in treating AERD, aspirin-induced urticaria and angioedema and aspirin-induced anaphylaxis.<sup>4</sup> It is not effective in chronic urticaria that is exacerbated by aspirin.<sup>4</sup> Desensitization therapy for COX-1 mediated reactions results in exhaustion of leukotrienes and downregulation of their receptors.<sup>11</sup> The mechanism by which desensitization to aspirin renders mast cells unresponsive in IgE-mediated reactions is not clear.

Upon its successful completion, therapeutic doses of aspirin can be ingested indefinitely. However, the tolerance is temporary, as individuals will become resensitized after 2–7 aspirin free days.<sup>12</sup> Hence it is advisable to provide a warning to the patient, and attending practitioners to repeat the induction of tolerance to these drugs if they are ever inadvertently ceased for 48 h or more. It should also be advised that the desensitization for an individual would not necessarily cover any increase in the dose of aspirin above that attained during the procedure. Traditional protocols desensitize patients over one or more days and were initially formulated for patients with AERD. The length of these protocols limits its utility in aspirin-sensitive patients that require its prompt administration after cardiovascular or cerebrovascular events. By contrast, rapid desensitization protocols enable therapeutic doses to be reached in less than 6 h. A

**Table 2** Clopidogrel desensitization protocol (modified from Walker *et al.*<sup>2</sup>)

| Time (min) | Dose (mg) |
|------------|-----------|
| 0          | 0.0002    |
| 15         | 0.002     |
| 30         | 0.02      |
| 45         | 0.05      |
| 60         | 0.15      |
| 75         | 0.5       |
| 90         | 1.5       |
| 105        | 5         |
| 120        | 15        |
| 135        | 45        |
| 150        | 75        |

5.5-h protocol, as devised by Rossini *et al.* was chosen to desensitize our patient.<sup>1</sup> This protocol had an 88.5 % success rate without the prior use of antihistamines or corticosteroids and all these patients were tolerant to aspirin after 1 year of continued ingestion. The Silberman protocol achieved similar results with a desensitization time of 2.5 h.<sup>13</sup>

Clopidogrel, an oral thienopyridine derivative, provides an alternative for individuals with aspirin hypersensitivity in the management of acute cardiovascular and cerebrovascular syndromes.<sup>14</sup> Dual anti-platelet therapy with aspirin and clopidogrel has been shown to be beneficial in preventing stent thrombosis.<sup>15</sup> However, hypersensitivity reactions to clopidogrel, including rash, angioedema and cardiorespiratory symptoms, have been reported in approximately in up to 1% of patients.<sup>16</sup> The basis of these reactions to clopidogrel has not been fully elucidated, but both IgE and non-IgE-mediated mechanisms have been proposed.<sup>17</sup> The alternative thienopyridine, ticlopidine, is not only more expensive, but has a severe side-effect profile, including neutropenia, thrombocytopenic purpura and severe diarrhoea.<sup>18</sup> Hence rapid desensitization protocols to clopidogrel ranging in duration from 2 to 8 h have been recently formulated and proven to be successful in up to 96% of patients at 6 months.<sup>2,19</sup> The mechanisms by which desensitization to clopidogrel renders mast cells unresponsive are not known, but may be similar to those involved in inducing tolerance in IgE-mediated aspirin sensitivity.

In conclusion, the precise incidence of hypersensitivity reactions in individuals to both aspirin and clopidogrel is unknown, although it would not be uncommon given the relative frequency of such reactions to each of these agents and the number of individuals exposed to both of these drugs. Therefore, consideration may need to be given to desensitizing patients to both agents in a rapid and timely manner, such as in the deployment of stents in coronary and cerebrovascular syndromes. Rapid desensitization protocols to aspirin and clopidogrel have a high success rate, but the optimal time interval between desensitization to each of these drugs remains to be determined.

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