



BRIEF COMMUNICATION

Aspirin sensitivity: acetylsalicylate or excipients

B. S. Hebron and H. J. Hebron

Pharmaceutical Services Sandwell and West Birmingham NHS Trust, City Hospital, Birmingham, UK

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CorrespondenceBrian S. Hebron, Pharmaceutical Services
Sandwell and West Birmingham NHS Trust, City
Hospital, Dudley Rd, Birmingham B18 7QH, UK.
Email brian.hebron@swbh.nhs.ukReceived 6 March 2008; accepted 13 April
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Abstract

We present three patients who developed urticaria while taking an enteric formulation of aspirin, confirmed on a second exposure. Although hypersensitivity reactions to aspirin, especially in asthmatic patients or those with nasal polyps, are well reported, our patients did not exhibit any underlying history of atopy. Furthermore, two of the patients were able to tolerate a soluble formulation. We review the literature and discuss whether these symptoms might be caused by pharmaceutical excipients, present in very small amounts in the enteric coating, rather than the active ingredient acetylsalicylate. Adverse reactions to excipients are fortunately rare but are occasionally reported.

Hypersensitivity reactions to aspirin in asthmatics subjects have been well reported and have been recently reviewed.¹ However, aspirin is also a potential non-immune releaser of histamine from mast cells representing an immediate type 1 hypersensitivity reaction.^{2,3} We describe three patients who were unable to take the enteric formulation of aspirin, 'Cartia', as they suffered from urticaria. These patients had 'Cartia' withdrawn with resolution of the urticaria, but had retaken the medication at a later date when the urticaria reappeared. The scale developed by Naranjo and colleagues⁴ to estimate the likelihood of an adverse drug reaction indicated a probable cause of the urticaria to be the aspirin. However, two of these patients were subsequently able to tolerate soluble aspirin with no sign of adverse effect, suggesting their response might have been caused by one of the excipients in the formulation.

Clinical cases

The first patient was an 85-year-old man, who initially presented to the emergency department with dizziness and ringing in ears. He appeared well otherwise. He had a history of moderate renal impairment, hypertension, atrial fibrillation and diverticular disease. He had been given a porcine atrial artificial valve in 2003, and was bilaterally deaf.

The impression was of acute transient vertigo with associated tinnitus, likely labyrinthine in origin. There was nothing to support brainstem ischaemia. He was discharged the same day on aspirin EC (Cartia) 100 mg, 1 tab daily, felodipine 5 mg, 1 tab daily, bendrofluzide 2.5 mg, 1 tab daily, and cilazapril 2.5 mg, 1 tab daily.

He re-presented 6 months later with increasing oedema of both legs with reddened lower legs, over 2 weeks. He also exhibited increasing shortness of breath, decreased exercise tolerance, orthopnoea, and appeared anaemic. Clinically he appeared in heart failure, and was treated with IV frusemide; with some improvement in symptoms and clindamycin was started for presumed cellulitis of legs.

An Echo cardiogram was performed that showed a normal sized left ventricle with normal systolic function. Pseudo normalization pattern for diastolic function was

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seen indicating a raised left arterial pressure and the left artery was dilated in size. His prosthetic valve was well seated with peak gradient across valve of 62 mmHg and mean of 32 mmHg. Mitral valve leaflets showed mild annular thickening. The right heart size and function appeared normal.

The above findings called into question the diagnosis of heart failure. An ultrasound scan of the lower legs was performed revealing no venous obstruction. The anaemia was considered likely to be caused by his renal failure.

Subsequently he developed an itchy rash on forearms. The patient recognized this as similar to previous rash that he felt was attributable to aspirin following the last admission. Aspirin had been stopped recently by his general practitioner (GP) with resolution of rash. Aspirin, as Cartia, had been restarted at this admission. The Cartia was discontinued, and hydrocortisone ointment and aqueous cream started. The rash subsequently disappeared. His other medication remained unchanged during this period: felodipine, 5 mg in the morning, frusemide, 60 mg each morning, and xylometazoline nasal spray, 2 sprays each nostril twice daily. Although the first rash experienced by the patient had not been documented, we believe that the rash on this presentation was caused when he was rechallenged with aspirin. Applying the Naranjo scale yielded a score of 5 suggesting a probable adverse drug reaction. We were unable to ascertain the brand of aspirin to which the patient had reported his first reaction.

Our second patient, a 68-year-old woman, presented with increasing shortness of breath over 3 weeks that was severely limiting her mobility. She had been advised by her GP previously to come in to hospital but had refused. She had a history of anxiety and depression associated with her chronic obstructive pulmonary disease (COPD), essential systolic hypertension, osteoarthritis and peptic ulcer disease presumed secondary to non-steroidal anti-inflammatory medications.

On this admission a chest X-ray showed no evidence of cardiac failure, but showed changes consistent with COPD (hyper-expansion and flattened diaphragm). An electrocardiogram showed non-specific ST/T wave changes. Blood gasses showed mild hypoxaemia but normal pH and p_aCO₂ reflecting the degree of progression of her COPD. Other results were unremarkable.

She had previously been taking enteric coated (EC) aspirin 100 mg (Cartia) following a transient ischaemic attack but had stopped this when she developed a rash. She did not volunteer this information and aspirin EC (Cartia) was restarted on admission. Within 2 days a red itchy rash appeared on her legs. She reported difficulty in swallowing so the EC aspirin was changed to a soluble formulation.

The patient admitted not taking any of her medications regularly at home. She was very keen to return home and was discharged without further investigations. Soluble aspirin was continued and the rash was subsiding at the time of discharge. During this admission she had continued to take her other medications of omeprazole, 20 mg twice daily, doxepin HCL, 75 mg at night, diltiazem CD, 180 mg twice daily, trimethoprim, 150 mg each morning, triazolam, 500 micrograms at night, lorazepam, 1 mg three times a day and fluticasone inhaler 125 mg, 2 puffs twice daily. The first rash experienced by the patient had not been documented, but the patient was aware that she had received the Cartia brand. We believe that the rash on this subsequent occasion was caused when she was rechallenged with Cartia. We calculated a score of 6 on the Naranjo scale, suggesting a probable adverse drug reaction.

The third patient presents an interesting variation as this 70-year-old woman was intolerant of enteric-coated aspirin (Cartia) but had taken soluble aspirin (Solprin), for several years. On the last occasion she presented with 5-h history of central chest pain, unresponsive to glyceryl trinitrate spray. She had had similar pain in the past brought on by cold and exercise. On admission she was found to be in atrial fibrillation but reverted spontaneously. Her electrocardiogram showed 2-mm ST depression II, V4-6 and a chest X-ray suggested pulmonary congestion. Her initial troponin was 0.74, which peaked at 20.4 suggesting a non-ST elevated myocardial infarction.

She was transferred for angiography and a coronary artery bypass graft procedure. She had developed a rash that she believed was caused by EC aspirin in 2000. However, she had been taking soluble aspirin 150 mg (half a tablet of Solprin) each morning since then. She received 100 mg EC for 2 days during this last admission and developed a rash over her stomach. She was subsequently given Solprin without any untoward effect. The rash disappeared without treatment. The first rash experienced by the patient had not been documented; we believe that the rash on this occasion was caused when she was rechallenged with Cartia, suggesting a highly probable adverse drug reaction. As she was able to tolerate a different brand of aspirin, we believe that the adverse reaction was attributable to an excipient of Cartia.

Discussion

We were surprised to encounter three patients with urticaria that they believed was caused by aspirin, presenting within 3 months of each other. Close questioning failed to find either any family relationship or other aspects of

atopy. Recent reviews have reported 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% of the general population.^{5,6} Aspirin sensitivity is most often manifested as rhinitis and asthma or urticaria/angioedema induced by cross-reacting non-steroidal anti-inflammatory drugs that inhibit cyclooxygenase 1. Genetic studies on aspirin-intolerant asthma showing chronic overproduction of cysteine leukotrienes have rekindled interest in intolerance to aspirin. It is not clear whether individuals with the cysteine leukotrienes abnormality are more likely to develop urticaria.⁷ Unfortunately, we were not able to determine the cysteine leukotriene status of our patients.

During the preparation of this report a recent review from the Netherlands Pharmacovigilance Centre [Lareb] has reported a case of urticaria associated with blue thyroxine tablets that settled after substituting white ones. On analysing their data base they found 30 cases where the excipient E132 (the blue dye indigo carmine) was identified as a possible contributory factor.⁸

Table 1 shows a list of excipients in the 'Cartia' brand of enteric-coated aspirin (M. Foster, pers. comm., 2006).

Guar gum is used medicinally to retard absorption of glucose and in combination with fibre as a bulk forming laxative. It contains 80% guaran, a galacto composed of D-mannose and D-galactose units, with a molecular weight of about 220 000. The gum is isolated from the endosperm of the Indian Cluster Bean. Its viscosity varies with the amount of galacto cross linkages. We would not expect the gum to cross the intestinal mucosal barrier, and so would be unlikely to cause systemic allergic reactions. A guar product (Dynexan) has been reported to cause severe urticaria after application to the mucosal membranes, in a patient who was subsequently shown to

develop contact dermatitis to it.⁹ Occupational asthma to the gum has also been reported.^{10,11} However, the authors of these reports did not describe the purity of the guar gum and the reactions may have been attributable to impurities that may not be present in gum that is of medicinal quality.

Titanium dioxide is a permitted whitener in food and pharmaceuticals. It is present in some of the other medicines taken by the latter two patients (Accupril, Betaloc CR, Losec, Inhibace or Plendil ER). These medications continued to be taken by our patients before the manifestation of the rash, during it and afterwards. This yields a very low score of causality, suggesting any adverse reaction is unlikely to be related to these medicines or their excipients. Furthermore, we have been unable to find any reference to cases of type 1 allergic reactions to titanium or its salts, though granulomatous disease has been reported from inhalation of titanium powder.¹²

In contradistinction, cases of adverse reactions to yellow dyes, most notably tartrazine, have been reported¹³ and other related azo dyes.¹⁴ These azo dyes are no longer permitted in pharmaceuticals. Sensitivity reactions have been reported to the dyes used in Cartia. Sunset yellow was attributed as a cause of urticaria in a patient taking rifampicin-isoniazid tablets.¹⁵ One of its metabolites has been linked to sensitivity of an antihistamine [Polaronil] in two patients sensitive to paraphenylenediamine.¹⁶ Quinoline yellow has been implicated as a cause of urticaria in a patient taking methylodopa.¹⁷ Contact dermatitis has also been reported to quinoline yellow.¹⁸ Other medications taken by our patients and maintained continued during the period of these events do not contain yellow dyes.

Cartia as aspirin EC is not marketed in the USA (where Cartia is a protected name for Diltiazem), the UK or Japan. It is available in the Middle East, Australia and New Zealand. Solprin is a global brand name. The manufacturer of Solprin states that it does not contain guar gum or these dyes (Bayer NZ, pers. comm., 2006).

Using the algorithm developed by Naranjo and others,⁴ we may assign a score of 6 suggesting that it is probable that the effects reported are caused by the medication. We have reported these cases to the New Zealand Centre for Adverse Drug Reactions, and the manufacturer, who had no similar reports. We suggest that either quinoline yellow or sunset yellow is the most likely cause, rather than acetylsalicylate.

Reports of hypersensitivity reactions such as those described confirm the importance of full disclosure of information on products in those parts of the world where they are marketed. If patients know they are allergic to certain dyes, they are more likely to check

Table 1 Excipients of Cartia

Active	Acetylsalicylic acid (aspirin) 100 mg
Excipients	Guar gum
Tablet coating ingredient listing:	Cellacephate (cellulose acetate phthalate)
	Diethyl phthalate
	Opaspray N-1-2564 [†]
	Dichloromethane [‡]
	Denatured absolute alcohol F3 [‡]
	Carnauba wax
	Denatured alcohol
	Quinoline yellow CI 47005 (D&C Yellow No.10 AI Lake)
	Titanium dioxide C177891
	Sunset yellow fcf CI 15985 (F.D & C. Yellow No.6 AI Lake)

[†]Composition of Opaspray N-1-2564. [‡]Lost through evaporation during the manufacturing process.

when a coloured medicament is dispensed, and health professionals need an accessible source to check this.

We suggest that governmental and licensing authorities stipulate that this information should be available in a format that is accessible at all times.

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