

Improvements in an oral aspirin challenge protocol for the diagnosis of aspirin hypersensitivity

L. J. Cormican*, S. Farooque*, D. R. Altmann† and T. H. Lee*

*Departments of Asthma, Allergy & Respiratory Science, King's College London, Guy's Hospital, London, UK and †Medical Statistics Unit, London School of Hygiene and Tropical Medicine, London, UK

Summary

Oral aspirin challenge (OAC) is used to confirm aspirin hypersensitivity (AHs) but there is no consensus on a standardized protocol. As a prior clinical history of adverse reactions to aspirin is poorly predictive of a positive result from formal aspirin challenge, many patients have an OAC performed.

We retrospectively identified and prospectively validated how a 1-day OAC protocol could be modified, and patient selection improved, to deliver a safe and more efficient service.

In a retrospective audit of 45 OACs using a 2 h dose interval, all reactions occurred within 90 min of the threshold dose. Forty OACs were then performed using a 90-min dose interval. This reduced the mean duration of a positive and negative OAC from 6 to 5 h and from 8 to 6 h, respectively.

Histories of multiple manifestations of AHs were found in 91.6% (11) of those with asthma, 87.5% (7) with angioedema, 70.6% (12) with rhinosinusitis, 63.6% (7) with chronic non-vasculitic urticaria and all with anaphylaxis, who developed a positive OAC. None of those with anaphylaxis, 8.3% (1) with asthma and 12.5% (1) with angioedema, with a positive OAC, had a history of a single manifestation of AHs.

The efficiency of an OAC service can safely be improved by reduction of the dose interval from 2 to 1 $\frac{1}{2}$ h, and more targeted patient selection, as the likelihood of a positive OAC increases among patients with a history of asthma, angioedema or anaphylaxis with multiple manifestations of AHs.

Keywords aspirin hypersensitivity, oral aspirin challenge

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Introduction

Aspirin hypersensitivity (AHs) may manifest as asthma, rhinosinusitis [1], urticaria and/or angioedema [2] and anaphylaxis [3, 4] upon aspirin ingestion. There is cross-reaction between aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), so the identification of AHs mandates avoidance of aspirin and other COX-1 NSAIDs. Furthermore, knowledge that a patient with chronic asthma and rhinosinusitis has AHs provides a scientific rationale for the use of anti-leukotriene agents in therapy [5], and sometimes even aspirin desensitization in intractable cases [6]. Therefore, a proven diagnosis of aspirin sensitivity can result in considerable benefits ranging from appropriate avoidance to targeted treatment. While 3–5% of asthmatic patients give a history of aspirin intolerance [7], provocation studies in consecutive asthmatic patients have suggested that the prevalence of aspirin sensitivity is higher, ranging from 8% to 19% [8, 9]. The clinical history is not only insensitive but it is also non-specific, with up to 16% with a history of aspirin-sensitive asthma failing to demonstrate any response when challenged [10].

There are no *in vitro* techniques to identify AHs, so the diagnosis has to be confirmed by oral, inhalation or nasal challenge. Oral aspirin challenge (OAC) is generally well tolerated and technically easier to conduct in most lung function laboratories than inhalation and nasal provocation. OAC has a similar specificity but higher sensitivity than inhalation challenge in the detection of AHs [11]. It is also the preferred form of challenge for the investigation of extra-pulmonary or systemic symptoms of AHs because of the uncertainty of systemic bioavailability following administration via the inhaled or nasal routes. However, there is no consensus protocol for the performance of an OAC. OACs are lengthy and demanding of physician and technician time, with observation periods varying from several hours to days. Furthermore, many tests are performed because of the difficulty in patient selection.

Our aim was to identify retrospectively and validate prospectively how a 1-day OAC protocol based on that of McDonald et al. [8] could be modified to deliver more efficient service without compromising patient safety.

Materials and methods

We initially reviewed 45 consecutive OACs performed in our department (a secondary and tertiary referral allergy service)

Correspondence: Dr Liam J. Cormican, Specialist Registrar in Respiratory Medicine, Department of Asthma, Allergy & Respiratory Science, Guy's Hospital, St Thomas' Street, London SE1 9RT, UK.
E-mail: cormitron@yahoo.com

over a 45-month period from April 1998 until December 2001. Demographic, clinical and oral aspirin challenge data of each patient were obtained from the laboratory database and the patient's medical records. Following the initial review, the interval between challenges was reduced to 90 min. The next 40 consecutive OACs was then analysed prospectively to validate this change.

Patients were referred for OAC by an allergist or respiratory physician following assessment at clinic. OAC was performed when AHs was suspected as contributing to recurrent angioedema or anaphylaxis, treatment-resistant rhinosinusitis, adult-onset-asthma and chronic non-vasculitic urticaria.

Atopic status was determined at clinic by skin prick testing to a panel of common aeroallergens, including grass pollen, tree pollen, cat fur, dog hair and house dust mite. A positive response was defined as a weal 3 mm or greater than the diluent control.

The OAC procedure was explained to the patients, who then gave their written informed consent. At 09:00 hours on the day of the OAC, baseline spirometry was measured on two occasions separated by 15 min before the administration of the first dose of aspirin. The patient was then given 30 mg of aspirin orally with a mouthful of water. Symptoms, external signs (urticaria, angioedema, rhinorrhoea) and food expiratory volume in 1 s (FEV₁) were documented every 15 min for a period of 2 h. A positive test was regarded as the development of any of the following: urticaria, angioedema, rhinorrhoea, anaphylaxis and/or a >15% fall in FEV₁.

In the absence of any symptoms or signs suggestive of AHs after 2 h, 60 mg of aspirin was administered and the same measurements were repeated. The procedure was repeated every 2 h, with doses of 100 and 300 mg until the patient developed a reaction. If no reaction occurred 2 h after the 300 mg dose, the test was deemed negative.

The threshold dose of aspirin that gave a positive reaction, the time of onset of symptoms and signs after the threshold dose and the actual symptoms and signs elicited were documented. The overall duration of each test was defined as the time interval between the administration of the initial 30 mg dose of aspirin and the cessation of formal observation.

The clinical and demographic characteristics of those who had positive OACs were analysed to determine whether they had any common characteristics that would enable the prediction of a positive test.

Statistics

Results were expressed as mean and range. Statistics were descriptive. A time-to-event analysis as previously described [12] was performed on the positive group, in order to determine the likelihood of a positive reaction occurring after 90 min.

Results

Eighty-five OACs were performed, 45 and 40 using the 2 and 1½ h dose interval protocols, respectively. Twenty-eight were positive (M:F 8:20, mean age 44.1 years) (Table 1) and 57

were negative (M:F 20:37, mean age 40.9 years). Within the 2 and 1½ h dose interval protocol groups, 21/45 (46.6%) OACs (M:F 11:34, mean age 40.8 years), and 7/40 (17.5%) OACs (M:F 18:22, mean age 43.3 years), respectively, were positive.

The indications for performing OAC were suspected AHs as a cause of asthma (38/85, 44.7%), rhinosinusitis (43/85, 51%), chronic non-vasculitic urticaria (26/85, 30.5%), angioedema (29/85, 34.1%) and anaphylaxis (8/85, 9.4%). Thirty-eight subjects (44%) who had OAC performed had single manifestations of suspected AH, asthma (8/85, 9.4%), rhinosinusitis (14/85, 16.5%), chronic non-vasculitic urticaria (6/85, 7%), angioedema alone (8/85, 9.5%) and anaphylaxis (3/85, 3.5%). The remaining 47 subjects (56%) had multiple manifestations of suspected AH (Tables 1 and 2).

All positive reactions in the initial 2 h dose interval group ($n = 21$) occurred within 90 min of the administration of the threshold dose of aspirin. Seventeen subjects (80.9%) reacted within 1 h, two reacted at 75 min and two at 90 min. In the subsequent prospective 1½ h dose interval group, all positive reactions ($n = 7$) occurred within 75 min (six (85.6%) occurred within 60 min). Taken as a whole, 85.6% of all positive OACs occurred within 1 h and all within 90 min of administration of the threshold dose of aspirin (Fig. 1). A time-to-event analysis of all the positive OACs, assuming a constant hazard of reacting, results in a 5.2% probability that a positive OAC occurs later than 90 min after the administration of the threshold dose of aspirin.

Bronchospasm occurred in 10 (35.7%) of the positive OACs. The mean decrement in FEV₁ was 26.2% (12.5–44%). Of those who developed bronchospasm during OAC, four (40%) did not have a previous history of asthma, and all episodes were precipitous (Fig. 2). Of the 12 patients with a positive OAC and a history of asthma, six (50%) developed extra-pulmonary manifestations without bronchospasm during the test.

Upper respiratory tract (nasal) symptoms occurred in 12 patients (42.9%), urticaria in nine patients (32.1%) and angioedema in six patients (21.4%). Eight patients (28.6%) developed multiple manifestations of AH, all of which involved either bronchospasm or upper respiratory tract symptoms. None developed anaphylaxis.

A distinction was made between the two categories of cutaneous manifestations of AHs (chronic non-vasculitic urticaria and angioedema). Of the 13 patients (46.4%) with positive OACs exhibiting a background history of cutaneous manifestations of AHS, 46.1% (6/13) had histories of both, 38.4% (5/13) had either alone, while 15.3% (2/15) had histories of either cutaneous reaction and a non-cutaneous manifestation of AHs. Three of the 10 (30%) positive OACs with a background history of cutaneous manifestations of AHs but without asthma developed bronchospasm during OAC.

Nebulized salbutamol was given in 9/10 patients (mean dose 2.5 mg) with bronchospastic responses and was effective. Oral antihistamine (cetirizine, mean dose 10 mg) was given in 3/15 with angioedemic or urticarial responses. No further adverse events were experienced and all were discharged home on the day of the challenge.

Within the 2 h dose interval protocol group, the total duration of the positive and negative tests was 5 (3–10) and

Table 1. Demographic and clinical characteristics of 28 patients with positive oral aspirin challenges

No	Age	Sex	Indication	Atopy	Clinical history	Threshold dose (mg)	OAC reaction type	Change in FEV ₁ L (%)
<i>2 h dose interval protocol</i>								
1	24	F	RS	N	Y	30	NAS	–
2	41	F	AA, RS	Y	Y	30	NAS, LRT	0.4 (12.5)
3	45	F	RS, AA	Y	Y	30	NAS, SK	–
4	41	F	ANG, U	N	N	60	LRT	0.6 (35.3)
5	35	F	U	N/A	Y	60	SK	–
6	57	F	RS	N	N	60	NAS	–
7	62	F	NAA, RS, NP, U	N	Y	60	SK	–
8	37	F	AA	Y	N	100	LRT	0.6 (40)
9	59	F	RS, NP, AA	Y	Y	100	NAS, LRT	0.75 (32.1)
10	34	F	RS, NP	Y	Y	100	NAS, SK	–
11	67	F	RS, AA	Y	Y	100	NAS	–
12	45	M	AA, RS	Y	Y	100	NAS, LRT	0.45 (20)
13	18	F	ANG, RS	N	Y	100	LRT, ANG	1.6 (44)
14	29	F	NAA, RS	N	N	300	LRT	0.55 (18.1)
15	39	M	U	N	N	300	LRT	0.32 (16)
16	40	F	U	Y	N	300	SK	–
17	32	F	RS	Y	N	300	SK	–
18	56	M	NAA, NP	N	N	300	ANG, NAS	–
19	61	F	ANG, U	Y	N	300	ANG	–
20	54	F	ANPY, ANG, U, NAA	N	N	300	LRT	0.4 (23)
21	52	M	ANPY, U, A, RS, ANG	N/A	Y	300	SK	–
<i>1½ h dose interval protocol</i>								
22	32	F	AA, RS	N/A	N/A	60	NAS	–
23	56	M	ANG, U	N	N/A	60	ANG	–
24	55	M	ANG	N/A	N	60	ANG	–
25	34	F	U, ANG	N	Y	100	SK	–
26	48	M	RS	N/A	N/A	100	LRT, ANG, NAS	0.56 (21)
27	43	F	RS	Y	N	300	NAS	–
28	41	M	U	Y	Y	300	SK	–

A, asthma; AA, atopic asthma; NAA, non-atopic asthma; RS, rhinosinusitis; NP, nasal polyposis; U, chronic non-vasculitic urticaria; ANG, angioedema; ANPY, anaphylaxis; LRT, bronchospasm; NAS, nasal symptoms; SK, urticaria/persistent skin symptoms; N/A, not available; M, male; F, female; Y, yes; N, no; OAC, oral aspirin challenge; FEV₁, forced expiratory volume in 1 s.

Table 2. Clinical phenotypes of patients who had positive oral aspirin challenges, with proportions expressed as a function of the total OAC and positive OAC populations, respectively

Phenotypes	Proportion of total OAC population, <i>n</i> = 85 (both positive and negative)	Percentage of total OAC population, <i>n</i> = 85 (both positive and negative)	Proportion of positive OAC population	Percentage of positive OAC population
Asthma (total)	38		12	
Asthma alone	1/8	12.5	1/12	8.3
Asthma associated with other manifestations of AHs	11/30	36.6	11/12	91.6
Rhinosinusitis (total)	43		17	
Rhinosinusitis alone	5/14	35.7	5/17	29.4
Rhinosinusitis associated with other manifestations of AHs	12/29	41	12/17	70.6
Urticaria (total)	26		11	
Urticaria alone	4/6	66	4/11	36.4
Urticaria associated with other manifestations of AHs	6/20	35	7/11	63.6
Angioedema (total)	29		8	
Angioedema alone	1/8	12.5	1/8	12.5
Angioedema associated with other manifestations of AHs	7/21	33.3	7/8	87.5
Anaphylaxis (total)	8		2	
Anaphylaxis alone	0/3	0	0	0
Anaphylaxis associated with other manifestations of AHs	2/5	40	2/2	100

AHs, aspirin hypersensitivity; OAC, oral aspirin challenge.

8 h, respectively. Within the 1½ h dose interval protocol group, the total duration of the positive and negative OACs was 5 (3–7) and 6 h, respectively.

The threshold dose of aspirin for a positive OAC was 30 mg in 10.7% (3/28), 60 mg in 25% (7/28), 100 mg in 28.6% (8/28) and 300 mg in 35.7% (10/28). Among those with positive

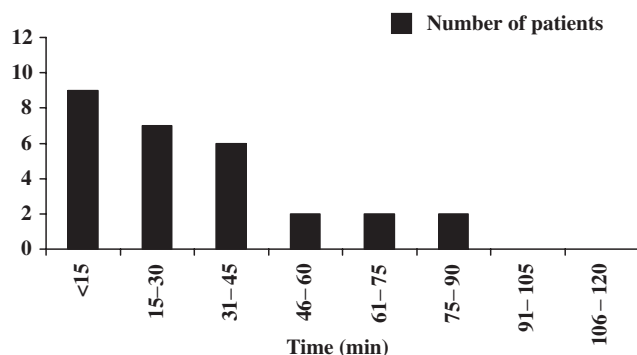


Fig. 1. Time period between ingestion of threshold dose of aspirin and onset of symptoms and/or signs, indicative of a positive oral aspirin challenge.

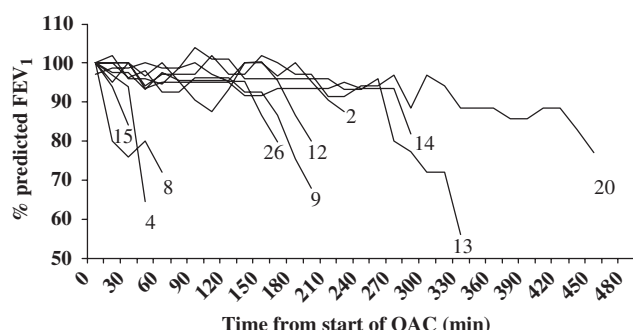


Fig. 2. Serial forced expiratory volume in 1 s (FEV₁) for patients with positive oral aspirin challenges (OACs) associated with bronchospastic responses (patient numbers correspond with those in Table 1).

OACs, the frequency at which bronchospasm occurred for each incremental dose of aspirin was one (10%) at 30 mg, one (10%) at 60 mg, five (50%) at 100 mg and three (30%) at 300 mg.

Forty-six percent (13) of those with positive OACs and 33.3% (20) of those with negative OACs had a clinical history of AHs or NSAID hypersensitivity. The drugs implicated in the groups with positive and negative OACs were aspirin (8/13, 61.5% and 12/20, 60%, respectively), ibuprofen (7/13, 46.1% and 3/20, 15%, respectively) and diclofenac (0% and 5/20, 25%). Two patients from the positive OAC group had clinical histories of hypersensitivity to more than one of these drugs. An atopic predisposition was found in 52% (13/23) and 51% (24/47) of those with positive and negative OACs, respectively, who had skin prick tests performed.

The presentation of AHs, as a history of either single or multiple symptoms (manifestations), was examined in the positive and total OAC population (Tables 1 and 2). Among the positive OAC population, 92% (11) of those with asthma, 87.5% (7) of those with angioedema, 70.6% (12) of those with rhinosinusitis, 63.6% (7) of those with chronic non-vasculitic urticaria and all of those with anaphylaxis had a history of two or more manifestations of AHs. Eight percent (1) of those with asthma and 12.5% (1) of those with angioedema, and none of those with anaphylaxis, and a positive OAC had a clinical history of a single manifestation of AHs.

Discussion

OAC was first used in the early 1970s to diagnose AHs [8]. The initial technique was 4 days in duration. This was modified to a 3-day procedure, with the first day involving a placebo challenge to ensure stability of bronchial hyper-reactivity [2, 13]. This was reduced subsequently to 2 days, where a cumulative dose of 500–625 mg was administered in divided increments [11, 14]. For studies using geometric dose increments, the duration between each dose increment ranged from 2 h [11] to 3 h [2].

In our study, positive reactions to OAC occurred in 86% of cases within 1 h and in all cases within 1½ h of the threshold dose of aspirin. By time-to-event analysis of these data and using the conservative estimate of a constant hazard of reacting after a threshold dose of aspirin, we calculated that the likelihood of a positive reaction occurring after 90 min in a positive OAC was 5.2%. We therefore propose that the observation period could be safely reduced from 120 to 90 min after each dose of aspirin. Reduction of the time interval between incremental doses to 90 min instead of 2 h [11] or 3 h [2] reduces OAC duration by 25–50%.

We confirmed that this particular OAC protocol was safe. While one asthmatic subject had a 44% drop in FEV₁, she responded well to treatment, emphasizing the importance of having medical supervision during the tests.

Even though none of the subjects developed anaphylaxis, we believe that starting an OAC at a higher dose (60 mg instead of 30 mg) may not be feasible as three subjects developed positive reactions after the ingestion of 30 mg (bronchospasm in one). Furthermore, starting OAC at a higher dose for those specifically with non-bronchospastic and non-anaphylactic manifestations of suspected AHs (i.e. rhinosinusitis, angioedema or chronic non-vasculitic urticaria) is possibly unsafe as four subjects developed bronchospasm during OAC in the absence of a history of asthma. Therefore, further abbreviation of the OAC by starting at a higher dose may not be advisable because patient safety could be compromised.

The population presented in this manuscript is a heterogeneous group of patients with diverse manifestations of aspirin sensitivity on history and on OAC. It is entirely different from the homogeneous asthmatic population examined by Jenkins et al. [1] in their meta-analysis. We therefore did not and cannot comment on the difference in the prevalence of asthma between the 2 and 1½ h dose interval protocol groups. Any difference could simply be a reflection of the heterogeneity of the population studied (44.7% suffered from asthma).

The purpose of this paper is to focus on the improvement of an oral aspirin challenge protocol for the detection of AHs (in its different manifestations and not just in asthma).

The investigation of possible AHs in the aetiology of unexplained chronic non-vasculitic urticaria, angioedema and anaphylaxis could potentially lead to a substantial increase in the number of referrals for OACs. It is therefore germane to try and identify distinct clinical features that may help predict a subject's response to OAC. In our study, the majority of those with positive OACs had a history of two or more manifestations of AHs (Table 2). This relationship was particularly strong for subjects suffering from asthma,

angioedema and anaphylaxis. Only 12.5% of those with asthma, 12.5% of those with angioedema and none of those with anaphylaxis as a lone manifestation of AHs had positive OACs. These findings could enable selection of subjects for OAC who are most likely to have a positive response, and exclusion of patients who are least likely to react to the test.

We believe it to be unlikely that the cutaneous manifestations of AHs belong to two distinct categories [15], nor that they are always distinct from the respiratory tract manifestations of AHs. Our data suggest that AHs is as likely to manifest itself at a combination of different sites as individual ones. Our data also suggest that it is important to monitor FEV₁ in patients challenged for aspirin-induced cutaneous reactions, in the absence of a history of asthma. We therefore believe that the application of anything shorter than a 90 min dose interval to an OAC could compromise patient safety, in a heterogeneous population, such as that presented here. This contrasts to the rapid dose escalation *aspirin-desensitization* protocol of Wong et al. [15], for those suffering only from angioedema or urticaria, associated historically only with aspirin or NSAID. It is also noteworthy that the majority of the patients from that study [15] received either an enteral antihistamine or corticosteroid before desensitization to aspirin.

Reliance on a history of AHs was unhelpful in the selection of patients for OAC. In our study, we found that a prior history of AHs was not predictive of a positive OAC, as 46.44% of the positive and 35% of the negative OAC groups gave such a history. Pleskow et al. [10] also found that 16% of asthmatic patients, who were assumed to be aspirin sensitive on the basis of their clinical history, had negative oral aspirin challenges. The predicted value of a test depends on the population studied and whether the test is used to confirm or exclude sensitivity. In the case of the population presented in this paper, OAC was performed predominantly to exclude AHs. Therefore, the finding that a large proportion of our patients, who gave a clinical history of AHs but yet had a negative OAC, probably reflects differences in the population studied when compared with that of Pleskow et al. [10]. Of the 85 patients examined in our study, 47 were not asthmatic and they underwent OAC for suspected extra-pulmonary manifestations of aspirin intolerance.

A placebo challenge was not performed, as this was an audit of a clinical service rather than a double-blind trial. The emphasis on a fall in FEV₁, which was precipitous, as one of the criteria for a positive OAC, reduced the likelihood that positive responses were caused simply by diurnal variation. The retrospective analysis is supported by the prospective analysis of a different group of patients who underwent aspirin challenge. The same results were observed (i.e. they all reacted within 90 min of the threshold dose of aspirin). It would therefore be surprising if the same data were obtained by coincidence and were simply explained by baseline drift. The same considerations apply to the lack of placebo challenge for those undergoing investigation for upper respiratory tract and dermatological manifestations of AHs.

In conclusion, a clinical history of developing a previous reaction after ingestion of aspirin is not a reliable guide to current AHs. As there are no *in vitro* tests of AHs, aspirin challenge is the only diagnostic tool available. It has been suggested that the oral route of aspirin challenge may be the

preferred route of choice because of its sensitivity and greater specificity than other forms of aspirin provocation [11]. This has been debated but, irrespective of one's viewpoint, it is agreed that OAC is very time consuming and labour intensive. This workload can be reduced by improved patient selection, recognizing that AHs is less likely to be a significant cause of anaphylaxis, angioedema or asthma in the absence of other manifestations of potential AHs.

Attempts to reduce test duration by starting at a dose higher than 30 mg of aspirin are potentially unsafe as a proportion of patients have positive reactions at the 30 mg level and a proportion of previously unknown asthmatics with other manifestations of AHs will develop bronchospasm. However, the overall test duration can be reduced by at least 25% through reduction of the interval between doses to 90 min.

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Supplementary Material

Supplementary material is available from <http://www.blackwellpublishing.com/products/journals/suppmat/CEA/CEA2261/CEA2261sm.htm>

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