

Refractoriness to inhaled sodium metabisulphite in subjects with mild asthma

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Refractoriness to inhaled sodium metabisulphite in subjects with mild asthma. I.D. Pavord, A. Wisniewski, A.E. Tattersfield. ©ERS Journals Ltd 1994.

ABSTRACT: Refractoriness occurs after challenges causing mediator release in asthma, by a mechanism which may involve inhibitory prostaglandins. Bronchoconstriction due to inhaled sodium metabisulphite is thought to involve neural pathways and to be independent of mediator release; whether it shows refractoriness is uncertain. We have sought evidence of refractoriness to the bronchoconstrictor response to inhaled sodium metabisulphite in subjects with mild asthma, and have tested the hypothesis that the development of refractoriness involves inhibitory prostaglandins.

Twelve subjects were challenged twice with a dose of sodium metabisulphite, previously shown to cause a 20% fall in forced expiratory volume in one second (FEV₁); the second challenge proceeded after recovery from the first. The response to sodium metabisulphite was expressed as the maximum % fall in FEV₁ and area under the change in FEV₁ curve over 20 min (AUC). Nine subjects were studied after double-blind treatment with oral indomethacin, 50 mg *t.d.s.*, or placebo, for 3 days.

The second sodium metabisulphite challenge caused significantly less bronchoconstriction than the first (mean maximum fall in FEV₁ 13.1 and 24.3%, respectively). Nine subjects showed a greater than 50% reduction in the response to the second challenge (mean reduction in AUC 73.7%). In these subjects, indomethacin did not alter the response to the first sodium metabisulphite challenge, or the mean maximum fall in FEV₁ in response to the second challenge (placebo 9.7%, indomethacin 11.2%), but significantly increased the AUC of the second challenge (placebo 55, indomethacin 114). The mean reduction in AUC from first to second challenge was 78% with placebo and 48% with indomethacin.

We conclude that subjects with mild asthma show refractoriness to sodium metabisulphite. Inhibitory prostaglandins may be partly responsible, but are unlikely to have a major role.

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Refractoriness, a reduced response to a second bronchoconstrictor challenge after recovery from the first, is well recognized with bronchoconstrictor challenges that act indirectly *via* mast cell mediator release, such as exercise and inhaled non-isotonic solutions and appears to be due to formation of inhibitory prostaglandins [1–3]. It is less clear whether refractoriness occurs following bronchoconstriction induced by sodium metabisulphite, a stimulus that is thought to act *via* release of sulphur dioxide (SO₂) and activation of neural pathways [4, 5].

Studies looking for evidence of refractoriness to sodium metabisulphite-induced bronchoconstriction have produced conflicting results [4–6], although there is clear evidence of refractoriness to the response to inhaled SO₂ in asthma [7]. The aim of this study was to establish whether refractoriness occurs to the response to inhaled sodium metabisulphite in patients with asthma, and to

assess the role of inhibitory prostaglandins, by studying the effect of the cyclooxygenase inhibitor indomethacin.

Material and methods

Subjects

Twelve subjects (10 male), aged 22–52 yrs, with mild asthma requiring inhaled therapy only, were recruited from the City Hospital asthma register. Six subjects were taking an inhaled corticosteroid regularly (beclomethasone 200–1,000 µg·day⁻¹), and all took an inhaled beta₂-agonist as required. Beta₂-agonists were withheld for 6 h before each visit; otherwise treatment was continued unchanged throughout the study. Eleven subjects were atopic, and one was a current smoker. All subjects had

Table 1. – Refractoriness to sodium metabisulphite (MBS): subject details, with maximum fall in FEV₁ after first and second challenge with single PD₂₀ dose of MBS on the assessment day and the two study days

Subj No.	FEV ₁ % pred	Dose MBS μmol	Maximum fall in FEV ₁ %					
			Assessment		Placebo		Indomethacin	
			1st	2nd	1st	2nd	1st	2nd
1	95	2.0	19	11	10	8	12	10
2	98	3.0	25	13	25	8	29	14
3	106	3.0	35	6	18	8	20	1
4	76	0.5	42	13	41	17	33	22
5	121	2.0	25	8	15	7	18	8
6	99	6.0	27	8	21	7	18	13
7	105	7.0	20	10	12	6	23	10
8	100	12.0	15	4	29	2	5	6
9	85	8.0	23	12	28	15	30	15
10	100	2.0	22	15	-	-	-	-
-								
11	97	6.0	11	21	-	-	-	-
12	105	1.7	27	37	-	-	-	-
Mean	99	3.2*	24	13	22	10	21	11
SEM	3		2.4	2.5	3.3	1.8	2.9	2.0

*: geometric mean. Subj: subject; FEV₁: forced expiratory volume in one second; % pred: percentage of predicted.

a forced expiratory volume in one second (FEV₁) of more than 70% predicted (table 1). None gave a history of non-steroidal anti-inflammatory drug-induced asthma, or bronchoconstricted in response to a test dose of indomethacin in the laboratory. After verbal and written explanation of the study, subjects gave signed consent to participate. The protocol was approved by the City Hospital Ethics committee.

Methods

FEV₁ was measured on a dry bellows spirometer (Vitalograph, Buckingham, UK) as the higher of two successive readings within 100 ml. The provocative dose of sodium metabisulphite required to cause a 20% fall in FEV₁ (PD₂₀) was established by giving increasing doses to a cumulative maximum of 128 μmol, using a MEFAR (Brescia, Italy) breath-activated dosimeter as described previously [8].

Protocol

In the first part of the study, subjects underwent a sodium metabisulphite challenge to determine the sodium metabisulphite PD₂₀. They returned on a separate day, at the same time of day, for a single dose challenge with approximately the PD₂₀ dose of sodium metabisulphite (table 1). FEV₁ was measured before (baseline) and at 1, 3, 5, 7, and 10 min and then at 5 min intervals after the challenge. Subjects were rechallenged with the same dose of sodium metabisulphite after recovery (FEV₁ >95% baseline value). FEV₁ was then measured at the same intervals for a further 20 min.

Subjects who had a reduction in the area under the % change in FEV₁ over 20 min (AUC) at the second challenge of more than 50% were chosen to proceed to the second part of the study. Subjects were treated with oral indomethacin (50 mg *t.d.s.*), or matched placebo, for 3 days before each visit, in a double-blind, cross-over study. The last dose was taken 1 h before the subjects were challenged with two single PD₂₀ doses of sodium metabisulphite, as described above.

Analysis

Sodium metabisulphite PD₂₀ was calculated by linear interpolation of the log dose-response curve. The airway response to single dose challenge with sodium metabisulphite was expressed as % change from the FEV₁ recorded immediately before the challenge (baseline), and described as maximum % fall in FEV₁ and AUC. Baseline FEV₁, the maximum fall in FEV₁ and AUC for the first and second challenge were compared within-subjects by paired t-tests, and differences calculated with 95% confidence intervals (95% CI). A refractory index was derived, by expressing the difference between the AUC for first and second challenge as a percentage of the values for the first challenge. Mean indices were compared within-subjects by a paired t-test, and differences expressed as a mean with 95% CI.

Results

Development of refractoriness

Inhaled sodium metabisulphite caused dose-related bronchoconstriction in all subjects, the geometric mean

Table 2. – Effect of indomethacin on refractoriness: area under the % change in FEV₁ curve over 20 min for first and second sodium metabisulphite challenge and refractory index (RI) on the assessment day and the two study days

Subj No.	Area under the % fall in FEV ₁ curve over 20 min								
	Assessment		RI %	Placebo		RI %	Indomethacin		RI %
	1st	2nd		1st	2nd		1st	2nd	
1	253	125	51	125	38	70	131	146	-11
2	398	128	68	325	122	62	413	126	69
3	564	28	95	190	22	88	194	2	99
4	508	60	88	623	109	83	461	228	51
5	147	19	87	151	28	81	88	26	70
6	204	67	56	106	42	61	116	88	24
7	211	37	83	107	18	84	322	98	70
8	77	11	86	246	4	98	94	79	15
9	248	123	50	426	109	75	432	229	47
Mean	290	66	74	255	55	78	250	114	48
SEM	55	16	5.9	58	15	4.1	52	26	11.3

For abbreviations see legend to table 1.

PD₂₀ being 3.2 µmol. Challenge with a single dose of sodium metabisulphite on the assessment day caused the development of rapid bronchoconstriction (fall in FEV₁), which reached a maximum between 1–3 min, and had usually recovered (FEV₁ >95% baseline) by 30 min. The mean maximum fall in FEV₁ was 24% (table 1). After the second challenge, the mean maximum fall in FEV₁ was 13% (mean difference 11%; 95% CI 3.6–18.9%; p<0.01). In nine of the 12 subjects, the refractory index was greater than 50% (mean 74%) (table 2).

Effect of indomethacin

After placebo treatment the mean maximum fall was 22% after the first challenge, and 10% after the second challenge (table 1). All subjects remained refractory, and the mean refractory index was similar to the assessment value (78%; table 2). Indomethacin treatment had no effect on the response to the first sodium metabisulphite challenge. There was no significant difference between placebo and indomethacin for the first challenge mean baseline FEV₁ (3.50 and 3.42 l), time to recovery (26.1 and 27.2 min), maximum % fall in FEV₁ (22 and 21%), and AUC (255 and 250) tables 1 and 2, and fig. 1). There was also no significant difference between placebo and indomethacin for baseline FEV₁ (3.37 vs 3.31 l) and maximum % fall in FEV₁ (10 vs 11%) for the second challenge. The AUC following the second challenge was, however, significantly greater with indomethacin treatment (114; mean difference from placebo 59; 95% CI 17.5–100.6; p<0.02) (table 2). The mean refractory index (48%) was significantly less than that following placebo (mean difference 30%; 95% CI 3.9–55.6%; p=0.03). Four subjects had a refractory index of less than 50% after indomethacin treatment (table 2).

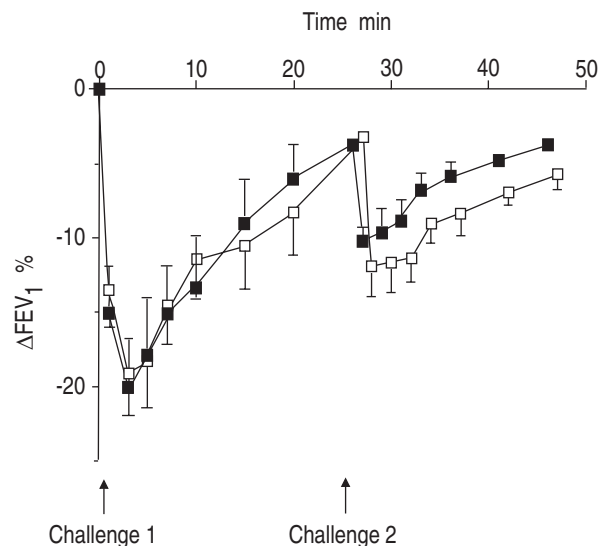


Fig. 1. – Mean (SEM) change in FEV₁, expressed as percentage fall from baseline, after first and second sodium metabisulphite challenge with placebo (■) and indomethacin (□) treatment. FEV₁: forced expiratory volume in one second.

Discussion

We have shown evidence of refractoriness to the bronchoconstrictor response to a repeat single inhaled dose of sodium metabisulphite in 12 subjects with mild asthma. Nine subjects showed a greater than 50% reduction in response to a second sodium metabisulphite challenge.

Studies looking for evidence of refractoriness to sodium metabisulphite in asthma have produced conflicting results. NICHOL *et al.* [4] showed refractoriness in five subjects rechallenged with a single dose of sodium metabisulphite 45 min after the first challenge, whereas

two studies using repeated cumulative or sequential dose challenges found no evidence of refractoriness [5, 6]. Refractoriness appears, therefore, to be less apparent when increasing, sequential doses of sodium metabisulphite are given, suggesting that refractoriness is starting to develop during the first challenge. The differences between studies might also be due to methodological differences. In all previous studies, the repeat challenge has been performed at fixed times after the first challenge [4–6]. This can lead to wide differences in baseline lung function before the first and second challenge, or a reduction in refractoriness when there is a long interval between challenges. We attempted to get over these problems by performing the second challenge as soon as the FEV₁ had returned to 95% of the baseline value before the first challenge. The second baseline FEV₁ was slightly lower than the first, so that by using it as baseline for the second challenge the degree of refractoriness may have been overestimated. This would not, however, affect the comparison between placebo and indomethacin treatment, since recovery had occurred to a similar degree before the second challenge with both treatments.

Sodium metabisulphite is thought to cause bronchoconstriction by releasing SO₂ [1, 2], since the bronchoconstrictor response to inhaled SO₂ is similar in time course to that of sodium metabisulphite [4, 9], and SO₂ is released by sodium metabisulphite solutions in a dose dependent manner [5]. Histamine release is unlikely to contribute to bronchoconstriction, since the response to sodium metabisulphite is not inhibited by terfenadine [10]. Our demonstration that indomethacin has no effect on the initial response to sodium metabisulphite suggests that production of constrictor prostaglandins is also unimportant.

Animal studies suggest that SO₂ causes vagally-mediated bronchoconstriction [9]. Such a pathway would fit with the rapid onset and lack of effect of terfenadine and indomethacin on sodium metabisulphite-induced bronchoconstriction in asthma. However, antimuscarinic agents have an inconsistent effect on sodium metabisulphite-induced bronchoconstriction [4, 10], suggesting that nonadrenergic, noncholinergic (NANC) excitatory nerve pathways may be important [4]. Refractoriness to sodium metabisulphite could, therefore, result from a reduction in neural activity or a reduction in the airway smooth muscle response to released neurotransmitters. Loss of airway smooth muscle responsiveness is less likely, since the bronchoconstrictor response to the direct airway smooth muscle agonists, histamine and methacholine, is unchanged after recovery from sodium metabisulphite challenge [5, 6].

A reduction in neural activity may be due to depletion of neurotransmitters, as has been shown to occur with neuropeptide release in animal studies after repeated neural stimulation [11]. Stimulation of sensory nerve endings by sodium metabisulphite in asthma might have a similar effect, and would provide a plausible explanation for the development of refractoriness. Our finding of a small reduction in refractoriness in subjects treated with indomethacin suggests that inhibitory prostaglandins may be playing a role. The most likely candidate is

prostaglandin E₂ (PGE₂) since this is produced by human airway epithelium [12], and smooth muscle [13], and studies on canine and human airway smooth muscle *in vitro* show that low concentrations of PGE₂ inhibit both cholinergic and noncholinergic neurally-induced contractions [14, 15]. Furthermore, inhaled PGE₂ provides very effective protection against sodium metabisulphite-induced bronchoconstriction in subjects with asthma [8].

The inhibitory effect of indomethacin on the development of refractoriness was small, however, and was only evident with AUC data, which would not support a major role for prostaglandins. Inhibition of prostaglandin production should have been adequate, since similar doses of indomethacin have been shown to inhibit production of pulmonary cyclooxygenase products in response to allergen [16, 17], and markedly attenuate the refractory period after exercise challenge in subjects with asthma [1].

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