Respiratory symptoms and inflammatory responses to Difflam throat-spray intervention in half-marathon runners: a randomised controlled trial

A J Cox,1,2 M Gleeson,2 D B Pyne,1 P U Saunders,1 R Callister,2 P A Fricker1

ABSTRACT
Objective: In this study, the effects of Difflam Forte Anti-inflammatory Throat Spray on the incidence of upper respiratory symptoms (URS) and inflammatory responses after a half-marathon race were investigated.

Design and setting: Double-blind placebo-controlled randomised trial conducted in association with a half-marathon event.

Participants: 45 well-trained half-marathon runners.

Interventions: Difflam (n = 25) or placebo (n = 20) throat sprays were self-administered three times daily for 1 week before and 2 weeks after the race.

Main outcome measures: Self-reported respiratory symptoms; plasma prostaglandin E2, myeloperoxidase, interleukin (IL) 6, IL8, IL10 and IL1 receptor antagonist (IL1ra) concentrations; and salivary myeloperoxidase and IL6 concentrations.

Results: All subjects completed the intervention without reporting any adverse events. The proportion of athletes reporting URS was not substantially different between Difflam (52%) and placebo (56%) groups (p = 0.82). However, symptom severity scores were ~29% lower during Difflam treatment (4.7 (7.4) vs 6.6 (9.6) AU). Post-exercise responses in plasma inflammatory markers did not differ substantially between Difflam and placebo groups. Post-race increases in salivary myeloperoxidase (~63%; trivial to moderate difference; p = 0.13) and salivary IL6 (~50%; trivial to moderate difference; p = 0.25) were greater in the Difflam group.

Conclusions: Prophylactic use of the Difflam reduced the severity, but not the frequency, of URS among half-marathon runners. Post-race increases in systemic inflammatory markers were not altered by Difflam use, but markers of local inflammation (salivary myeloperoxidase and IL6) were augmented in the Difflam compared with the placebo group.

The impairment of athletic performance during periods of upper respiratory symptoms (URS) is a concern for athletes and coaches. The risk for upper respiratory illness in elite athletes is greatest during periods immediately before and after high-level competition, with some athletes more susceptible than others. The impact of URS on athletic performance has been poorly characterised to date. In a non-exercise setting, there is considerable evidence of impaired pulmonary function during upper respiratory tract infection (URT). Decreases in respiratory volumes and flow rates and abnormalities in respiratory muscle function have been reported during uncomplicated, naturally acquired URT. There is no evidence to suggest that athletes experiencing URS would be protected from similar changes in pulmonary function. In addition, there is growing evidence confirming disruptions in training schedules among athletes experiencing symptoms of respiratory illness. Despite these links between illness and performance, there have been few therapeutic intervention trials aimed at preventing or limiting URS in athletes.

Recent studies indicate that not all bouts of URS in athletes have an infectious aetiology. Accordingly, traditional treatment and management strategies may be ineffective for a proportion of athletes. Examination of the causes of URS in a population of elite athletes revealed that only ~30% of episodes were associated with an identified respiratory pathogen. Signs of airway inflammation have been noted in elite athletes in the absence of any underlying pathology, leading to speculation that non-infectious inflammation may contribute to the appearance of URS in some athletes. This possibility is further supported by evidence demonstrating that a combination anti-inflammatory/antibacterial throat spray used after a marathon was able to reduce the post-race incidence and severity of URS in distance runners.

If localised inflammation, in the absence of infection, accounts for the appearance of URS in some athletes, then a topical anti-inflammatory agent may offer some relief. One such product is Difflam Forte Anti-inflammatory Throat Spray, an over-the-counter non-steroidal anti-inflammatory agent (NSAID). The use of a self-administered anti-inflammatory throat spray during the weeks before and/or immediately after high-level competition may prove to be an effective prophylactic strategy against URS in athletic populations. There are no reported studies investigating the use of Difflam in alleviating URS in highly trained athletes; however, the product has proven efficacy in relieving pain, soreness and swelling associated with inflammatory conditions of the mouth and throat. There are a number of mechanisms by which the active ingredient in Difflam, benzydamine hydrochloride (BH), exerts its anti-inflammatory actions, including inhibition of the cyclooxygenase (COX) and phospholipase pathways; reduced neutrophil chemotaxis; attenuation of proinflammatory cytokine production; and reduced neutrophil oxidative burst, although it is unclear whether this is a direct consequence of other membrane-stabilising properties. The measurement of prostaglandins, as end-products of the COX pathway, of proinflammatory (interleukin (IL) 6 and IL8) and anti-inflammatory cytokines.
analyses were not included in the design.

The experimental design is illustrated in fig 1. Given the way. The experimental design is illustrated in fig 1. Given the
alter their training, pre-race routine or dietary practices in any
consent before participation. Athletes were not required to
in a half-marathon race.

investigate the effectiveness of Difflam in alleviating post-race

inflammatory medications and a predicted half-marathon race
time exceeding ~100 min for men and ~110 min for women.

Demographic information for the cohort is shown in table 1.

Two runners failed to start the race because of concerns
regarding existing injury and were withdrawn from the study at
this point. The study was undertaken with approval from the
Ethics Committees of the University of Newcastle and the
Australian Institute of Sport. The study was designed with
consideration of the CONSORT Statement on randomised
controlled trials.20 All subjects provided written informed
consent before participation. Athletes were not required to
alter their training, pre-race routine or dietary practices in any
way. The experimental design is illustrated in fig 1. Given the
short duration of the treatment period (3 weeks), interim
analyses were not included in the design.

Treatment allocations
Athletes provided their personal-best half-marathon race time as
an indicator of performance ability and were matched on predicted race times. To ensure that the proportion of male and
female athletes in each of the treatment groups was similar, female athletes were paired only with other female athletes, and
likewise, male athletes were paired only with other male athletes. One member from each pair was then randomly
allocated to the Difflam treatment group (DIF), the other to the placebo group (PLA). The active and placebo sprays were
manufactured specifically for the trial (iNova Pharmaceuticals,
Sydney, Australia) and were identical in appearance with the
identical in composition to the Difflam except for the omission
provided with a placebo throat spray (iNova Pharmaceuticals)
identical in composition to the Difflam except for the omission
of the active ingredient (benzydamine hydrochloride). Athletes
self-administered the throat spray for 1 week before and after the half-marathon. Athletes were provided with
written and verbal instructions to deliver four sprays, three
times daily (morning, afternoon and night) directly onto the
oropharynx. Difflam Forte and placebo sprays were weighed
before and after the intervention period and a total dose for each
subject estimated based on the change in weight of the sprays.

Sample collection
Blood samples were collected from runners ~24 h pre-race and
again immediately post-race. Samples were collected directly
into K3EDTA and lithium heparin collection tubes (Greiner Bio-
one; Frickenhausen, Germany). Plasma was separated by
centrifugation at 3000 rpm and 4°C for 8 min and stored
frozen at ~80°C until analysis. Whole, mixed, unstimulated
saliva (~1 ml) was collected from subjects by passive drool
directly into collection tubes. Subjects were directed to avoid
bringing saliva, phlegm or sputum forward from the back of the
throat. Samples were frozen immediately after collection and
were stored at ~80°C until analysis.

Illness records
Athletes maintained a prospective illness record across the
6 weeks of the study to indicate the presence of any illness
symptoms. The illness record was designed at the Australian
Institute of Sport and has been used previously in similar study
designs.24 An episode of URS was recorded if symptoms
persisted for two or more consecutive days. In addition to
indicating the type of symptoms experienced, athletes also
graded the symptom severity based on the impact on training.
Symptoms were given a score of 1, if mild in severity (normal
training); a score of 2, if moderate in severity (modified
training); and a score of 3, if severe (discontinued training).
Global episode severity scores were calculated by totalling daily
severity scores for the duration of the episode.

Plasma prostaglandin E2 and myeloperoxidase
The concentration of prostaglandin E2 (PGE2) concentrations in
K3EDTA plasma samples was determined using commercially
available enzyme immunoassay kits (Amersham Biosciences,
Buckinghamshire, UK). Samples were pretreated with 0.4 M
indomethacin (Sigma-Aldrich, St Louis, Missouri, USA) imme-
diately after collection to prevent ex vivo PGE2 production.
The concentration of myeloperoxidase (MPO) in lithium heparin
plasma samples was determined using commercially available
enzyme immunoassay kits (HyCult Biotechnology, Uden, The
Netherlands). Both PGE2 and MPO assays were completed
according to the manufacturers’ instructions. The coefficients
of variation (CV) for the low and high controls, respectively, were
PGE2: 11.6% and 5.8%, and MPO: 9.4% and 4.4%. All samples

Figure 1 The study design included a 3-week treatment period with either a Difflam or placebo throat spray. Blood and saliva samples were collected ~24 h pre-race and immediately post-race. A prospective illness record was maintained for the duration of the study.
from individual subjects were analysed in a single assay to avoid any inter-assay variation.

Plasma cytokines

Plasma concentrations of IL6, IL8, IL10 and IL1ra were determined simultaneously using a Bio-Plex Suspension Array System (Bio-Rad Laboratories, Hercules, California, USA) and custom-manufactured Multiplex Cytokine Kits (Bio-Rad Laboratories) according to the manufacturer’s instructions. The CV for the low and high controls, respectively, were IL6: 7.2% and 5.3%; IL8: 7.7% and 7.1%; IL10: 6.3% and 6.9%; and IL1ra: 11.7% and 3.2%. All samples from individual subjects were analysed in a single assay to avoid any inter-assay variation.

Table 1  Demographic and performance characteristics for runners in Difflam and placebo groups, including previous best half-marathon (HM) race time and performance time achieved in the Canberra Half-Marathon (CHM)

<table>
<thead>
<tr>
<th></th>
<th>Difflam group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female (n)</td>
<td>20:5</td>
<td>16:4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.1 (7.7)</td>
<td>35.2 (8.4)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177.6 (11.2)</td>
<td>176.7 (8.6)</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>72.5 (12.2)</td>
<td>72.4 (12.1)</td>
</tr>
<tr>
<td>Years of training</td>
<td>8.9 (8.1)</td>
<td>8.1 (7.1)</td>
</tr>
<tr>
<td>Previous best HM time (min)</td>
<td>9.7 (5.1)</td>
<td>10.7 (4.1)</td>
</tr>
<tr>
<td>CHM race time (min)</td>
<td>91.4 (10.7)</td>
<td>88.9 (10.8)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).

Salivary MPO and IL6

The concentration of MPO in saliva was determined using commercially available enzyme immunoassay kits (BioCheck, Foster City, California, USA). The concentration of IL6 in saliva samples was determined using commercially available high-sensitivity enzyme immunoassay kits (R&D Systems, Minneapolis, Minnesota, USA), as described previously. The coefficients of variation (CV) for the low and high controls, respectively, were MPO: 8.1% and 5.5%; and IL6: 3.4% and 6.1%. All samples from individual subjects were analysed in a single assay to avoid any inter-assay variation.

Statistical analysis

An analysis combining traditional statistical methods and magnitude-based inferences (effect sizes) and precision of estimation (90% confidence limits) was employed to overcome some of the shortcomings associated with traditional statistical significance testing. Sample size estimations revealed a sample of 45 distance runners provided adequate power (>80%) to detect meaningful differences in key inflammatory markers and a >50% difference in the reporting of URS. Descriptive statistics (mean (SD)) were used to summarise the physical and performance characteristics of the athletes. Concentrations of inflammatory markers (blood and saliva) were log-transformed before statistical analysis. Given their large magnitude, post-exercise changes in concentrations are reported as a percentage (%) or “x-fold” changes where appropriate. Race time was included as a covariate in subsequent analyses. t Tests for independent samples and standardised mean changes were used to compare responses between Difflam and placebo groups.
completed within humidity at the race finish. All 43 participants starting the race u humidity at the race start and 14.0 u. The ambient temperature was 8.2 u. The race was conducted on a fine and dry autumn morning. Race performance and throat spray dose of subjects assigned to the DIF and PLA groups. In keeping with the CONSORT Statement Checklist, partici-

### RESULTS

#### Participant flow

In keeping with the CONSORT Statement Checklist, participant flow and retention is summarised in fig 2. A number of subjects withdrew their participation between subject pairing and treatment allocation, accounting for the differing numbers of subjects assigned to the DIF and PLA groups.

#### Race performance and throat spray dose

The race was conducted on a fine and dry autumn morning. The ambient temperature was 8.2°C with 90% relative humidity at the race start and 14.0°C with 68% relative humidity at the race finish. All 43 participants starting the race completed within ~3.2% of their predicted race times and completed the intervention without reporting any adverse events. Mean race times were not substantially different (2.5% difference; p = 0.46) between the DIF (91.24 (10:42) min:s) and PLA groups (88.54 (10:48) min:s). The estimated treatment dose of the throat spray over the 3 weeks of administration was also not significantly different (3.1% difference; p = 0.18) between the DIF (33.7 (4.1) g) and PLA groups (30.6 (8.3) g).

#### Symptoms of upper respiratory illness

Twenty-three (51%) of the athletes reported at least one episode of URS over the 6 weeks of the study. Four athletes (9%) reported URS on more than one occasion. In total, 28 episodes of URS were reported during the study. There was substantial variability in the duration and severity of reported symptoms. The mean episode duration (regardless of intervention group) was 5.3 (4.6 days), with eight of the episodes (29%) 2 days or less in duration and involving mild, local symptoms only. These presentations are not consistent with the typical presentation of viral URTI.

The proportion of athletes reporting URS across the duration of the study was not appreciably different between DIF and PLA groups (p = 0.89) (table 2). Similarly, rates of reporting were not different between groups during the 3 weeks of throat spray use (p = 0.57) (table 2). Over the entire 6 weeks of the study,

#### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Difflam (n = 25)</th>
<th>Placebo (n = 18)</th>
<th>Difference (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire study (6 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of episodes</td>
<td>14</td>
<td>14</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Proportion of group reporting (%)</td>
<td>52</td>
<td>56</td>
<td>8</td>
<td>0.82</td>
</tr>
<tr>
<td>Mean duration (days)</td>
<td>3.9 (4.9)</td>
<td>4.1 (3.7)</td>
<td>5.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Mean episode severity score (AU)</td>
<td>4.7 (7.3)</td>
<td>5.2 (7.3)</td>
<td>9.3</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Treatment period (3 weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of episodes</td>
<td>8</td>
<td>10</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Proportion of group reporting (%)</td>
<td>32</td>
<td>50</td>
<td>56</td>
<td>0.23</td>
</tr>
<tr>
<td>Mean duration (days)</td>
<td>3.8 (5.6)</td>
<td>5.0 (4.6)</td>
<td>23.7</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean episode severity score (AU)</td>
<td>4.7 (7.4)</td>
<td>6.6 (9.6)</td>
<td>28.9</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) where appropriate. The episode severity score is reported in arbitrary units.

Original article

Table 3 Concentrations of plasma PGE2 and both plasma and salivary (sal) MPO and cytokines in the Difflam and placebo groups pre-race and post-race

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>% Change</th>
<th>p Value</th>
<th>ES (90% CI)</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PGE2</strong> (pg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIF</td>
<td>230.6 (139%)</td>
<td>390.8 (74%)</td>
<td>70</td>
<td>0.02</td>
<td>0.71 (0.47)</td>
<td>Small–moderate</td>
</tr>
<tr>
<td>PLA</td>
<td>259.9 (149%)</td>
<td>293.8 (142%)</td>
<td>13</td>
<td>0.63</td>
<td>0.13 (0.54)</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>MPO</strong> (ng ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIF</td>
<td>75.0 (61%)</td>
<td>318.9 (89%)</td>
<td>325</td>
<td>&lt;0.001</td>
<td>2.54 (0.47)</td>
<td>Very large</td>
</tr>
<tr>
<td>PLA</td>
<td>71.7 (62%)</td>
<td>271.9 (63%)</td>
<td>280</td>
<td>&lt;0.001</td>
<td>2.69 (0.54)</td>
<td>Very large</td>
</tr>
<tr>
<td><strong>IL6</strong> (pg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIF</td>
<td>2.1 (195%)</td>
<td>19.3 (54%)</td>
<td>841</td>
<td>&lt;0.001</td>
<td>2.66 (0.47)</td>
<td>Very large</td>
</tr>
<tr>
<td>PLA</td>
<td>2.0 (105%)</td>
<td>15.7 (73%)</td>
<td>696</td>
<td>&lt;0.001</td>
<td>3.18 (0.53)</td>
<td>Very large</td>
</tr>
<tr>
<td><strong>IL8</strong> (pg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIF</td>
<td>2.9 (75%)</td>
<td>13.7 (39%)</td>
<td>366</td>
<td>&lt;0.001</td>
<td>3.28 (0.47)</td>
<td>Very large</td>
</tr>
<tr>
<td>PLA</td>
<td>3.2 (66%)</td>
<td>12.9 (61%)</td>
<td>306</td>
<td>&lt;0.001</td>
<td>2.78 (0.5)</td>
<td>Very large</td>
</tr>
<tr>
<td><strong>IL10</strong> (pg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIF</td>
<td>1.8 (88%)</td>
<td>26.2 (99%)</td>
<td>1337</td>
<td>&lt;0.001</td>
<td>3.98 (0.48)</td>
<td>Very large</td>
</tr>
<tr>
<td>PLA</td>
<td>2.0 (49%)</td>
<td>21.6 (102%)</td>
<td>980</td>
<td>&lt;0.001</td>
<td>4.04 (0.55)</td>
<td>Very large</td>
</tr>
<tr>
<td><strong>IL1ra</strong> (pg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIF</td>
<td>41.3 (108%)</td>
<td>126.8 (55%)</td>
<td>207</td>
<td>&lt;0.001</td>
<td>1.83 (0.47)</td>
<td>Large to very large</td>
</tr>
<tr>
<td>PLA</td>
<td>36.9 (60%)</td>
<td>102.6 (49%)</td>
<td>178</td>
<td>&lt;0.001</td>
<td>2.29 (0.54)</td>
<td>Large to very large</td>
</tr>
<tr>
<td><strong>salMPO</strong> (ng ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIF</td>
<td>304 (181%)</td>
<td>827 (97%)</td>
<td>172</td>
<td>&lt;0.001</td>
<td>1.13 (0.47)</td>
<td>Moderate to large</td>
</tr>
<tr>
<td>PLA</td>
<td>459 (143%)</td>
<td>744 (126%)</td>
<td>72</td>
<td>0.09</td>
<td>0.56 (0.54)</td>
<td>Trivial to moderate</td>
</tr>
<tr>
<td><strong>salIL6</strong> (pg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIF</td>
<td>1.2 (207%)</td>
<td>3.0 (150%)</td>
<td>156</td>
<td>0.003</td>
<td>0.90 (0.49)</td>
<td>Small to large</td>
</tr>
<tr>
<td>PLA</td>
<td>1.3 (197%)</td>
<td>2.3 (116%)</td>
<td>62</td>
<td>0.09</td>
<td>0.56 (0.54)</td>
<td>Trivial to moderate</td>
</tr>
</tbody>
</table>

Cl, confidence interval; ES, effect size.

Concentrations are back-transformed means (CV %). Outcome statistics relate to the percentage change in concentrations from pre-race to post-race.
episode duration and severity scores did not differ between DIF and PLA groups (table 2). However, during the 3-week treatment period, there was a trend for reduced episode severity among the athletes receiving the Difflam compared with placebo (severity scores 4.7 vs 6.6 AU; ~29% difference).

**Plasma PGE2 and MPO concentrations**

There was a substantial increase in mean plasma PGE2 concentrations among the DIF group immediately post-exercise (70%; small to moderate; p = 0.02). In contrast, mean PGE2 concentrations were not substantially elevated post-exercise in the PLA group (p = 0.63). There were substantial increases in mean plasma MPO concentrations among both the DIF (4.3-fold; very large; p < 0.001) and PLA (3.8-fold; very large; p < 0.001) groups immediately post-exercise. The magnitude of post-exercise increases was not significantly different between the groups (12%, p = 0.53).

**Salivary MPO and IL6 concentrations**

There were substantial increases in mean concentrations of salivary MPO (salMPO) and IL6 (salIL6) post-exercise for both DIF and PLA groups (table 3). Post-exercise increases in salMPO concentrations were substantially greater (63%; p = 0.13, trivial to moderate difference) among the DIF (2.6-fold) compared with the PLA group (1.6-fold) (fig 5A). Similarly, post-exercise increases in salIL6 concentrations were substantially greater (50%; p = 0.25; trivial to moderate difference) among the DIF (2.5-fold) compared with the PLA group (1.7-fold) (fig 5B).

**DISCUSSION**

The prophylactic use of Difflam did not alter the incidence of URS in trained distance runners preparing for and completing a half-marathon race. However, in keeping with the proven efficacy of Difflam in a range of clinical settings, the PLA (11.7-fold) group (23%; p = 0.40; trivial to moderate difference) (fig 4A). The magnitudes of increase in IL1ra concentrations were not substantially different (5.9%; p = 0.76) between the DIF and PLA groups (3.1-fold vs 2.9-fold, respectively) (fig 4B).

**Plasma cytokine concentrations**

There were substantial increases in mean IL6, IL8, IL10 and IL1ra concentrations post-race for both DIF and PLA groups (table 3). The magnitudes of increase in IL6 concentrations post-exercise was not substantially different (7.8%; p = 0.81) between DIF and PLA groups (9.4-fold vs 8.7-fold, respectively) (fig 3A). Likewise, post-exercise increases in IL8 concentrations were not substantially different (7.1%; p = 0.32) between DIF and PLA groups (4.7-fold versus 3.9-fold, respectively) (fig 3B). In contrast, post-exercise increases in IL10 concentrations tended to be greater among the DIF (14.4-fold) compared with the PLA (11.7-fold) group (23%; p = 0.40; trivial to moderate difference) (fig 4A). The magnitudes of increase in IL1ra concentrations were not substantially different (5.9%; p = 0.76) between the DIF and PLA groups (3.1-fold vs 2.9-fold, respectively) (fig 4B).

The prophylactic use of Difflam did not alter the incidence of URS in trained distance runners preparing for and completing a half-marathon race. However, in keeping with the proven efficacy of Difflam in a range of clinical settings, the PLA (11.7-fold) group (23%; p = 0.40; trivial to moderate difference) (fig 4A). The magnitudes of increase in IL1ra concentrations were not substantially different (5.9%; p = 0.76) between the DIF and PLA groups (3.1-fold vs 2.9-fold, respectively) (fig 4B).

**DISCUSSION**

The prophylactic use of Difflam did not alter the incidence of URS in trained distance runners preparing for and completing a half-marathon race. However, in keeping with the proven efficacy of Difflam in a range of clinical settings, the PLA (11.7-fold) group (23%; p = 0.40; trivial to moderate difference) (fig 4A). The magnitudes of increase in IL1ra concentrations were not substantially different (5.9%; p = 0.76) between the DIF and PLA groups (3.1-fold vs 2.9-fold, respectively) (fig 4B).
The URS reported in the current study varied in nature. Approximately 30% of the self-reported episodes were of very short duration (2 days or less) and involved only localised, mild symptoms. It is unlikely that these short episodes were associated with an infectious aetiology. This finding is consistent with other reports in which a considerable proportion of episodes of URS in elite athletes were not associated with an identified infectious aetiology. It is likely that these symptoms result from ongoing mechanical damage to the mucosal surfaces of the upper airways as a consequence of the increased ventilatory loads during intense exercise and a subsequent inflammatory response. Although the prophylactic administration of Difflam is unable to prevent mechanical damage to the upper airways, relief from the subsequent sequelae of a localised inflammation is plausible. The usefulness of Difflam in alleviating URS in other athletic populations, where mechanical damage to the upper airways is less likely, warrants further investigation.

Despite the variable pattern of reported symptoms, the reduced symptom severity observed in response to Difflam is consistent with the previously demonstrated clinical benefits of BH treatment. There did not appear to be any residual carryover effects in the 2 weeks after the cessation of Difflam use, which can be explained by the short half-life of BH after topical administration. In the current study, a prophylactic approach was favoured over a simple treatment approach where differences in the duration of treatment and the onset of treatment relative to the onset of symptoms were identified as potential confounding variables. However, it is likely that reduced symptom severity would also be observed when throat sprays are used in accordance with traditional prescription guidelines, that is, at the onset of and for the duration of respiratory symptoms. While a treatment rather than a prophylactic approach is more practical for competing athletes, all athletes in the current study completed the prophylactic dosing regimen without any adverse clinical or performance outcomes supporting the safe use of Difflam in athletic populations.

The substantial post-exercise increases in plasma cytokine concentrations were consistent with reported responses to events of similar duration. Alterations in plasma MPO in response to exercise have been less well-characterised, but the large increases after the half-marathon are consistent with known changes in neutrophil degranulation post-exercise. Prostaglandin responses were highly variable between individuals preventing any clear conclusions. Few studies have examined in vivo changes in inflammatory markers after topical BH treatment in humans, with most focused solely on clinical outcomes. Studies that provide evidence of attenuated inflammatory responses after BH treatment have been completed in animal models or in vitro systems. In the current study, the apparent lack of effect of Difflam treatment on plasma cytokine and MPO responses may reflect that the effects of BH are mediated only at a local rather than a systemic level, in line with the topical application of the throat spray.

In contrast to systemic responses, exercise-induced changes in local inflammatory markers in saliva were augmented with Difflam treatment. This observation is counterintuitive, although it is similar to reports of greater post-exercise changes in plasma cytokines and oxidative stress markers after use of NSAID. Altered prostaglandin production after NSAID treatment may disrupt feedback inhibition mechanisms resulting in increased production of downstream inflammatory mediators. Given that the mechanisms of action of BH include reduced prostaglandin synthesis, disrupted feedback inhibition may be one explanation for the augmented local responses observed in the current study.

The augmented local inflammatory responses observed post-exercise with Difflam treatment raise interesting questions about the mechanisms contributing to the observed reduction in the severity of URS in this cohort of distance runners. It was anticipated that the topical administration of the BH would attenuate any increases in local pro-inflammatory cytokine concentrations, mediating a clinical benefit via a reduction in localised inflammation. While it remains possible that local inflammatory responses may have been attenuated during acute episodes of symptoms in the Difflam Forte-treated group, this was not measured directly in the current study. It is also interesting to consider the augmented local proinflammatory response in conjunction with documented evidence that proinflammatory cytokines, through interaction with the central nervous system, induce the classic “sickness behaviours” typically seen in response to infection. Sickness behaviours include malaise, lethargy, loss of appetite and changes in sleep and are recognised as an organised response to help fight infection. The augmented pro-inflammatory cytokine responses may therefore have the potential to contribute to an improved clinical outcome and may simply reflect the classic stress response.

In conclusion, the current investigation of the effects of Difflam on respiratory symptoms and inflammatory responses in half-marathon runners identified the potential for Difflam Forte to reduce the severity, but not the incidence of URS. The
References