Adverse Effects of Aspirin, Acetaminophen, and Ibuprofen on Immune Function, Viral Shedding, and Clinical Status in Rhinovirus-Infected Volunteers

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A double-blind, placebo-controlled trial was conducted to study the effects of over-the-counter analgesic/antipyretic medications on virus shedding, immune response, and clinical status in the common cold. Sixty healthy volunteers were challenged intranasally with rhinovirus type 2 and randomized to one of four treatment arms: aspirin, acetaminophen, ibuprofen, or placebo. Fifty-six volunteers were successfully infected and shed virus on at least 4 days after challenge. Virus shedding, antibody levels, clinical symptoms and signs, and blood leukocyte levels were carefully monitored. Use of aspirin and acetaminophen was associated with suppression of serum neutralizing antibody response ($P < .05$ vs. placebo) and increased nasal symptoms and signs ($P < .05$ vs. placebo). A concomitant rise in circulating monocytes suggested that the suppression of antibody response may be mediated through drug effects on monocytes and/or mononuclear phagocytes. There were no significant differences in viral shedding among the four groups, but a trend toward longer duration of virus shedding was observed in the aspirin and acetaminophen groups.

In 1975, Stanley et al. [1] reported that aspirin significantly increased virus shedding in rhinovirus-infected volunteers compared with those taking placebo. Because volunteers were started on aspirin before any symptoms had developed, this study did not replicate usual clinical practice but nonetheless suggested that aspirin might suppress the normal immune response to upper respiratory tract infection (URI). Mogabgab and Pollock [2] reported a subsequent experiment that found no differences in virus shedding between aspirin- and placebo-treated volunteers. In that study, volunteers were not given medication until symptoms started, more closely reflecting the situation in community-acquired infections. Unfortunately, pharyngeal washings were used to detect virus shedding instead of the significantly more sensitive method of obtaining nasal or nasopharyngeal washings [3], yielding a very low infection rate. Thus, the evidence is equivocal, and the question of aspirin effects on virus shedding remains open.

In addition to aspirin, acetaminophen and ibuprofen are available as over-the-counter medications, and all three are taken to reduce fever, myalgia, and general malaise from URI. These drugs are known to have effects on immune function and could influence virus shedding in URI. Aspirin has been reported to inhibit antibody formation and secondary antibody responses [4, 5], the interferon-mediated antiviral state in mouse L cells [6], incorporation of thymidine in DNA by mitogen- and antigen-stimulated lymphocytes [7], granulocyte adherence to foreign particles and the inflammatory response to *Staphylococcus aureus* peritonitis in mice [8], and phagocytosis by neutrophilic leukocytes [9]. On the other hand, it has also been shown to enhance thymidine uptake in mitogen-stimulated lymphocytes [10], production of interleukin-2 by mitogen-stimulated peripheral blood lymphocytes [11], and interferon production by stimulated lymphocytes [12]. It has also been postulated that the observed association between aspirin and Reye's syndrome [13] may be explained by an immune-enhancing effect of aspirin [10]. Ibuprofen does not appear to influence neutrophil phagocytosis [14] but has inhibitory effects on other human polymorphonuclear leukocyte functions [15] and on chemotactic peptide-receptor binding of granulocytes [16]. Acetaminophen may also have both immune-enhancing [17] and inhibitory effects [18] and has been recently associated with exacerbation of varicella infection in children [19].

To determine if these drugs exert a clinically significant effect on virus shedding and immune function in rhinovirus URIs, we challenged 60 volunteers with rhinovirus type 2 (RV2) and randomized them to receive aspirin, acetaminophen, ibuprofen, or placebo. Virus shedding, serum neutralizing antibody response, hematologic parameters, and clinical symptoms and

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signs were carefully monitored. The primary hypothesis was that aspirin and ibuprofen would increase the magnitude and duration of virus shedding and suppress antibody responses, but acetaminophen (with only limited cyclooxygenase-inhibiting effects) would have smaller or negligible effects on both. We expected that all drugs would suppress myalgia, headache, and malaise with equal efficacy. As fever does not commonly accompany uncomplicated rhinovirus infections, no specific hypotheses were tested in this regard.

Materials and Methods

The study was a randomized, double-blind, placebo-controlled clinical trial with four treatment arms. Sixty healthy volunteers, predominantly university students aged 18–30 years, were randomized within three strata based on their initial serum antibody titer (≤2, 3–4, 6–8) to RV2. Participants were all free of URI (runny or blocked noses, sore throat, or cough for ≥2 days) for 2 weeks before challenge and were instructed not to take aspirin, acetaminophen, ibuprofen, or other related drug during this period. After intranasal challenge with RV2, the volunteers received medication on the first day of upper respiratory symptoms or on day 3 if no symptoms had developed. Subjects were treated for 7 days unless side effects necessitated early cessation of treatment. All subjects were paid $A40/day to compensate for time of involvement, travel expenses, and inconvenience.

Laboratory methods. A preparation of pooled nasal washings containing RV2 obtained from the MRC Common Cold Unit in Salisbury (UK) was the source of the inoculum virus. The virus had been passaged only in human volunteers and was free from adventitious mycotic, bacterial, and viral agents. Each volunteer was inoculated intranasally with 200 $TCID_{50}$ of virus in 1 ml of antibiotic-free Hanks' balanced salt solution (pH 7.4, with 0.15% bovine serum albumin).

Daily nasal washings with 10 ml of PBS (5 ml in each nostril) were done to recover the virus. These were done the day before challenge (day −1), on challenge day just before challenge (day 0), on the 10 subsequent mornings, when the volunteers were kept isolated in accommodations in the Adelaide Hills (days 1–10), and on day 14. Each washing recovered 5–8 ml. Antibiotics were added to the nasal wash specimens, which were then diluted with an equal volume of maintenance medium (CMRL 1969 medium + 1% fetal calf serum and antibiotics) and stored at −70°C until being tested. HeLa T cells of known sensitivity to RV2 were used for virus isolation. Tube cultures at 24 h were inoculated in triplicate with 0.2 ml of thawed nasal washing and incubated at 33°C in roller drums. Tubes were examined microscopically on alternate days for characteristic cytopathic effect and discarded if negative after 10 days of incubation. The earliest isolate from each volunteer was identified by further passage of the harvest in HeLa tube cultures, followed by neutralization with specific rabbit antiserum of known titer against RV2. In addition, prechallenge nasal washings taken on day 0 were inoculated into three other cell types (HEp-2, human diploid fibroblast, primary monkey kidney) to exclude the presence of other respiratory viruses.

Each nasal washing positive for RV2 was titrated. A second aliquot stored at −70°C was thawed, 10-fold dilutions of this aliquot were made in the maintenance medium, and 0.2 ml of each dilution was inoculated in quadruplicate into 24-h HeLa T cell tube cultures. Tubes were incubated at 33°C in roller drums and examined microscopically 2 days after inoculation and then three times per week until day 10. A positive control virus sample of previously determined titer included in each assay demonstrated interassay variability $\leq 10^{0.4}$ from the mean positive control titer. Assays were repeated in the few instances where negative control (uninoculated) cells developed significant degeneration during the observed period. Calculation of the $TCID_{50}$ titer was made by the Karber method [20]. RV2 titers are presented here as $\log_{10}$ $TCID_{50}$ of virus shed on each day of the study.

Sera collected during screening and on days −1, 7, 14, and 28 were tested for neutralizing antibodies by titration in twofold dilutions against 100 $TCID_{50}$ of standard RV2 in a microtiter assay [20]. Each assay included a back titration of the challenge virus and titration of a standard control antibody-positive serum sample. Testing was batched according to the sequence of receipt of samples by the laboratory, and accordingly, each assay contained samples from all four patient groups distributed randomly.

Blood was taken for hematology at screening and on days −1, 5, 10, 14, and 28 and for serum biochemistry estimations at screening and on days −1 and 28.

Medications. The study medications were presented in identical capsules containing aspirin (500 mg), acetaminophen (500 mg), ibuprofen (200 mg), or placebo (McNeil Consumer Products, Fort Washington, PA). Daily doses of the medications were 4 g of aspirin (four doses of two capsules), 4 g of acetaminophen (four doses of two capsules), or 1.2 g of ibuprofen (three doses of two capsules and one dose of two placebo capsules). The placebo recipients received four doses of two capsules. To maintain compliance, dosing was observed by a study nurse, and spot urine samples were tested for study drug levels on days 0 and 5. Acetaminophen and ibuprofen doses were designed to be comparable with recommended over-the-counter doses. A relatively high dose of aspirin was chosen to maximize the probability of detecting any real effects on immune function and virus shedding. This approach was believed to be appropriate in view of the findings of Stanley et al. [1] and the funding-restricted sample size.

Clinical methods. Medical histories were taken and examinations were done on days −1 and 28. During the isolation phase of the study (days 0–10), the ENT (ear, nose, throat) system was examined daily. On each day, all ENT signs (nasal discharge, crusting, obstruction, mucosal inflammation, turbinate swelling, pharyngitis, and cervical lymphadenopathy) were scored 0, 1, 2, or 3 for absent, mild, moderate, or severe signs, respectively. The daily scores were then summed to calculate a total score for each sign, and the totals for all signs were summed to give an overall ENT score for each subject. Temperatures were taken orally four times daily.

For days 0–14, volunteers recorded daily the presence and severity of a range of common cold symptoms (sneezing, nasal obstruction, sore throat, cough, postnasal drip, hoarseness, watery or burning eyes, headache, malaise, chilliness, and face or earache) and symptoms of possible drug side effects (nausea, stomach pain, indigestion, diarrhea, constipation, and tinnitus). These symptoms were scored on a daily basis by the volunteers as 0, 1, 2, or 3 for absent, mild, moderate, or severe symptoms, respectively. Scores for each cold symptom were totaled for each subject by adding scores from days 1–14 and subtracting the baseline score (day 0). The total scores for each cold symptom were then summed to give an overall cold

symptom score; in a similar fashion, drug side-effect symptom scores were summed to give an overall side-effect score (see table 1).

An illness was defined if two of the three following criteria were met: a total symptom score of ≥6 above the baseline level (day 0); increased nasal discharge for ≥3 consecutive days; and the subjective impression of the volunteer after the first 6 days after challenge that he or she had a common cold similar to previous naturally acquired illnesses. Volunteers were considered infected if they experienced a fourfold or greater rise in their serum antibody titer (for RV2) above the screening antibody titer or if the challenge virus was recovered from one or more postchallenge nasal wash specimens.

Immediately after use of paper tissues, volunteers sealed them in plastic bags to reduce evaporation loss. Nasal secretion weights were measured daily by weighing the tissues and subtracting the weight of the same number of unused tissues and the plastic bag. Summary or total mucus weight and paper tissue usage measures were calculated by adding the daily mucus weights and number of tissues used during days 1–9.

Statistical analyses. All analyses were conducted on an "intention to treat" basis, such that treatment dropouts were included in their originally assigned treatment group [21]. Comparisons of RV2 titers between treatment groups on each day were carried out using the Kruskal-Wallis nonparametric analysis of variance (ANOVA). Dichotomized variables were analyzed with χ^2 tests (with Yates's correction where indicated). Ordinal and continuous variables were compared between treatment groups with t tests, parametric one-way ANOVA, and analysis of covariance (ANCOVA), using the MGLH module in SYSTAT (Macintosh version 3.2; SYSTAT, Evanston, IL). Between-group differences in the change in monocyte counts from baseline were analyzed 5, 10, 14, and 28 days after challenge. At each of these time points, the ANCOVA model included a main effect for treatment group and the baseline monocyte level as a covariate. One-way ANOVA was used to test the differences in geometric mean antibody levels (to RV2) between treatment groups on days 7, 14, and 28. To increase the power of these analyses, the effects of the three active treatment drugs (aspirin, acetaminophen, and ibuprofen) on antibody level were combined and simultaneously contrasted with results from the placebo group, using the MGLH procedure in SYSTAT.

Results

The 60 study participants were a mean age of 20.1 years; 34 were male and all were nonsmokers.

There were 56 volunteers (93.3%) who shed RV2 from the nose for at least 4 days after challenge. The 4 who did not shed virus also did not experience a significant rise in antibody titer, so they were considered uninfected and were excluded from further analyses. There was 1 nonshedder in the acetaminophen group, 2 in the ibuprofen group, and 1 in the placebo group. Forty-eight volunteers seroconverted after challenge (fourfold or greater rise in serum neutralizing antibody to RV2).

By our study criteria, 42 (75%) of the 56 infected volunteers experienced an episode of upper respiratory illness. The infected subjects experienced a mean total symptom score of 23.9 ± 17.3 SD. Nasal obstruction, nasal discharge, sneezing, sore throat, and cough were the predominant symptoms. Total mucus weights ranged from 0 to 32.5 g (mean, 10.7 ± 12.1 SD) during the 10-day isolation phase of the study. Mucus secretion and tissue use peaked on day 2. The most prevalent clinical signs were nasal mucosal inflammation and discharge, followed by pharyngitis, crusting, turbinate swelling, and nasal obstruction. Significant pyrexia was uncommon; only 5 subjects experienced a rise in oral temperature >37.4°C (2 taking placebo, 1 each taking ibuprofen, aspirin, and acetaminophen).

Table 1. Characteristics of volunteers in each of the four treatment arms.

	Aspirin	Acetaminophen	Ibuprofen	Placebo	*P*
No.	15	15	15	15	
No. of noncompleters	5	0	0	0	
No. shedding virus	15	14	13	14	.54
No. of males	9	6	12	7	.13
Mean age, years	19.9	19.5	21.1	19.9	.25
Baseline antibody titer					
≤2	4	4	4	4	
3–4	7	7	7	7	
6–8	4	4	4	4	
No. of illnesses	12	9	10	11	.76
Mean mucus weight, g	8.0	10.4	12.4	12.1	.76
Mean tissue count	15.8	22.1	25.2	24.7	.63
Mean overall symptom score	19.1	27.7	24.5	24.8	.61
Mean overall ENT score	19.3	19.4	20.8	20.6	.97
Mean overall side-effect score	4.3	1.2	1.0	0.6	.02

The characteristics of the volunteers in each medication group are shown in table 1. There were no significant differences among medication groups in terms of demographic characteristics, the number of volunteers successfully infected, or baseline rhinovirus antibody levels. Mean overall symptom score, overall ENT score, mucus weights, and number of tissues used did not differ significantly among groups, nor did the number of illnesses experienced. However, the aspirin group experienced more side effects than the other groups. Five in the aspirin group did not complete the full course of medication, because of tinnitus in all 5 cases and gastrointestinal symptoms in 1 of those; they stopped on days 3 and 4. Despite stopping medication, these volunteers continued to participate and completed all other aspects of the study.

Antibody responses, viral shedding, and individual symptoms and signs. On both days 14 and 28, a lower proportion of volunteers taking the three active preparations seroconverted than in the group taking placebo. When we dichotomized antibody responses into high (a greater than fourfold rise in antibody titer) and low groups (a fourfold rise in titer or less), this effect persisted at day 14 and was accentuated on day 28 (table 2). On day 14, 9 of 15 taking aspirin, 7 of 14 taking

Table 2. Comparison of antibody levels, nasal obstruction scores, nasal turbinate swelling, cervical lymphadenitis, and virus shedding duration by type of medication.

	Aspirin (n = 15)	Acetaminophen (n = 14)	Ibuprofen (n = 13)	Placebo (n = 14)	Overall χ^2 (3 df)	Overall P
Antibody rise						
Fourfold or less, day 14	9*	7	6	2	7.5	.06
Fourfold or less, day 28	5	6*	3	0	10.7	.01
Nasal obstruction score >5	6*	3	2	0	9.6	.02
Nasal turbinate swelling score >0	5	5*	3	0	9.3	.03
Cervical adenitis score >0	0	1	1	4	7.1	.07
Virus shedding duration >8 days	7	7	4	3	3.4	.34

* Significantly different from placebo, $P < .05$ (1 df).

Table 3. Geometric mean antibody titers (95% confidence intervals) before challenge and on days 7, 14, and 28 after challenge by type of medication.

	Aspirin	Acetaminophen	Ibuprofen	Placebo
Before challenge	3.4 (2.7–4.2)	3.3 (2.6–4.2)	3.8 (2.9–4.9)	3.5 (2.8–4.5)
Day 7	2.5 (2.1–3.0)	2.5 (2.0–3.2)	3.2 (2.1–4.7)	3.6 (2.3–5.6)
Day 14	13.1 (6.7–25.6)	13.3 (5.2–34.3)	19.1 (8.6–42.5)	31.2 (17.6–55.5)
Day 28	24.4 (20.7–45.0)	18.9 (11.3–31.5)	34.4 (17.9–65.9)	52.3 (33.7–81.1)

acetaminophen, and 6 of 13 taking ibuprofen were in the low group compared with only 2 of 14 taking placebo. On day 28, significantly more of those taking acetaminophen were in the low group than those taking placebo ($\chi^2 = 5.3$, $P < .05$, 1 df). Significantly more of those taking aspirin had low antibody levels on day 14 ($\chi^2 = 4.6$, $P < .05$, 1 df) than those taking placebo, and a similar nonsignificant trend was seen on day 28 ($\chi^2 = 3.5$, $P = .06$, 1 df). The differences in proportions experiencing high and low rises in antibody to RV2 in the ibuprofen and placebo groups did not approach statistical significance at day 14 or 28.

In addition to the overall symptom scores and overall ENT examination scores presented in table 1, the individual symptom and ENT scores for the four treatment groups were compared (table 2). Headache, malaise (tiredness), and face or earache were infrequent, and no significant differences were seen among treatment groups. The only significant differences were observed in nasal obstruction and nasal turbinate swelling scores (ENT examination), while a nonsignificant trend was observed for adenitis (table 2). Those reporting total nasal obstruction scores >5 were all taking active drugs, but only the aspirin group differed significantly from the placebo group ($\chi^2 = 4.8$, $P < .05$, 1 df). Participants who had significant turbinate swelling were also all in active drug groups, with the difference between acetaminophen recipients and placebo recipients reaching significance ($\chi^2 = 3.9$, $P < .05$, 1 df). These results were not anticipated and have not been previously reported, to our knowledge. The trend toward suppression of cervical adenitis in the active drug groups was also worth noting in light of the antibody findings. All six volunteers who experienced cervical lymphadenitis had a greater than fourfold rise in antibody titer on days 14 ($P = .07$) and 28 ($P = 0.32$).

Virus shedding peaked 2 days after challenge (median RV2 titer = $10^{3.4}$ $TCID_{50}$). The median titer fell steadily over subsequent days to 0 on day 10; by day 14 only two volunteers were still shedding virus. There were no significant differences in median titers among the four groups on any post-treatment day. These results did not alter when aspirin noncompleters were excluded nor when daily virus shedding titers were grouped and examined by medication type. A greater proportion of volunteers taking aspirin and acetaminophen shed virus on >8 days than those taking placebo (see table 2), but none of the differences among the four treatment groups was significant ($\chi^2 = 3.36$, $P = .336$). Volunteers who shed virus on >8 days were more likely to have a low antibody rise (fourfold or less) than those shedding for ≤8 days ($\chi^2 = 4.29$, $P = .038$). Thus, extended virus shedding coincided with a poor immune response in a significant proportion of cases.

Table 3 presents the geometric mean antibody titers in the four treatment groups. As seen in the categorical data (table 2), a trend toward suppression of antibody response is seen in the three active treatment groups (particularly aspirin and acetaminophen), but the 95% confidence intervals are wide and overlap those of the placebo group. To improve the power of this analysis, results from the three active treatment groups were combined and compared with those of the placebo group. Although the mechanisms of action of the drugs on antibody response differed, the results were similar, although aspirin and acetaminophen suppressed antibody response more strongly than did ibuprofen. Using the MGLH ANOVA pro-

cedure in SYSTAT, the three active-drug groups were simultaneously contrasted with the placebo group. The differences in the resulting two groups reached significance on day 28 ($F = 4.97$; $P = .03$).

Monocyte count and other laboratory investigations. There were no significant differences between type of medication taken and change in total white blood cell, granulocyte, or lymphocyte count on days 5, 10, 14, or 28. However, volunteers taking aspirin, ibuprofen, and acetaminophen all experienced a rise in monocyte count by day 28 (figure 1). Similar effects were seen on days 10 and 14, but the rises were limited to ibuprofen recipients and to a lesser extent aspirin recipients. The difference between the ibuprofen and placebo groups reached statistical significance on day 14, but the other trends did not reach significance at the .05 level.

When results from all medication groups were pooled, the mean rises in monocyte counts on day 28 were significantly lower in those volunteers who experienced a greater than fourfold rise in antibody titer (15.6 vs. 159.6; $t = 2.10$; $P = .04$), while volunteers who experienced cervical lymphadenitis experienced a significant fall in monocyte count compared with the others (−124.0 vs. +72.7; $t = 2.04$; $P = .04$).

The other hematologic and serum biochemistry parameters did not change appreciably during the study, nor did they differ significantly between medication groups. Drug compliance tests on day 5 were positive in all active-drug group participants.

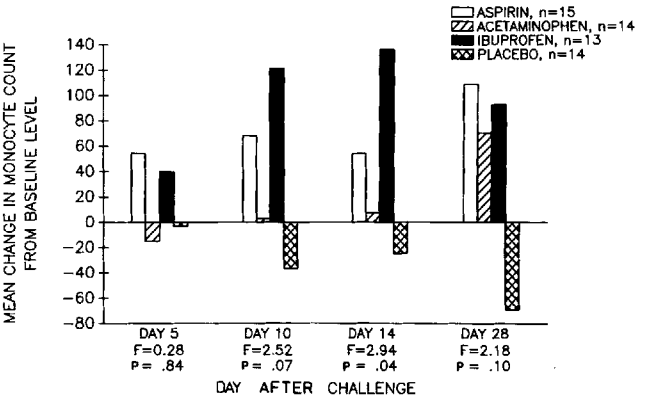

Figure 1. Change in monocyte count by type of medication taken, controlling for baseline monocyte count, on postchallenge days 5, 10, 14, and 28.

Discussion

The specific antibody response to challenge by many respiratory viruses occurs late and exerts relatively little influence on the control of acute infections [22–24]. Protection from specific antibody is therefore conferred only against subsequent challenge with the same virus serotype. In the control of acute, established viral infections, the role of nonspecific proteins, such as interferon, are much more important [24]. In our present study, aspirin and acetaminophen were significantly associated with suppression of the serum neutralizing antibody response to the study challenge virus, RV2. The effect of ibuprofen on antibody level was weaker and did not differ significantly from that of placebo.

In healthy adults, the clinical consequences of the level of immunosuppression observed in this study may not be worrisome, particularly if other components of the immune response to rhinovirus infection (e.g., interferon antiviral activity) remain unimpaired. However, in groups relatively immunosuppressed or at increased risk for acute respiratory infections, the effects of these drugs are potentially more problematic. For example, children, particularly those in developing countries, are more susceptible to acute respiratory infections than were the adults in this study. If widely used over-the-counter medications significantly suppress immune function, there may be a real risk of increasing the severity of infection. A recent study showing that acetaminophen lengthened the duration of varicella infections in children lends empirical support to this hypothesis [19]. If specific antibody production is suppressed, this might attenuate the humoral response to subsequent rechallenge with the same agent. However, this remains speculative, and further research is needed to determine if other parts of the immune response to respiratory viruses are affected by over-the-counter antipyretics/analgesics and whether children, the immunosuppressed, or other at-risk groups would be adversely affected in a clinically significant manner.

In addition to a previous reported association between acetaminophen and clinical severity of varicella infection in children [19], there was evidence in our study that aspirin and acetaminophen might adversely influence clinical status. These two drugs were associated with increased turbinate edema and nasal obstruction in comparison with placebo. This level of increased clinical severity in a URI would present few problems for most healthy adults and could be quickly reversed with pseudoephedrine. However, nasal obstruction might be more important in infants, where sucking and breastfeeding could be impaired. In developing countries in particular, impairment of sucking or feeding in infants can have serious consequences. Nonetheless, given that Stanley et al. [1] did not report similar findings, these results should be treated with some caution until further data are available to confirm or refute them.

Aspirin, acetaminophen, and ibuprofen did not significantly increase virus shedding in comparison with placebo, but as shown in table 2, duration of shedding in the aspirin and acetaminophen groups tended to be slightly longer ($P = .34$). Duration of shedding was also associated with an attenuated antibody response ($P = .038$). Nevertheless, these findings do not support a strong effect of aspirin on virus shedding as reported elsewhere [1]. A weaker effect, if present, would require a substantially larger study than this to detect it.

The rise in the number of circulating monocytes in the three

active treatment groups contrasted with a fall in the placebo group. Although only the comparison between ibuprofen and placebo on day 14 reached statistical significance, the higher levels of circulating monocytes were significantly related to suppressed antibody response and the absence of cervical adenitis. These data suggest that the effects of the over-the-counter drugs on immune function might be mediated by an effect on peripheral monocytes. This might occur by preventing migration of circulating mononuclear leukocytes to infected tissues and therefore limiting their differentiation to mononuclear phagocytes. Mononuclear phagocytes (e.g., macrophages) appear to play a role in initiating the immune response to some respiratory viruses and may help restrict viral replication [25–27]. Macrophages help initiate antibody production by processing and presenting viral antigens, complexed with class II major histocompatibility complex antigens, to T helper lymphocytes, which in turn (via lymphokine and direct contact pathways) stimulate B lymphocyte differentiation and specific antibody production [28, 29].

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