CORRESPONDENCE

Beneficial Effect of Nonsteroidal Anti-inflammatory Drugs and Cyclooxygenase-2 Inhibitors in Patients with Asthma during Viral Infection

To the Editor—I read with interest the report by Seymour et al. [1] regarding the induction of 5-lipoxygenase and cyclooxygenase-2 (COX-2) in the bronchial airway during experimental rhinovirus infection in nonatopic subjects and their suggestion that leukotriene-modifying agents or COX-2 inhibitors may benefit the prevention of viral induced wheezing in patients with asthma.

Several years ago, I proposed that the increased prevalence of childhood asthma was related to the decreased use of aspirin in children because of the threat of Reye syndrome [2] and suggested that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit COX-2 could prevent virus-induced asthma attacks if taken at the onset of symptoms of a viral respiratory tract infection [3]. Patients with asthma have been told to avoid the use of aspirin and NSAIDs because of concern over hypersensitivity reactions to these agents. However, recent data suggest that the use of acetaminophen, the preferred analgesic and antipyretic agent, may be associated with an increased incidence and severity of asthma symptoms [4]. Indeed, Lesko et al. [5] recently reported that the use of ibuprofen, as opposed to acetaminophen, reduced by half the risk of asthma attacks in a double-blinded study of >1800 children with asthma and febrile respiratory tract infection.

Therefore, in my practice, I have encouraged the use of ibuprofen for children (because aspirin and NSAID sensitivity is rare) and selective COX-2 inhibitors for adults (which appear to be safe even in patients with documented aspirin sensitivity [6, 7]) at the onset of symptoms of a respiratory viral infection. Although it seems that this treatment has been successful, this remains anecdotal in nature.

Therefore, I recently performed a survey of 121 pediatric and adult patients with mild-intermittent to severe-persistent atopic asthma in my practice to ascertain retrospectively whether the treatment was truly of benefit. Viral respiratory tract infections increased asthma symptoms in 76% of the patients, and 54% of patients required systemic corticosteroids for virus-induced asthma exacerbations. NSAIDs or COX-2 inhibitors had been used by 44% of the patients to prevent virus-induced asthma exacerbations. In these patients, 83% thought NSAID or COX-2 inhibitor treatment was beneficial, and 85% said they planned to take the medication in the future to prevent virus-induced asthma attacks. More important, 77% of the patients who had required systemic corticosteroids for virus-induced asthma exacerbations found the treatment to be helpful, confirming my impression that the need for steroids had decreased in these patients.

These data, along with the report by Lesko et al. [5], suggest that patients with asthma prone to attacks with respiratory tract viral infections may experience benefit with use of NSAIDs and COX-2 inhibitors at the onset of symptoms of a respiratory tract viral infection. Asthma exacerbations due to viral infection continue to be the Achilles’ heel of present asthma therapy, and, hopefully, this report will encourage further study of these medications in viral-induced asthma, as Seymour et al. [1] suggest.

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References

Reply

We thank Dr. Varner for his interest in our work and for his comments [1] and are aware of Dr. Varner’s hypothesis and find it interesting. We strongly agree with him that further study of the role of leukotriene-modifying agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors in the treatment of virus-induced asthma exacerbations is warranted.

With regard to the data Dr. Varner quoted to support his hypothesis, the study by Lesko et al. [2] is interesting in that the relative risk of needing an outpatient visit for asthma in the group treated with ibuprofen was 56% of that in the group treated with acetaminophen. However, because there was no placebo control, whether the observed difference in morbidity according to treatment group was attributable to increased risk after acetaminophen use or to a decrease after ibuprofen use could not reliably be determined. The authors observed that the reduction in risk with use of ibuprofen was greatest among children who were treated for respiratory infections but not other infections (otitis...
and pharyngitis), which was compatible with a protective effect of ibuprofen. Furthermore, it was considered that the results were unlikely to be attributable simply to an anti-inflammatory effect of ibuprofen, because no dose-response relationship was observed. The alternative possibility that these results could actually reflect an increased risk among children who are treated with acetaminophen is supported by the observation that risk was increased only among children who received the highest dose of acetaminophen. However, these interpretations must be treated with great caution, because the data were derived from parental reports and, therefore, no objective measures were ascertained to support the conclusion and there was no reduction in hospitalizations for asthma.

Several studies have reported symptomatic benefit among nonasthmatic adults with experimental or naturally occurring common colds after treatment with NSAIDs used either alone or in combination with other agents [3–6]. However, a further study reported adverse outcomes in similar patients treated with aspirin, ibuprofen, or acetaminophen [7]. There are no published studies on the treatment of common colds with COX-2 inhibitors in healthy subjects, although our recent study suggests that they may have some benefit [8].

To date, there are no published studies of the effects of any of these drugs (acetaminophen, NSAIDs, or COX-2 inhibitors) on proven virus-induced asthma exacerbations. As Dr. Varner correctly states [1], virus induced asthma is a major problem for both adults and children. In view of the possibility that acetaminophen may have deleterious effects among patients with asthma [9], properly controlled studies of this drug in virus-induced asthma are urgently required. Although the rationale for their use in the treatment of asthma is obvious, clinical experience with COX-2 inhibitors is limited. Initial studies have shown them to be safe in aspirin-sensitive patients with asthma [10], but properly controlled prospective clinical studies are required before recommendations for their use in virus-induced asthma can be made.

In addition to our recent study [8], clinical data suggest that leukotrienes are produced in increased quantities in virus-induced wheezing [11]. These studies combined provide support for clinical studies with antileukotriene compounds in virus-induced asthma in both adults and children.

We are cautious in interpreting Dr. Varner’s retrospective survey data with regard to NSAIDs and COX-2 inhibitors [1], because such data are notoriously prone to bias, and no virologic testing appears to have been undertaken. We therefore strongly support his call for further studies of these medications in virus-induced asthma. Such studies should include placebo control and acetaminophen, as well as the study drug, so that antipyretic and analgesic effects can be separated from other properties possessed by NSAIDs or COX-2 inhibitors and so that any possible detrimental effect of acetaminophen can be observed in relationship to placebo.

References


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Preemptive Therapy for Cytomegalovirus Infections and the Development of Resistance to Ganciclovir

To the Editor—The recently published article by Limaye et al. [1] carried a rather alarming conclusion in its title, stating that the widely used approach of preemptive treatment of cytomegalovirus (CMV) in transplant recipients led to a "high in-
cidence” of ganciclovir-resistant viruses. As such, the finding is surprising, considering the evidence obtained with the use of the preemptive treatment strategy, as opposed to the alternative approach of prophylactic or suppressive drug administration. Prophylactic strategies, which usually use lower drug levels for longer periods, have been found to carry a risk of the development of resistance in CMV; this is well known in patients with AIDS but also clearly demonstrated in transplant recipients by Limaye et al. [2]. Now they present evidence that resistance may also develop after preemptive treatment, but a point of major concern is the way treatment regimens are labeled as either “prophylactic” or “preemptive.”

For this reason, we were surprised by the description of the treatment used in this recent study. Although it was fairly complex and differentiated according to several patient variables, we found that if patients who were CMV-positive before transplantation had to be treated, they received 5 mg/kg of ganciclovir once daily for at least 4 weeks. The patients with primary infection received treatment with 5 mg/kg twice daily for 5–7 days followed by 5 mg/kg daily for at least 4 weeks, sometimes even longer. Part of this seronegative population also received routine intravenous prophylaxis for 100 days, and, according to Limaye et al. [1], “some” patients also received oral ganciclovir as secondary prophylaxis.

Clearly, none of these approaches appears to be compatible with what is intended by the term preemptive therapeutic strategy. The principle of that approach is to provide effectively dosed therapy, guided by the early and sensitive detection of an infection, independent of clinical signs, and to withhold any therapeutic intervention if the specified indications are not present. The therapeutic dosage of ganciclovir is 5 mg/kg twice daily for 14–21 days, according to all existing guidelines and literature [3]. Therefore, the strategy described in the recent article [1] is strikingly different from what is commonly regarded as genuine preemptive therapy. This refers to the dosage regimen (1 category is only treated with one-half of the therapeutic dose, and the other category is treated with the therapeutic dose for 5–7 days instead of for 14–21 days), as well as to the total duration of treatment (the lower, prophylactic dose was administered for at least 4 weeks in both categories and, in some instances, up to 100 days intravenously or orally for undefined periods).

Therefore, one could argue that the regimen, as it was predominantly applied, was suppressive in nature rather than therapeutic and that, in this way, the results are not applicable to what is more commonly understood to be preemptive treatment. Lower dosing for longer periods may well be suboptimally effective in suppressing viral replication and, in addition to facilitating recurrence of infection, may also lead to viral adaptation and thus resistance. We did not find such considerations of the influence of drug dosing in the discussion [1]. In our opinion, more-definitive conclusions on the relative risks of treatment strategies with regard to drug resistance in CMV should be based on studies using strategies that are more truly preemptive in nature.

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Reply

To the Editor—We appreciate the comments of Kroes and Kalpoe [1] regarding our recent publication on preemptive therapy in lung transplant recipients [2]. We retrospectively analyzed the incidence of cytomegalovirus (CMV) disease and ganciclovir resistance in a cohort of lung transplant recipients receiving preemptive therapy—a group of patients known to be at high risk for both CMV disease and resistant CMV. Because this was neither a prospective nor a controlled study, we were only able to analyze the incidence of CMV disease and resistance according to the antiviral strategy used. We made 3 observations: first, we confirmed that ganciclovir resistance is more common in CMV-seronegative recipients of organs from CMV-seropositive donors (D+/R−) transplant recipients; second, we found that preemptive therapy in D+/R− recipients did not appear to be protective against the emergence of resistance; and third, we found a high incidence of CMV disease in association with the preemptive strategy used to treat CMV-seropositive lung transplant patients (R+) patients [2].

There is no consensus on how preemptive therapy should be administered. Rather, there are a number of published regimens [2–7], and the field is evolving on the basis of the results of clinical studies and new insights into the in vivo dynamics of viral replication of CMV [8]. In general, preemptive therapy is started with an induction course of ganciclovir (e.g., 5 mg/kg twice daily) given for 1–3 weeks, followed by maintenance dosing (5 mg/kg daily) given either for a fixed duration or until cessation of viral replication [2–7]. Recently, regimens using oral ganciclovir have also been proposed [9]. The rationale for our analysis was that preemptive therapy has been proposed to be
less likely to lead to antiviral resistance, on the basis of theoretical grounds, but there are few data on the incidence of resistance among patients receiving preemptive therapy.

The preemptive ganciclovir regimen used in R+ patients in our study did not include an induction course (5 mg/kg given for 4 weeks for pp65 antigenemia of ≥10 cells/slide). Interestingly, despite this low-intensity dosing, only 1 (6.7%) of 15 patients who were treated preemptively progressed to CMV disease while receiving preemptive therapy, and overall development of resistance was minimal (1 [2.9%] of 34 of all patients and 1 [6.7%] of 15 of those treated preemptively developed resistance). The one case of resistance presented had persistent viremia that required pro-

of those treated preemptively developed resistance). The one case was minimal (1 [2.9%] of 34 of all patients and 1 [6.7%] of 15 receiving preemptive therapy, and overall development of resistance were treated preemptively progressed to CMV disease while re-

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3 D+/R− patients, 8 of whom received 100 days of prophylactic intravenous ganciclovir at a dose of 5 mg/kg once daily, as described elsewhere [2], and 3 of whom received pp65 antigenemia-guided preemptive therapy (≥1 cells/slide) using ganciclovir at a dosage of 5 mg/kg twice daily for 5–7 days followed by 5 mg/kg once daily for 4 weeks. Only the 3 D+/R− patients who received preemptive therapy were included in the comparison of ganciclovir resistance with the R+ patients. Both D+/R− patients who developed ganciclovir resistance cleared antigenemia with their first course of ganciclovir (which was given for 8 weeks in patient number 3 [table 2 in (2)] and for 4 weeks in patient number 4) but then relapsed into ganciclovir-resistant CMV syndrome. Thus, antigenemia was not present at the end of the prescribed course in both patients.

In summary, the preemptive therapeutic regimen used in this study resulted in clearance of antigenemia; however, this did not prevent the emergence of resistance. Thus, although the numbers are small, the use of preemptive therapy per se may not prevent resistance. Because prolonged viral replication in the presence of antiviral drugs is believed to be the underlying condition that is required for the development of resistance, we speculated in our article that more aggressive antiviral therapy (i.e., longer induction dosing administered at lower thresholds), combined with highly sensitive monitoring, might be necessary to more effectively control CMV and the development of resistance in the setting of lung transplantation. Whether this will reduce the incidence of resistance should be evaluated in prospective trials.

Ajit P. Limaye and Michael Boeckh

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lavage (VL) human immunodeficiency virus (HIV) RNA level that was missed by use of the Wilcoxon rank sum test [1]. A more appropriate nonparametric statistical test, the Friedman $Q$ test, showed that the HIV RNA level in VL at day 7 was significantly higher more often than levels on days 14 and 21 and that levels on days 14 and 21 were highest equally often ($P = .01$). A repeated-measures regression model showed that the within-subject VL SD was 0.55 log$_{10}$ HIV RNA copies/mL and that the day 7 VL level was 0.35 log$_{10}$ HIV RNA copies/mL higher than the day 21 level and that the day 14 level was 0.02 log$_{10}$ copies/mL higher than the level at day 21 ($P = .04$) [2]. We also showed a menstrual effect on genital tract HIV RNA levels [2], but our data differ from those of Villanueva et al. in several important respects.

First, in the Villanueva study [1], only 78% of the women achieved a maximum progesterone level >3.0 ng/mL during 1 menstrual cycle (their table 2), which is suggestive of ovulation, whereas, in our study, 96% of the women had a maximum progesterone level >3.0 ng/mL over the course of 2 menstrual cycles. Consequently, some of the Villanueva study subjects may have had anovulatory menstrual cycles. Anovulation will affect the assignment of specimens to the correct menstrual phase [3].

Second, in collecting vaginal specimens for HIV RNA, Villanueva et al. [1] lavaged the posterior vagina and specifically avoided lavage of the cervix, a major source of virus [4]. In contrast, we used cervicovaginal lavage (CVL) but did not find a significant difference in mean HIV RNA levels for the 3 weeks after menses, although the trend was opposite to that reported by Villanueva et al. (i.e., the follicular, early luteal, and late luteal phase mean HIV-1 RNA levels were 0.95, 1.08, and 1.32 log$_{10}$ HIV RNA copies/mL of CVL, respectively; $P = .14$).

The measurement of small HIV RNA changes in either VL or CVL is imprecise because of the high within-subject variability in HIV RNA levels. For the Villanueva data, we calculated the 95% confidence interval for the upper limit of expected VL variation to be 33-fold, which is similar to, although smaller than the 200-fold variation for the expected difference between 2 CVL samples collected 1 week apart [5]. Because vaginal-associated HIV likely arises from both the blood compartment and locally from the mucosal-associated lymphoid tissue in the cervix [6], we sampled endocervical canal fluid with the more precise Sno-strip (Chauvin Pharmaceuticals) wick and cells with the cytobrush [2].

We found that endocervical cell-free and cell-associated HIV RNA levels had follicular phase nadirs after menses, increased significantly throughout the luteal phase, and peaked at menses. Moreover, the mean wick HIV RNA levels were not only greater than CVL or cytobrush levels but were significantly greater than the HIV RNA levels in blood plasma. The wick HIV RNA level peaked during the week before menses ($P = .03$), whereas the cytobrush HIV RNA levels showed a weaker menstrual effect ($P = .04$) [2]. These findings have a biologic basis, because vaginal but not blood plasma proinflammatory cytokines are also up-regulated at the time of menses [7]. This difference between the wick and cytobrush HIV RNA levels reflects not only technical differences in sample collection but also the compartment from which HIV RNA was sampled.

Villanueva et al. [1] discuss that HIV RNA levels may be higher in menses but did not present data to support this conclusion, since sampling at menses was not done. Although they discuss the potential effect of blood contamination in VL samples (a specific concern during menses), earlier work suggests that the contribution of blood contamination is minimal [6, 8, 9]. We found that blood-contaminated wick samples taken during menses had HIV RNA levels a mean of 0.24 log$_{10}$ copies/mL lower than levels in blood-free wick samples obtained prior to menses. Thus, evaluations of the effect of the menstrual cycle on HIV-1 parameters should not ignore sampling during menses.

Clearly, the complex biological interactions among the microbiological, hormonal, and immunological components of the female genital tract throughout the menstrual cycle will influence the level of HIV shedding and thus the potential for sexual transmission. Definitive statements about the absence of a menstrual-associated effect on genital HIV require revision. The use of sensitive and precise genital subcompartment-directed sampling techniques, along with repeated-measures analysis, demonstrates the effect of the menstrual cycle on HIV-1 RNA levels in the female genital tract.

**References**

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Reply

To the Editor—Reichelderfer et al. [1] propose that a reanalysis of our data by use of the Friedman test reveals a menstrual cycle effect on human immunodeficiency virus (HIV) type 1 RNA levels in vaginal lavage. However, as we stated in our report [2], we considered changes of <0.5 log_{10} in vaginal virus load to be within the bounds of interassay variability and therefore equivalent. When this criterion is incorporated into the Friedman test, the lack of a menstrual cycle effect on vaginal virus loads is reaffirmed (P = .08). They also propose that a repeated-measures regression model showed a higher vaginal virus load at day 7 of the menstrual cycle. By using the model supplied by Reichelderfer et al., no significant menstrual effect was found if samples with a virus load result below the level of quantification in our assay are assigned any value >0.

Reichelderfer et al. [1] also propose that samples from many women in our cohort, as opposed to theirs, were collected during an anovulatory cycle. However, it is well accepted that weekly measurements of plasma progesterone cannot accurately predict the absence of ovulation [3]. Nonetheless, by use of the Friedman test, we have confirmed that there was no menstrual cycle–associated change in vaginal virus loads in the subgroup of women who had a peak plasma progesterone level >3 ng/mL (P = .1).

There are other important differences between our 2 cohorts that deserve similar emphasis. Samples from participants in the study by Reichelderfer et al. [1], unlike those in our study, were more likely to have been collected from a woman receiving antiretroviral therapy (83% vs. 20%, respectively) with a vaginal virus load that was undetectable (66% vs. 27%, respectively) [4]. In addition, in our study, samples were not collected during menses, since we anticipated a significant effect of menstrual blood on vaginal virus loads. This decision was validated by Reichelderfer et al., who found that cervicovaginal virus loads were increased ∼10-fold during menses.

Reichelderfer et al. [1] acknowledge that their study detected no significant changes in cervicovaginal virus loads during the 3 weeks following menses. This result supports our conclusion regarding vaginal virus loads. Their letter then reviews their data regarding changes in cervical virus load. Our study did not address cervical virus loads. However, we believe that certain statements by Reichelderfer et al. deserve comment.

First, our primary interest is in heterosexual transmission of HIV. Changes in cervical virus load are unlikely to influence transmission rates if similar changes are not produced in vaginal virus levels. Second, although the cervix is a source of HIV-1 replication, there is no conclusive evidence that it is the predominant source of virus in the female genital tract. We and other researchers have found no differences in HIV vaginal loads between women with and without hysterectomies [5, 6]. Moreover, we have also shown that the cervix is not the major source of HIV-1 in vaginal secretions in most women [5] and that there is a strong correlation between virus load and the level of HIV-1 cellular replication in vaginal secretions [7]. These results clearly show that vaginal HIV-1 levels are not largely dependent on cervical shedding of the virus.

Finally, Reichelderfer et al. [1] chose not to comment on our important finding of no discernible pattern of change in vaginal virus loads from women sampled throughout 2 menstrual cycles. If the menstrual cycle affects genital tract virus loads, as proposed by Reichelderfer et al., then the effect should produce a consistent pattern of change. Since Reichelderfer et al. also collected samples throughout 2 cycles, we encourage them to determine whether cervical virus loads show a reproducible pattern of change from cycle to cycle.

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