

Correspondence

Evaluation of the Efficacy of Intranasal Zinc Gluconate

SIR—I am writing to express my concerns regarding a major article entitled “Ineffectiveness of Intranasal Zinc Gluconate for Prevention of Experimental Rhinovirus Colds” [1], which was electronically published by *Clinical Infectious Diseases* on 25 October 2001. Although Dr. Turner’s study [1] provides a preliminary evaluation of workable research paradigms to assess the efficacy of intranasal zinc gluconate (Zicam; Gumm Tech) in the prevention of experimentally induced rhinovirus colds, I believe that the research findings are inconclusive for 3 key reasons.

First, Dr. Turner stated in his article that “there was no significant effect of intranasal zinc treatment on rhinovirus-induced illness” [1, p. 1868], and he reported that the mean total symptom score (\pm SE) for volunteers infected with rhinovirus type 39 (RV39) was 19.8 ± 3.8 for the group given placebo and 15.6 ± 2.2 for the group given active treatment ($P = .85$). A simple power calculation shows that the sample size in this study was too small for any conclusion to be drawn (power, 17%). In fact, given the analysis used, a minimum of 148 subjects would need to be included in each group before statistically valid conclusions could be drawn. Furthermore, if both the standard deviation mentioned in the study and an appropriate sample size would have been used, it is likely that a significant effect on total symptom score would have been noted for the group given intranasal zinc gluconate ($P = .05$).

Second, the study results were generalized to reflect a single virus-infected group rather than to note the different

rates of infection associated with the 2 different viruses evaluated. If the virus-infected groups had been stratified according to whether participants had been inoculated with rhinovirus type 23 (RV23) or RV39, then the sample size would have been even smaller and variability would have increased, thereby throwing off the results even further.

Third, Dr. Turner’s study [1] was not adequately blinded. Six participants (12%) in the placebo group and 18 participants (44%) in the group with experimentally induced rhinovirus colds reported that they could taste the study medication and therefore were likely to be aware that they had received medication.

Finally, although my concerns are focused on the statistical analysis used in the study, I am also concerned because, even though Dr. Turner does, in fact, suggest that some antiviral activity was noted during the study, he does not offer any explanation of or further elaboration on this point in his Discussion section. This omission may have been a result of the small sample sizes used in the study and Dr. Turner’s inability to draw any conclusions from the results. Furthermore, I believe that the study design also required the use of a real placebo, such as a saline nasal solution, rather than Zicam’s gel matrix without zinc, to create a research paradigm that would accurately provide an evaluation of the effectiveness of the Zicam product in the prevention of colds.

I wrote to Dr. Turner on 29 January 2001 to express my concerns, but I have received no response. On the basis of my analysis, I believe that the findings of Dr. Turner’s investigation [1] should be carefully evaluated and that the effectiveness of intranasal zinc gluconate in the prevention of rhinovirus infection merits fur-

ther evaluation with irrefutable scientific and research protocols.

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Reference

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Reply

SIR—Thank you for the opportunity to respond to Dr. Yiu’s comments [1] concerning my article on the ineffectiveness of intranasal zinc gluconate for the prevention of experimentally induced rhinovirus colds [2]. I am pleased that he finds the experimental rhinovirus challenge model to be an acceptable method for the evaluation of treatments for the common cold. This model has been used for the study of the pathogenesis and treatment of the common cold for >30 years. When treatments have been studied in both the model and the natural setting, the model has generally been a reliable predictor of treatment efficacy for naturally occurring colds.

The first concern raised by Dr. Yiu relates to the experimental power of the study. As noted in the first paragraph of the Discussion section of the article [2], the experimental power of the study was 80% for detection of a 52% reduction in clinical colds. Treatment effects of at least

this magnitude have been consistently observed when agents with well-documented antiviral activity are used as prophylaxis in the experimental challenge model reviewed in a series of studies mentioned elsewhere [3] and in a single study reported in a separate article [4]. In light of this experience, I believe it is unlikely that our study missed clinically important effects of intranasal zinc on rhinovirus colds.

Dr. Yiu also questions the decision to combine data from volunteers challenged with 2 different rhinovirus serotypes in the analysis. The 2 rhinovirus serotypes used in our study are representative of the major group of rhinoviruses that bind to cells via intercellular adhesion molecule 1 (ICAM-1). None of the variety of mechanisms that have been suggested as explanations for the potential effects of zinc on rhinovirus colds, with the exception of inhibition of ICAM binding, would be serotype specific. From a practical perspective, it is difficult to imagine that a treatment that is effective against only a fraction of rhinovirus serotypes would be clinically useful. For these reasons, an analysis that examines the effect of treatment on rhinovirus infection and illness, regardless of serotype, seems appropriate.

Adequate blinding has been particularly difficult to achieve in studies of zinc therapies. In this study, we evaluated and reported (1) whether the volunteers could taste the study medication; (2) if the volunteers could taste the medication, their perception of the quality of taste; and (3) the volunteers' belief regarding whether they were receiving active medication or placebo. We also evaluated whether a difference in the rate of occurrence of side effects in the 2 treatment groups might have biased the study. Dr. Yiu correctly notes that the volunteers who received active medication were significantly more likely to report that they could taste the medication. No differences between the placebo and active treatment groups were found for any of the other measures of blinding in the study. It also seems likely that, had the study been inadequately

blinded, this would have favored the active treatment rather than placebo.

The observation of a significant reduction in the virus titers of the nasal lavage samples obtained from volunteers treated with zinc is discussed in some detail in the second paragraph of the Discussion section. Although this antiviral effect is of some modest interest from a biological perspective, the practical significance of an antiviral effect that is not associated with a reduction in either the infection rate or clinical illness is not clear.

Finally, I am not aware of having received previous communication from Dr. Yiu. The article was not publicly made available until it was electronically published in *Clinical Infectious Diseases* on 25 October 2001. Under the conditions of the study agreement, a draft of the article was provided to the sponsor of the study for comment before it was submitted to *Clinical Infectious Diseases*. The comments I received from the sponsor, some of which were similar to those of Dr. Yiu, were considered, and changes to the manuscript were made at my discretion. I was not asked to respond to the sponsor's comments, nor do I believe that a response was expected. I am sorry if Dr. Yiu misunderstood this arrangement.

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Thrombosis, Vasculitis, and Cytomegalovirus Infection

SIR—Ofotokun et al. [1] recently described a previously healthy adult who had cytomegalovirus (CMV) infection that was complicated by mesenteric arterial and venous thrombosis attributable to extensive vasculitis. In their report, the authors said that they considered a hypercoagulable state, but no cause was detected.

Ofotokun et al. [1] claimed that their case was the first reported case of thrombosis associated with CMV infection in an immunocompetent host who had no predisposing risk factors for thrombosis. In 1997, in this journal, we reported a case of mesenteric and right femoropopliteal venous thrombosis associated with CMV infection in an immunocompetent host [2]. We found a transient elevation of both the IgM and the IgG anticardiolipin antibody titers in our patient. After 6 months, the anticardiolipin antibody titers returned to normal levels, and treatment with anticoagulants was discontinued.

The patient described in the report by Ofotokun et al. [1] had extensive thrombosis, and the authors explained that this phenomenon was associated with vasculitis related to CMV infection. However, the histopathologic evidence of vasculitis that was provided in the report was not conclusive. Extensive thrombosis with no detected hypercoagulable state is not uncommon. In fact, when a thrombophilic state is suspected, the cause is found for only 30%–50% of cases [3, 4].

There is evidence that certain viral infections, including CMV infection, are associated with an increased risk of thrombosis. Among the hypothetical mechanisms that have been postulated as

the cause of this increased risk are the following: loss of anticoagulant factors, such as thrombomodulin, prostacyclin, and tissue plasminogen activator; increasing levels of procoagulation factors (such as factor VIII, the importance of which is now recognized); vasculopathy; endothelitis [5–8]; and anticardiolipin syndrome [2]. Of interest, immunization with CMV peptides induces pathogenic antiphospholipid antibodies in mice. These peptides share sequence similarity with the phospholipid-binding region of B2-glycoprotein 1, the most probable antigen against which antiphospholipid antibodies are directed [9].

Several clinical observations can be made about the case reported by Ofotokun et al. [1]. Venous thrombosis was diagnosed in the patient 6 weeks after the onset of CMV infection. At that time, the patient did not necessarily have active viral infection, and no data regarding either new evaluation of the hypercoagulable state or histologic evidence are provided. Common predisposing factors for thrombosis, such as prolonged rest and surgery, could have contributed to this case. Because an increase in factor VIII recently has been described in association with thrombosis in patients who have CMV infection, it would be convenient to attempt to detect an increase in the factor VIII level of the patient [7, 8]. In addition, it has been reported that antiphospholipid antibodies can be consumed during an acute episode of thrombosis and that the results of laboratory tests therefore can be normal if the tests are done at the same time that the thrombosis occurs [10].

We think that the patient described by Dr. Ofotokun and colleagues had an extensive and unusual thrombosis that was temporarily related to acute CMV infection. As usually occurs in many cases of hypercoagulable syndrome, a definitive cause of a hypercoagulable state was not found in this patient. There is insufficient evidence of a definitive association with vasculitis, although vasculitis is a valuable alternative mechanism. In patients who

have viral infections, such as CMV infection, it is important to look for different mechanisms of thrombosis (especially transient alterations) because anticoagulant therapy can be discontinued when they are present.

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Reply

SIR—We read with interest the letter of Labarca et al. [1] concerning our description of a patient who had acute cytomegalovirus (CMV) infection complicated by vascular thrombosis [2]. We regret not having cited the report previously published by this group [3], but we hasten to add that there were clear differences between the patient whom we described and the patient described by Labarca et al.

Although both patients had thrombosis that was temporally associated with CMV infection, our patient had no predisposing factors for thrombosis. In contrast, the patient described by Labarca et al. [1] had antiphospholipid antibody syndrome with anticardiolipin antibodies. Although the authors believe that the relatively transient nature of these antibodies suggests that they were associated only with the CMV-induced disease, transient anticardiolipin antibodies are also seen in patients with true autoimmune disease. The patient described by Labarca et al. also had a decrease in the protein S level. Thus, although we suspect that these 2 patients are part of the same clinical continuum, the patient whom we described was, to our knowledge, the first who was immunocompetent and had no predisposing risk factors for thrombosis. We see no basis for Dr. Labarca and colleagues' statement that prolonged bed rest and surgery might have led to the thrombosis seen in our patient, because our patient was a previously very healthy, active man who presented with acute thrombosis.

In addition, although factor VIII levels were not assessed, the normal activated partial thromboplastin time noted at the time that the patient was admitted to our hospital suggested the presence of factor VIII levels that were within the normal

range. After admission, it was no longer possible to interpret factor VIII levels, in view of the antithrombotic and heparin therapy that our patient received.

In their letter, Dr. Labarca and colleagues [1] further stated that we attributed the hypercoagulable state in our patient to vasculitis. Indeed, both the initial arteriogram that demonstrated irregular, beaded vessels and the presence of inflammatory cells in a biopsy specimen suggested that there was a vasculitic component to this process. However, in our original report, we actually stated that "No true vasculitis was seen" [2, p. 984].

Finally, Dr. Labarca and colleagues seem to doubt that CMV played a significant role in the hypercoagulable state noted in our patient. However, in our patient, clear evidence of CMV infection could be as seen in the patient's clinical presentation, the positive results of CMV serologic tests (for detection of IgM and IgG), the presence of CMV antigenemia, the presence of inclusion bodies in splenic specimens, and the presence of CMV in the spleen, as shown by histochemical staining. The first thrombosis occurred in our patient within days of the clinical presentation. The patient originally underwent surgery for the removal of an infarcted spleen that resulted from thrombosis of the splenic vessels; therefore, this first thrombosis could not have been explained by surgery or prolonged bed rest. Laboratory testing that was performed at the time of the initial presentation and repeated during a second hospitalization that occurred 6 weeks later revealed no other abnormalities that predisposed the patient to a hypercoagulable state. Thus, one can readily conclude that the vascular thromboses in our patient likely resulted from CMV infection.

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Interleukin-2, Ganciclovir, and High-Dose Zidovudine for the Treatment of AIDS-Associated Primary Central Nervous System Lymphoma

SIR—Primary CNS lymphoma is a complication of AIDS that is almost always fatal. More than 90% of HIV-infected men with primary CNS lymphoma have a CD4⁺ count of <50 cells/ μ L at the time of diagnosis, and they frequently have comorbid illnesses [1]. As pointed out by Skiest [2], although radiation therapy can provide patients with some palliative benefit, improvements in the duration of survival are modest, typically on the order of 1–3 months [3]. Surgery is also of limited utility, except as a diagnostic tool, because the tumors are often multifocal [4] and complete surgical resection is rarely possible. Highly active antiretroviral therapy (HAART) has had a profound influence not only on the clinical expression of AIDS-associated opportunistic infections, but also on the clinical expression of sev-

eral malignancies, including primary CNS lymphoma [5]. A recent retrospective analysis of 29 HIV-infected patients with primary CNS lymphoma noted significant benefit for patients who were treated with whole-brain radiation therapy and who then experienced HAART-associated immune reconstitution [6]. Rarely, patients with AIDS and primary CNS lymphoma have achieved long-term remission with HAART alone [7].

HIV-infected patients with primary CNS lymphoma invariably show evidence of previous Epstein-Barr virus (EBV) infection; this, in conjunction with prolonged immunosuppression and long-term B lymphocyte stimulation, is believed to be a key element that contributes to the pathogenesis of primary CNS lymphoma [8]. A novel approach to the treatment of AIDS-associated primary CNS lymphoma was first described by Raez et al. [9]. Of 5 patients who were treated with parenteral zidovudine, ganciclovir, and IL-2, 4 achieved a good response. The AIDS Malignancy Consortium (AMC) is currently sponsoring a phase II study using these 3 agents in conjunction with HAART. The rationale for this regimen is based on the following considerations: (1) because of the further immunosuppression that is caused, conventional chemotherapy is unlikely to have overall benefit for patients with AIDS and primary CNS lymphoma; (2) AIDS–primary CNS lymphoma occurs in patients with severe immunosuppression, and intensive therapy directed against EBV and HIV, coupled with partial immune reconstitution (IL-2), may benefit these patients; (3) EBV DNA is detected in the CSF of patients with AIDS and primary CNS lymphoma, and there is evidence of low-level EBV replication in patients with certain lymphomas; and (4) zidovudine is active against AIDS-related, EBV-positive Burkitt's lymphoma. Here, I describe my experience with a patient who had AIDS and primary CNS lymphoma and who was treated in accordance with this protocol.

A 42-year-old man with a long history

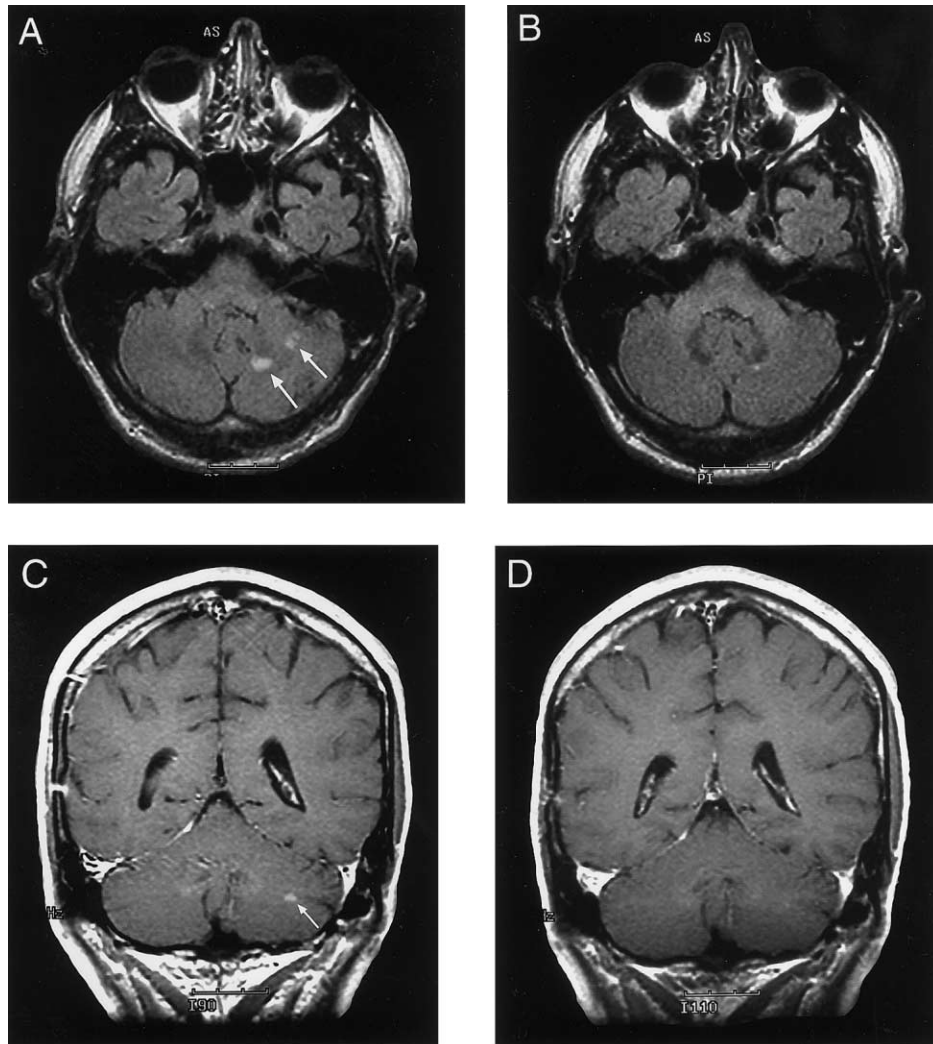


Figure 1. A, Gadolinium-enhanced, T1-weighted MRI (axial cut). MRI reveals 2 cerebellar lesions that enhance with gadolinium. B, Significant resolution of left cerebellar lesions. C, Coronal MRI with gadolinium demonstrating a left cerebellar lesion. D, Significant tumor shrinkage after 6 months of therapy.

of AIDS (CD4⁺ cell count, <10 cells/ μ L; HIV load, >250,000 copies/mL) and poor compliance with various HAART regimens experienced fever, weight loss, headache, and focal neurologic deficits. Over the next 2 months, he became progressively lethargic and bed-bound. MRI studies of the CNS revealed multiple, small, ring-enhancing lesions with modest mass effect and surrounding edema. The findings of initial blood and CSF studies were unrevealing.

While hospitalized, the patient began receiving a salvage HAART regimen of lopinavir-ritonavir, stavudine, and didanosine. The results of PCR of CSF spec-

imens were positive for EBV DNA and negative for cytomegalovirus, herpes simplex virus, and JC virus. Examination of a stereotactic brain biopsy specimen revealed large-cell lymphoma. After providing informed consent, the patient began a 14-day induction course of zidovudine (1.5 g iv b.i.d.), IL-2 (2 million U iv b.i.d.), and ganciclovir (5 mg/kg iv b.i.d.). By day 10 of primary CNS lymphoma therapy, his lethargy and fever had diminished, his appetite had improved, and his headaches had resolved. While receiving maintenance therapy with IL-2 (3 million U sc 3 times per week), ganciclovir (1 g orally t.i.d.), and HAART, his HIV load became

nondetectable and his CD4⁺ cell count increased to 125 cells/ μ L. The findings of his neurologic examinations are now normal, and representative MRI scans obtained before (figure 1A, 1C) and 6 months after the start of treatment (figure 1B, 1D) demonstrate continued shrinkage of the CNS lesions.

Although primary CNS lymphoma is one of a few opportunistic malignancies for which the prevalence is decreasing in the HAART era, all too often, it remains a fatal complication of AIDS. Only a small subset of patients with favorable prognostic factors reportedly benefit from receipt of conventional therapy [10]. Novel

immunomodulatory or pathogenesis-directed studies, such as this one, which is sponsored by the AMC, will hopefully improve the outcome of patients who develop this devastating complication.

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Beekeeper's Arthritis Caused by *Pseudomonas aeruginosa*

STR—A new disease called “beekeeper’s arthropathy” has been described in recent years in Spain by Cuende et al. [1] and Peña et al. [2]. This type of arthritis exclusively affects the hands and is related to bee stings. Until now, neither the etiology nor the pathogenesis of this condition has been completely elucidated.

The clinical characteristics and radiological signs of beekeeper’s arthropathy are similar to those described in children with foot osteochondritis and arthritis that occur after receiving a puncture wound [3]. In cases of the latter, *Pseudomonas aeruginosa* is carried by the puncturing element from the sole of the person’s athletic shoes into the foot tissues [4].

A 51-year-old male beekeeper was referred to our hospital in July 1999. He had very intense pain in the interphalangeal joint (IPJ) of his right first finger; the pain was so intense that he avoided even minimal rubbing of the finger. He also reported having progressive inflammation of this joint develop during the month before presentation. He had received multiple bee stings on this area of the hand. He did not have fever or systemic signs.

The patient’s WBC count was 13,400 cells/mm³ (75% polymorphonuclear leukocytes) and his erythrocyte sedimentation rate was 37 mm/h. A radiograph of his right hand revealed swelling of the soft tissues, periarticular osteoporosis, narrowing of the joint space, and cortical erosion of the IPJ of his right first finger. The results of 3 serial blood cultures were negative. However, *P. aeruginosa* was isolated in pure culture of an aspirate obtained from the IPJ affected by arthritis/osteomyelitis.

Drainage of purulent exudate was performed, and ciprofloxacin (500 mg b.i.d. by mouth) was administered for 1 month. The acute episode resolved, although the patient still has sequela associated with the marked limitation flexion in this IPJ.

If an apiarist’s gloves do not allow the hands to adequately perspire, cutaneous hyperhidrosis can occur. Overgrowing of *P. aeruginosa* is thus favored in a manner similar to spread from the athletic shoe via a puncture wound in children with foot osteochondritis [4]. A bee sting, which acts as a puncturing device, can carry *P. aeruginosa* from the skin surface into the joint. Because beekeepers’ gloves are commonly manufactured with materials that do not allow adequate perspiration, and because beehives are intensively exploited, there has been an increase in the incidence of this condition, particularly in the summer. Of the 93 cases reported in the literature [1, 2, 5], only 2 had microbiologic data indicating that *P. aeruginosa* was found in a joint aspirate; we report a third case.

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