

Vitamin C and the Common Cold

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Straw man: a logical fallacy, based on misrepresentation of an opponent's position. To "set up a straw man" means to create a sham position that is easy to refute, and then attribute that position to the opponent.

Introduction

The controversy over vitamin C and orthomolecular medicine began with the publication of Linus Pauling's book, *Vitamin C and the Common Cold*. Since that time, a proportion of the population have been experimenting with high dose vitamin C, reflecting a belief in its efficacy as a treatment or preventative for this minor illness. However, some elements of conventional medicine continue to assume that vitamin C is ineffective. Here, we show that the available scientific evidence supports the use of this simple substance.

In their recently updated Cochrane review, "Vitamin C for preventing and treating the common cold",¹ Douglas, Hemilä, Chalker, and Treacy (2007) state their objectives as being to discover whether oral doses of 0.2 g or more daily of vitamin C reduce the incidence, duration, or severity of the common cold, when used either as continuous prophylaxis or after the onset of symptoms. This statement is their "straw man". They conclude: "The failure of vitamin C supplementation to reduce the incidence of colds in the normal population indicates that routine mega-dose prophylaxis is not rationally justified for community use."

The review's conclusions were widely reported in the world's press, with headlines, such as "Vitamin C useless for preventing colds" (*Reuters*, July 18, 2007),

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trumpeting the failure of vitamin C to prevent or cure colds. More recently, the *Los Angeles Times* (February 18, 2008) ran a similar headline, also based on the Cochrane review: "Cold sufferers mindlessly reach for vitamin C." This article claimed that vitamin C may not be as beneficial as most Americans think.

As a result of this publicity, orthomolecular practitioners are likely to get questions from concerned patients, as to whether the Cochrane reviews' data and analyses support such negative interpretations. This paper provides a robust answer to such questions.

Orthomolecular Claims for Vitamin C

The Cochrane review on vitamin C and the common cold has several shortcomings. Fundamentally, it fails to understand the orthomolecular claims for vitamin C in prevention and treatment of the common cold. Such claims for the actions of vitamin C against colds and other infections have been made over a period of at least 50 years.²⁻⁶ They specify a definitive and uniquely effective response.⁷⁻¹⁰ The clinical data upon which these claims are based have been replicated repeatedly.¹¹⁻¹³ However, the claims are often wrongly stated and misunderstood.

The review by Douglas et al. is apparently based on such (admittedly widespread) misconceptions, rather than the original claims.¹⁴ It is important to stress that the doses Douglas et al. refer to as "mega-dose vitamin C supplementation" range from just 200 mg given once or twice daily. We would not consider these as high doses.

To avoid further misunderstanding, we must state the orthomolecular claims for vitamin C clearly.

Prevention of Common Cold

Vitamin C given to human subjects at frequent intervals (< 6 hourly) and sufficiently high doses (8+ grams per day) will prevent the common cold.

Klenner, one of the earliest clinical investigators, provides a quantitative indication of the dose required: 10 grams of vitamin C per day, given in divided doses, will prevent colds in 90% of individuals, but some people will require more.¹⁵ Hoffer indicates a similar dose response relationship (95% prevention at 8 grams per day or more, depending on individual variability).¹⁶ Reported dosing intervals vary slightly, but 4-6 doses a day would indicate a maximum interval of 4-6 hours.

Treatment of Common Cold

Vitamin C, given at short intervals and very high doses to a subject with the common cold, can eliminate the symptoms and may bring about a cure within hours.

These claims are based on high (pharmacological) doses and are subject to high levels of individual variation. Cathcart provides an indication of the dose and interval: 30-150 grams per day, in divided doses at intervals of one hour or less.¹⁷ The Vitamin C Foundation recommends 8 grams every 20 minutes, from the onset of symptoms.¹⁸

Treatment Threshold Effect

The dose-response relationship for the treatment claim is described as a threshold effect;¹⁹ unless a minimum threshold dose is reached, little or no clinical response is achieved.²⁰ For a mild cold, the threshold is close to the subject's bowel tolerance level. Above this threshold, the symptoms are "quenched"; below it, there is little clinical benefit. In some individuals, with a virulent infection, reaching the threshold may be unfeasible with oral doses. However, recent research indicates oral liposomal formulations may be more effective.

Now that we have specified the ortho-

molecular claims explicitly, we can examine the Cochrane review in context.

Shortcomings of the Cochrane Review

It is clear that the Cochrane review fails to address the orthomolecular claims for vitamin C. Firstly, the reviewers base their view of the "failure of vitamin C" on inadequate dosing regimes. Secondly, the review relies on social and epidemiological medicine, rather than on a biological understanding of the proposed anti-viral effects of vitamin C. Thirdly, there are methodological defects: those selecting studies for inclusion or exclusion had knowledge of the results, therefore their choices were susceptible to bias. Finally, the reviewers extrapolated beyond their data, leading to over-generalisation of conclusions, particularly in their press releases. We will examine these points individually.

Inadequate Dosing Regimes

Dose Size

The review does not include data for intakes of the same order of magnitude as those described in the orthomolecular prevention claim. The intakes studied are too small. Similarly, the review does not consider intakes of the same order of magnitude as those claimed to be effective for treatment.

These objections were stated clearly by Hickey and Roberts,²¹ and Higgins,²² in response to an earlier version of the Cochrane review. Emerson, who also points out the discrepancy in the doses, has reinforced these early objections.²³ Douglas et al. responded tangentially and failed to explain how their data could be extrapolated to cover the doses claimed to be effective.

Dose Frequency

The review covers longer dose intervals than those claimed to be effective. Hickey and Roberts published this

objection, and once again, the response by Douglas and Hemilä did not indicate how the data they presented could be extrapolated to more frequent doses. Furthermore, Douglas et al. failed to provide a specific explanation of how and why they ignored the dose-response mechanism; a rigorous response was required, as this failure breaches basic principles of pharmacology.

Lack of Scientific Understanding

Epidemiology lacks the power of direct and replicated observation; socially-based medical studies must comply with the underlying rules of science. Epidemiology is a secondary statistical discipline, and requires consistency with findings from fundamental sciences, such as chemistry or biophysics.

The Cochrane reviewers have ignored the pharmacokinetics of vitamin C. The half-life for kidney excretion of high-dose vitamin C from plasma is about 30 minutes.^{24,25} At the dose levels and intervals studied by Douglas et al., there would be little, if any, consistent increase in plasma ascorbate levels or body content. The antioxidant action of ascorbate depends on its ability to donate and transfer electrons (we are unaware of any other significant effects being postulated for this molecule). Clearly, a dose-response relationship requires the presence of the molecule in question: if the ascorbate has been excreted, as would be the case for the studies described in the Douglas et al. review, it cannot be expected to have a physiological effect.

Furthermore, the reviewers have excluded relevant published clinical data. They dismiss the observations of Cathcart and others, on the grounds that "their uncontrolled observations do not provide valid evidence of benefit". This overlooks repeated, independent observations of large and easily replicated effects.

Scientifically, such experimental results are more valid than large-scale clinical trials or epidemiological studies. By way of analogy, we might consider whether it would be necessary to carry out large-scale randomized double-blind controlled trials of the guillotine, to find out whether removing a person's head results in death. Clearly, a single experiment would provide the answer to this question, and double blind controls would be superfluous.

On the clinical dose-response relationship, Cathcart claimed a reversible cessation of symptoms at the oral threshold near bowel tolerance: increasing the dose slightly removes the symptoms, while lowering the dose brings them back. However, Levy reports that he has not achieved this effect with standard oral doses and that intravenous, or liposomal, doses may be required. Levy claims intakes of 4-5 grams per hour of liposomal vitamin C, taken orally, have the reported effects with substantial biological variation in the doses required.²⁶ This discrepancy may relate to carbohydrates inhibiting the absorption of ascorbate.

The scientific method involves hypothesis and refutation.²⁷ Simple, easily replicable experiments, like those reported by internationally-known physicians, such as Cathcart, Klenner, Hoffer, Levy, Kalokerinos, and Brighthope, have greater scientific validity than the Cochrane meta-analysis. If the clinical observations of the above mentioned doctors were in error then, over the last half century, any physician or scientist could have refuted the claims directly, with little effort or cost. However, no such refutation exists in the scientific literature. This could be because the relevant doses have not been studied; alternatively, results obtained by conventional physicians attempting a refutation may have been declined for publication.

Methodological Issues

A sequence of systematic errors in the Cochrane review invalidates both its conclusions and the untenable extrapolations, associated particularly with comments from Hemilä, in the popular press.

Predetermined Opinion and Social Pressure

The Cochrane review provides a meta-analysis of low-dose studies of vitamin C and the common cold. Unfortunately, its authors have limited the range of intakes to low values, which are unlikely to be effective, and excluded clinical data on higher doses, which have been shown to provide positive results.

When choosing studies for a review paper, it is important to avoid selection errors. To avoid such errors, the studies should be selected on objective criteria, and without knowledge of the results. If the results of the studies are known before the selection criteria have been determined, then the people making the selection can be unconsciously biased. In the Cochrane review, the researchers were aware that the criteria used to select their studies would exclude all clinical reports of high (orthomolecular) doses.

Further selection bias can be introduced when papers are considered for inclusion. If a reviewer choosing a paper is aware of the author's names, experimental details, and results, she can largely influence the outcome of the study by unfair selection. Such experimenter bias is well known and is the reason blind and double blind experiments are performed. Even the most honest experimenters are unconsciously subject to these effects. Moreover, obedience to authority (the Milgram effect),^{28]} social pressures (Ashe conformity),²⁹ and Groupthink³⁰ can combine to produce erroneous results. In the Cochrane study, the reviewers who selected or excluded studies had prior knowledge of the literature on vitamin C and the common cold, as well

as specific information about the papers under consideration.

These problems have been communicated to the Cochrane authors, though their response to date has been unsatisfactory. A clear and objective response, focusing on these specific objections, might provide reassurance that the potential for such bias was being addressed.

Exclusion of Non-placebo Controlled Trials

Although the review acknowledges that the placebo effect is not relevant except for minor subjective effects, it excludes data from any trials without placebo controls.

As described in another Cochrane review,³¹ and elsewhere,³²⁻³⁴ the placebo effect is irrelevant in the case of definitive and objective clinical effects. The effects claimed for vitamin C, as described above, are large, objective, and definitive, and have not been replicated using any other antiviral substance. Authors report complete, dose-related, reversal of symptoms, or rapid cure: these substantive results are unambiguous clinical observations.

The review required placebo controls on the basis that the authors considered "that with the expected small effects of vitamin C, and the greatly subjective outcome definitions, only placebo-controlled trials could yield information of adequate rigour to meet our study objectives." Such an expectation is based on a misconception of the claims for vitamin C. The reported outcomes for appropriate doses are large and objective, rendering this explanation spurious. The reason provided was particularly inadequate for this review, as it restricted the doses studied to outliers of the range claimed to be effective.

Overgeneralization

The authors failed to make clear the limitations of their review. They did not specify clearly enough that their results

relate to low doses. The doses studied were approximately an order of magnitude less than those claimed to be effective. Similarly, the review did not specify that its results and conclusions do not apply to the clinical claims for the effectiveness of vitamin C.

Taken as a whole, the review and its resultant media generalizations are misleading, as they deflect attention away from the actual claims for vitamin C's effectiveness.

Discussion

Cochrane reviews generally provide an excellent scientific resource to medicine, as illustrated by the review of the placebo effect. However, with the review of vitamin C, the authors have failed to provide an effective response to objections. They have promoted their conclusions widely, resulting in media generalisations that are out of proportion to a scientific interpretation of the data.

The current Cochrane review exemplifies the dangers of systematic error. Bias and confusion can be primary sources of inaccuracy, even when a statistical analysis obeys the technical rules. The review by Douglas et al. is an example of "cargo-cult science," as initially described by the physicist Richard Feynman: it has the appearance and techniques of proper science, while avoiding the constraints required for an effective and accurate investigation.³⁵

In previous responses to objections on dose raised by Higgins, and Hickey and Roberts, Douglas et al. did not address the specific criticisms. Rather, their responses deflected the readers' attention from a rational consideration of the central issues. In particular, by excluding high dose studies, the Cochrane reviewers set up a straw man, demolished it, and highlighted their "achievement" (or misleading claims) in the worldwide press.^{36,37}

Linus Pauling's initial pragmatism in suggesting lower dose levels was overly

optimistic, particularly for preventing the common cold; his suggested daily doses increased with time, to a recommended optimal intake of 1-18 grams per day, depending on individual variation.³⁸ Pauling was aware of the difference between intakes for prevention of infection and those for therapeutic intervention, and he reported the massive doses described by Cathcart.

Before the current minor review update, Hemilä and Douglas used their results to claim that the "lack of effect of prophylactic vitamin C supplementation on the incidence of common cold in normal populations throws doubt on the utility of this wide practice."³⁹ A widely quoted press release from Douglas' university begins "vitamin C has been proven ineffective in combating the common cold in most people." Douglas goes on to claim, "vitamin C has proven not to be a magic bullet to solve the common cold."⁴⁰

We can find no evidence in either version of the Cochrane review to support such unscientific claims, let alone provide anything close to "proof."⁴¹ The hypothesis that appropriate doses of vitamin C can prevent or cure the common cold has not been refuted.

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