Winter illness and vitamin C: the effect of relatively low doses

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Summary: After their random allocation to one of three treatment groups, 622 volunteers received either vitamin C or placebo in a maintenance dose of 500 mg once weekly and a therapeutic dose of 1500 mg daily on the 1st day and 1000 mg on the next 4 days of any illness. Two forms of vitamin C were employed: a sustained-release capsule containing ascorbic acid and a regular tablet containing a mixture of sodium and calcium ascorbate. In the 448 subjects who completed an average of 15 weeks in the study a total of 635 episodes of illness were recorded. Respiratory symptoms were recorded on at least 1 day in 95% of these episodes. There were no consistent or significant differences in the sickness experience of the subjects receiving the sustained-release vitamin capsules compared to those receiving the vitamin tablets, but subjects in both vitamin groups experienced less severe illness than subjects in the placebo group, with approximately 25% fewer days spent indoors because of illness ($P < 0.05$). These results are compatible with the belief that supplementary vitamin C can reduce the burden of winter illness, but the intake need not be as high as has sometimes been claimed.

Résumé: *Les maladies hivernales et la vitamine C: l'effet de doses relativement faibles*

Nous avons étudié les résultats de la vitamine C sur la maladie hivernale chez 622 volontaires. Ceux-ci ont été répartis au hasard en trois groupes thérapeutiques distincts. Ces volontaires recevaient soit de la vitamine C, soit un placébo. La dose d'entretien était de 500 mg une fois par semaine et la dose thérapeutique de 1500 mg le 1er jour, puis de 1000 mg par jour durant les 4 jours suivants, durant une maladie quelconque. Nous avons utilisé deux formes de vitamine C: une capsule à libération progressive renfermant de l'acide ascorbique, et un comprimé ordinaire contenant un mélange d'ascorbate sodique et d'ascorbate calcique. Parmi les 448 sujets qui ont suivi le traitement pendant une moyenne de 15 semaines, on a noté 635 épisodes de maladie hivernale. Dans 95% de ces épisodes on a observé des symptômes respiratoires pendant au moins 1 journée. Aucune différence conséquente ou significative n'a été observée, concernant la maladie, entre les sujets du groupe recevant la capsule et ceux qui prenaient le comprimé. Toutefois, la maladie a été moins sévère chez les sujets traités par la vitamine que chez ceux qui recevaient le placébo, si on en juge par le fait qu'ils ont été confinés chez eux, par suite de maladie, 25% de jours en moins ($P < 0.05$). Ces résultats confirment la croyance qu'un supplément de vitamine C peut réduire le fardeau de la maladie hivernale. La dose utile semble toutefois moins forte que celle qu'on estimait nécessaire autrefois.

This is the report of the third in a series of large-scale double-blind studies of the effect of supplementary vitamin C on the incidence and severity of "colds" and other winter illness in an otherwise healthy working population.

The first study was undertaken during the winter of 1971-72 to test Professor Linus Pauling's claim that the daily intake of 1 g of vitamin C would lead to a 45% reduction in the incidence of colds and a 60% reduction in total days of illness.[1,2] Anticipating a negative result, we enrolled a large number of subjects (1000), made sure that the design was strictly double-blind, and instructed our subjects to increase their daily intake to 4 g during the first 3 days of any illness.[3] To our surprise, among the 818 subjects who completed the trial, those on the vitamin experienced 30% fewer days of disability (confined to the house) than those on the placebo, and this difference was highly significant ($P < 0.001$).

In the following winter (1972-73) we conducted a second trial[4] to examine the effect of the "prophylactic" and "therapeutic" features separately, the effect of different dosages on sickness experience, and whether there was any rebound increase in sickness after discontinuing the regular "prophylactic" dose. In addition, blood ascorbate concentration was monitored in a few subjects during and after prolonged

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ingestion of high daily doses of vitamin C.

Some of the results of this trial were less than clear-cut, in part because of problems arising from the complexity of the experimental design (eight treatment groups) and the large number of subjects (an initial enrolment of 3520). Nonetheless, it seemed that neither the prophylactic nor therapeutic features alone could have been responsible for the effect seen in the first study, and that a regular "prophylactic" dose of 2 g/d was no more effective than one of 250 mg. The measurement of blood ascorbate concentration in a few well nourished individuals also indicated that, apart from a transitory rise during the first few days, there was no persistent increase in values from either the 1-g or 2-g daily dose, and that there was a profound (but again transitory) depression of blood values on discontinuation of this high intake.[5]

Examining these results in conjunction with those obtained by some other investigators[6-7] led to the suggestion that tissue saturation might be the limiting factor and the key to understanding the results of the different studies.[8] To test this possibility a third study was planned in which subjects would receive a regular intake that, although relatively small, should be enough in our predominantly well nourished subjects to maintain tissue saturation, plus a therapeutic dose that would hopefully be enough to maintain high blood concentrations during episodes of illness. (We recognize that the term "tissue saturation" is somewhat ambiguous and controversial. It is used in this paper to designate the state in which leukocyte or whole blood concentrations of vitamin C are at or close to their maximum. There is evidence that in normal healthy adults this state can usually be achieved with a daily intake of 60 to 100 mg.[9])

Two forms of vitamin C were tested: tablets containing a mixture of sodium and calcium ascorbate, and capsules containing a sustained-release form of ascorbic acid. The latter had been found to produce a more prolonged elevation of blood ascorbate concentration than the regular quickly absorbed, quickly excreted tablets,[5] and it therefore seemed possible that they might be more effective than the tablets in maintaining adequate blood ascorbate concentrations during infection. Unfortunately, because of technical problems, it was not possible to carry out the intended monitoring of blood ascorbate concentration during episodes of illness and consequently we were unable to compare the effectiveness of the tablets and capsules on blood ascorbate concentration during illness. This report is therefore restricted to a comparison of the illness experience associated with taking the two forms of vitamin C and placebo.

Material and methods

The majority of subjects were recruited from the staff of the Toronto East General Hospital, the Ontario Hydro-Electric Commission and the Ontario Ministry of Transportation and Communications. In addition, some staff and students were recruited from the school of hygiene and the medical sciences building of the University of Toronto. To be eligible for the trial, subjects were required to be in good general health but usually to suffer at least one cold between January and April each year.

Three types of medication were used: a 500-mg tablet containing sodium and calcium ascorbate in an approximate 2:1 ratio, a placebo tablet of the same appearance and taste, and a capsule containing 500 mg of ascorbic acid in sustained-release form. (An inherent weakness in this design was that it did not control for the possibility that the placebo effect of capsules may be different from that of tablets. However, as it turned out, there were no significant differences in the sickness experience associated with the two types of presentation.)

The vitamin and placebo tablets were the same as those used in the 1972-73 trial and were in fact the surplus tablets left over from that trial. The vitamin tablets were reassayed to ensure that they had not deteriorated, and were found to contain approximately 98% of the stated dose. It was not possible to obtain placebo capsules that were truly indistinguishable from the active sustained-release form because the contents of the capsules (ascorbic acid pellets) proved prohibitively expensive to imitate. The explanatory notes provided to the subjects were therefore deliberately phrased to give the impression that, as with the tablets, half of the capsules contained a placebo preparation. This subterfuge was successful, in that at the end of the study, of the 424 subjects who answered the question "Do you think you were on the vitamin, the placebo, or don't know?" 287 (68%) answered "Don't know", and among those on the capsule the proportion was almost identical, at 69%. Among the subjects who believed they could tell whether they were on vitamin or placebo, 52% were right and 48% were wrong.

Bottles were numbered from a list of consecutive numbers computer-randomized in groups of three and were then issued to subjects as they registered. Subjects were instructed to take one tablet (or capsule) each week and an extra tablet (or capsule) at the onset of any symptoms of illness. If symptoms persisted this dose was to be repeated twice at 4-hour intervals on the 1st day, then once every 12 hours for up to 4 more days. The "therapeutic" dose of vitamin received during an illness was thus 1500 mg on

Table I—Time in study and recorded characteristics (means or %) of initial total enrolment, dropouts and treatment groups

Variable	Initial total group (N = 622)	Vitamin C: Tablet Subjects (n = 150)	Vitamin C: Tablet "Dropouts" (n = 57)	Vitamin C: Capsule Subjects (n = 152)	Vitamin C: Capsule "Dropouts" (n = 56)	Placebo Subjects (n = 146)	Placebo "Dropouts" (n = 61)
No. of days in study	—	106.6	—	106.9	—	106.1	—
Age (yr)	32.7	34.2	27.1	34.1	28.8	34.1	31.1
(range)	(14-67)	(18-66)	(18-47)	(14-67)	(18-54)	(18-66)	(20-67)
Sex (% male)	50	49	37	54	40	58	48
Nonsmokers (%)	62	67	49	64	57	64	57
Usual no. of episodes*	1.77	1.63	1.91	1.74	1.82	1.77	1.98
Usual no. of days indoors	2.20	2.25	2.60	2.09	1.76	2.04	2.77
Usual no. of days off work	1.82	1.86	2.14	1.66	1.55	1.75	2.21
Contact with children (%)	42	43	44	41	36	47	36
Frequently in crowds (%)	68	62	70	69	69	71	67
Daily juice (oz)	4.1	4.5	3.8	4.0	3.9	4.1	4.0
Other vitamin C† (%)	17	13	12	18	24	17	16

*All winter illness (colds, 'flu, etc.)
†Subjects were permitted to continue taking other vitamin supplements provided that the additional daily intake of vitamin C did not exceed 75 mg.

the 1st day and 1000 mg daily on days 2 through 5. Each subject also received a calendar-type of symptom record similar to that used in the previous two trials.[3,4] Distribution of bottles and record sheets took place between Jan. 7 and 18, 1974 and the study ran until Apr. 30, 1974, giving a maximum study duration of 16 weeks.

Data from record sheets were coded and transferred to punch cards before the tablet code was broken and without knowing whether an individual had been on tablets or capsules. Other procedural rules were the same as described previously.[3,4] One-tailed z tests were used to compare the sample means. To avoid the restrictive assumption of equality of variances, the formula $S_1^2/n_1 + S_2^2/n_2$ was used to estimate the variance of the difference between means.

Results

Of the 622 subjects initially enrolled 448 completed at least 2 months of recordkeeping. The dropout rate was approximately the same in all three treatment groups, and the overall rate of 28% was intermediate between the 18% and 33% rates in the first two studies.[3,4] Loss of interest appeared to be the main reason for leaving the study, since although subjects were invited to report unusual symptoms, there were no complaints of suspected side effects.

In terms of recorded personal characteristics the three groups were reasonably similar, with none of the differences in means and proportions shown in Table I approaching statistical significance.

The overall morbidity of the three groups is summarized in Table II, based on all recorded episodes of illness, with no attempt to separate "colds" from other types of illness. However, symptoms affecting the nose were recorded at some stage in 80% of all episodes, and respiratory symptoms (i.e. involving nose, throat or chest) were recorded in 95% of episodes.

Thirty-four (22%) of the subjects taking the sustained-release capsules remained free of illness throughout the study period, compared to 27 (18%) in the vitamin tablet group and 23 (16%) in the placebo group. These differences were not significant.

Very brief (1 day or less) episodes accounted for 24% of all, compared to 40% in the second study.[4] There were also relatively few prolonged episodes of illness (15 days or more) in this study and they accounted for only 22 of the total of 598 days indoors and 9 of the 300 days off work. Furthermore, the very brief and very long episodes were distributed fairly evenly between the three treatment groups, so that (unlike the situation in the second study) simple comparisons of total sickness experience could be made.

Overall, the experience of the vitamin subjects on the sustained-release capsules was slightly more favourable than the experience of those on the tablets (Table II) but the differences were not consistent and none of the differences between the two vitamin groups was significant. The experience of these two groups may therefore reasonably be combined to provide a more accurate estimate of the vitamin effect. However, even when this is done, the confidence limits are wider in this study than in the first because of the smaller number of subjects involved (Fig. 1). For the mean of the combined vitamin groups the difference from the placebo mean was significant ($P < 0.05$) for days indoors, for days feeling "feverish" and for days feeling "cold and shivery".

Correlations between initial characteristics (Table I) and subsequent overall sickness experience were extremely weak. As in the second study, "days indoors" correlated most highly with "usual days indoors" but even here the correlation coefficient was barely 0.1 ($P < 0.05$). The effect of adjusting sickness experience by initial characteristics was explored using stepwise multiple regression. The effect

Table II—Mean numbers of days of symptoms reported by subjects in three experimental groups

Complaint	Mean no.* of days' morbidity: Vitamin C Tablet (n = 150)†	Vitamin C Capsule (n = 152)†	Placebo (n = 146)†
Any symptoms	5.047 *0.381*	4.974 *0.505*	5.384 *0.421*
Confined indoors	1.187‡ *0.142*	1.217 *0.148*	1.610 *0.204*
Off work	0.713 *0.112*	0.546 *0.093*	0.753 *0.121*
Nose running or plugged	3.767 *0.269*	3.697 *0.381*	3.911 *0.303*
Throat soreness	2.513 *0.231*	2.066‡ *0.245*	2.644 *0.231*
Chest soreness or tightness	0.820‡ *0.131*	1.059 *0.196*	1.322 *0.210*
Felt feverish	1.100‡ *0.147*	1.059‡ *0.162*	1.527 *0.184*
Cold and shivery	1.040 *0.136*	0.908‡ *0.129*	1.336 *0.163*
Limbs aching and heavy	1.367 *0.168*	1.322 *0.168*	1.692 *0.195*
Mentally depressed, no ambition	1.520 *0.178*	1.322 *0.178*	1.548 *0.188*

*Means are given to third decimal place to permit calculation of original numbers.
†Mean no. (and SEM) of episodes associated with each group: tablet, 1.420 (*0.085*); capsule, 1.375 (*0.093*); and placebo, 1.459 (*0.089*).
‡Significantly different ($P < 0.05$) from placebo mean.

Table III—Mean number of days indoors per subject, subdivided by various characteristics

Characteristic	No. of subjects	Mean no.* of days: All vitamin (V)	Mean no.* of days: Placebo (P)	V/P (%)	V/P (%): 1971-72 study[3]
Total	448	1.202	1.610	75	70
Age					
<30	203	1.058	1.672	63	70†
≥30	245	1.325	1.561	85	69†
Sex					
Male	240	1.161	1.541	75	64
Female	208	1.245	1.705	73	74
Usual days indoors					
<2	193	0.876	1.188	74	87†
≥2	255	1.445	1.939	75	57†
Contact with young children					
Yes	195	1.008	1.676	60	54
No	253	1.343	1.551	87	83
Frequently in crowds					
Yes	302	1.106	1.471	75	66
No	146	1.385	1.952	71	83
Daily juice (oz)					
≥4	288	1.313	1.689	78	78
0-3	160	0.990	1.482	67	52
Vitamin supplement					
Yes	72	1.043	1.520	69	57
No	376	1.231	1.628	76	72
Smoker					
Yes	157	1.135	1.642	69	70
No	291	1.237	1.591	78	69
Episodes involving nasal symptoms					
Yes	(508)	1.013	1.212	84	70
No	(127)	0.189	0.397	48	70

*Means are given to third decimal place to pemit calculation of original numbers.
†Figures for the 1971-72 study were based on an age separation at 25 years and on "usual colds".

was very small and did not change any of the reported levels of significance.

The association between the vitamin C intake and reduced disability was more pronounced in younger subjects, those in frequent contact with young children, and smokers (Table III). However, none of these differences was significant and some were in conflict with the findings of the initial study, which was based on larger numbers. Also, despite the emphasis on the common cold in much of the recent controversy over vitamin C, illnesses involving nasal symptoms were no more susceptible to the "vitamin effect" than were other types of illness.

Discussion

In spite of the much lower doses of vitamin C used in this study, the present results are generally similar to those obtained in our first study.[3] Comparison with results of our second study (1972-73) is less meaningful because of the brief duration of the therapeutic component in that study (1 day only, compared to 3 and 5 days in the other studies) and the poor final matching of some of the experimental groups.[4] Nonetheless, the second study also showed the same general pattern as the first and third: a small and inconclusive reduction in the number of episodes but a more substantial reduction in total days of disability

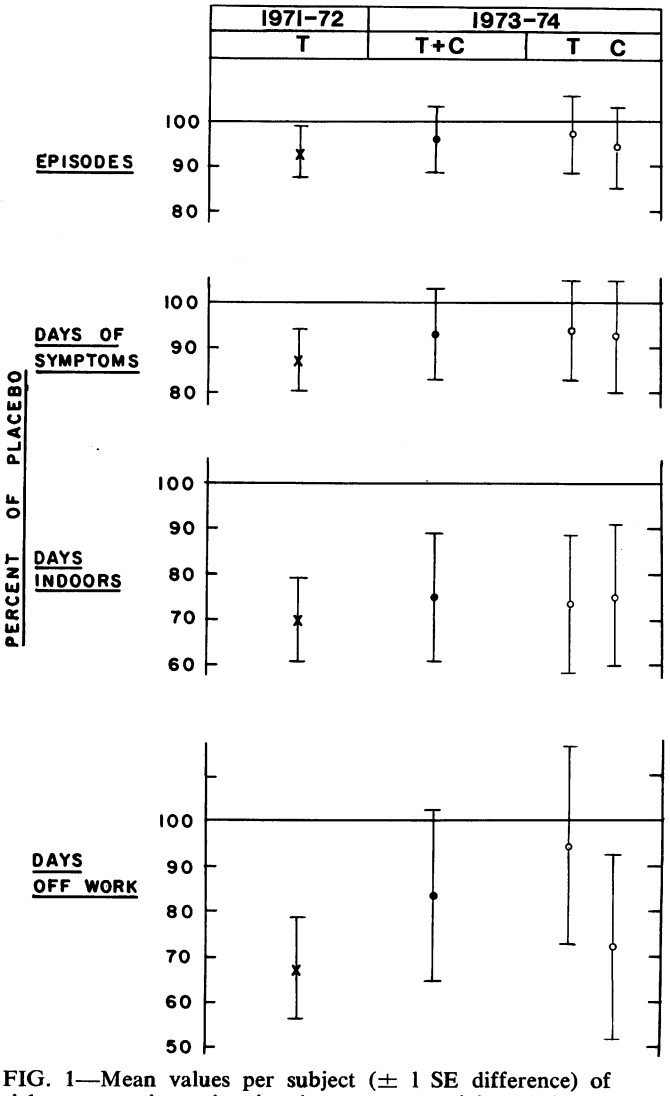

FIG. 1—Mean values per subject (± 1 SE difference) of sickness experience in vitamin groups (receiving tablets or sustained-release capsules), expressed as percentage of corresponding mean values in placebo group. Results of the 1971-72 study are provided for comparison. T = tablet; C = capsule.

from the combined prophylactic and therapeutic regimen.

Taken in conjunction with the positive results reported by other investigators,[6,7] there is now little doubt that the intake of additional vitamin C can lead to a reduced burden of "winter illness". Contrary to Pauling's initial claims, however, there appears to be little effect on the frequency of illness, and massive regular doses do not appear to be necessary. Furthermore, the effect does not seem to be restricted to "colds", for the effect observed was as great or even greater on illness not involving the nose (Table III), and in terms of total days of symptoms (Table II) the effect on nasal symptoms has been rather unimpressive in all three of our studies.[3,4] Thus, although the possibility remains that large doses of vitamin C may sometimes have a specific antiviral effect, our results are more readily explained in terms of a generalized nonspecific improvement in the host's ability to cope with infection (or possibly any type of stress?).

Similarly, although it is possible that a larger therapeutic dose of vitamin C might have yielded an even more impressive reduction in disability in this study, this seems unlikely in view of the similar results obtained in the first study, in which an approximately fourfold therapeutic dose was employed. Unfortunately, because of our inability to carry out the planned blood ascorbate analyses on our subjects during episodes of illness, we were unable to establish whether the dosage used was sufficient to maintain high blood concentrations and whether the long-acting capsules were more effective in this regard than the vitamin tablets. It would, however, be premature to rule out the possibility that much larger therapeutic doses might be more effective, because in our second study there was some evidence that an 8-g therapeutic dose was more effective than a 4-g dose.[4]

Although more research clearly needs to be done to define fully the limits of benefit and hazard from the use of supplementary vitamin C, we believe that there is now enough information from this and other studies to justify the following general observations:

1. There is an upper limit to useful regular supplementation with vitamin C and this upper limit may be related to "tissue saturation". Regular intake of greater quantities risks the possibility of direct toxic effects and the indirect hazard of dependency.[10]

2. Increased daily intake appears to be beneficial at times of illness, but just how great an increase is useful, and whether the benefit is related to maintaining "tissue saturation" remain to be determined; indeed, whether this is truly a "vitamin" effect or a pharmacologic effect of ascorbic acid remains a matter of conjecture.

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