The effects of ascorbic acid and flavonoids on the occurrence of symptoms normally associated with the common cold[1, 2]

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ABSTRACT A controlled study was made of the effects of natural orange juice, synthetic orange juice, and placebo in the prevention of the common cold; both natural and synthetic orange juices contained 80 mg of ascorbic acid daily. Three-hundred sixty-two healthy normal young adult volunteers, ages 17 to 25 years, were studied for 72 days with 97% of participants completing the trial. There was a 14 to 21% reduction in total symptoms due to the common cold in the supplemented groups that was statistically significant ($P < 0.05$). Ascorbic acid supplementation also increased the number of "episode-free" subjects. However, the clinical usefulness of the results does not support prophylactic ascorbic acid supplements in the well-nourished adult. The results in this study with both natural and synthetic orange juice of physiological content of ascorbic acid, are similar to those obtained using a "megadose" of ascorbic acid. *Am. J. Clin. Nutr.* 32: 1686–1690, 1979.

There are reports in the literature of some 15 trials designed to assess the efficacy of vitamin C (ascorbic acid, (AA)) in the prevention or treatment of the common cold (1–3). The results have, for the most part, provided little generally accepted evidence of any clearly definable relationship and their interpretation would often appear to be a matter of individual judgment. Chalmers (4), in his critical review of the field considered that only eight of these trials satisfied the accepted canons of scientific experimentation and his detailed assessment of the eight failed to convince him that a large dose of "megadose" of AA offered any clearly-definable advantage in the prevention or treatment of the common cold.

Animal studies have indicated that flavonoids (particularly those of the citrus-fruit type) are able to modify the metabolism of AA under defined experimental conditions (5); administration of flavonoids raises the concentration of AA in certain tissues and appears to potentiate its nutritional activity (5, 6). The current study was designed to examine the effect of small supplements of AA, in the presence and absence of flavonoids, on the frequency and duration of the common cold in a defined population of young adults.

Many of the earlier studies emphasized the importance of the administration of megadoses of AA (7), but tissue saturation is attainable by using a much lower dose of AA than those advocated by the "megatherapists" (8). In a separate study a daily supplement of 80 mg of AA produced leucocyte AA concentrations not significantly different from those resulting from a daily megadose intake of 1000 mg (H. K. Wilson, I. M. Baird, A. N. Howard, J. E. W. Davis, and R. E. Hughes, unpublished observations). In the current study, designed primarily as a prophylactic one, a daily supplement of 80 mg of AA was used; the estimated daily intake from dietary sources was 50 mg, thus giving a total daily intake of about 130 mg—sufficient to achieve tissue saturation (9, 10).

Methods

Three-hundred seventy-seven possible healthy normal volunteers in the age range of 17 to 25 years were contacted. All were either 6th form pupils at a local comprehensive school or university students. Three-hundred sixty-two volunteered for the study and were

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consequently admitted to the trial. The volunteers from both courses were treated as a single population and randomly allocated to three color-coded groups, yellow (120), blue (121), and red (121); there was no deliberate equalization of age/sex distribution between the three groups. Color coding was necessary to facilitate the daily distribution and consumption of drinks. The yellow (control) group received daily a synthetic orange juice drink containing no flavonoid material and no AA; the blue group received the synthetic orange juice with 80 mg of AA added; the red group received natural orange juice containing 80 mg of AA. The volume of each drink was approximately 180 ml. The orange juice was prepared daily from Shamouti oranges using a California Fruit Tree juice expressor and the volume to be dispensed calculated after the determination of AA using the 2, 6 dichlorophenolindophenol dye technique (11). The beakers for dispensing the drinks were colorcoded and the distribution points for the three groups were spatially removed from each other, thus reducing the possibility of "drink comparisons" between the groups. Participants were not informed of the nature of their drinks until the conclusion of the experiment; distribution of the drinks was between 10:30 and 11:30 AM daily. The trial continued for 72 days, from January 7, 1975 to March 20, 1975.

Participants were required to complete daily a record card by indicating whether they had been well, or whether they had experienced one or more of a number of symptoms usually associated with the common cold, e.g., running nose, sneezing, headache, sore throat, stuffed nose, cough, confinement to bed, fever, and any other symptoms that were detailed by the participant. Subjects were also required to indicate the days on which they were absent from their studies because of illness. Records were not kept for the first 3 days of supplementation. Record cards were collected at the end of each month and transferred in toto and without grouping, to the statisticians, who were not aware of the separate group supplements, but only a participants group color.

Results

Three-hundred fifty-three participants (97%) completed the trial. Of these, one (red group) with evidence of chronic bronchitis was eliminated after examination of the record cards by an independent clinician and two (both in yellow groups) were eliminated because they took daily mega supplements of vitamins. This left 350 participants—112 in the yellow (nonsupplemented) group, 120 in the blue (80 mg of AA supplement) group, and 118 in the red (80 mg of AA in orange juice) group. The reason for the discrepant withdrawal pattern between the three groups is not known.

The criteria of definition of the common cold and the analysis of the episodes were those used by Anderson et al. (12). If two episodes of symptoms were separated by no more than 2 symptom-free days, a single episode was recorded; if the interval was 3 to 6 days two episodes were counted unless the symptoms were exactly the same, in which case a single episode was counted. Episodes with intervals of 7 days or more were counted separately, irrespective of any similarity of symptoms. In addition to symptom-based analyses, the results were also assessed in terms of symptom-free days in each group and absences from school or college.

Table 1 shows the total number of symptoms recorded. The AA supplemented groups had a 14 to 21% reduction in the total symptoms recorded which for the combined groups (i.e., males and females) was statistically significant ($P < 0.05$). The results in Table 2 indicate the relative occurrence of short term episodes (Table 2A) and longer ones (Table 2B); AA supplementation significantly increased the number of 'episode free subjects'

TABLE 1
Total number of symptoms recorded in the three groups during the survey

	Males			Females			Combined		
	Synthetic drink	Orange juice	Synthetic drink	Synthetic drink	Orange juice	Synthetic drink	Synthetic drink	Orange juice	Synthetic drink
Vitamin C (mg/day)	0	80	80	0	80	80	0	80	80
No. of participants	61	62	71	51	56	49	112	118	120
Total symptoms recorded in group during test period[a]	1452	1179	1343	1368	1264	1132	2820	2443[b]	2475[b]
Symptoms/participant during test period[a]	23.8	19.0	18.9	26.8	22.6	23.1	25.2	20.7	20.6
Percentage reduction		20.1	20.5		15.8	13.9		17.8	18.1

[a] This is the sum total of all the symptoms recorded (see text for list of symptoms); during periods of heavy infection participants frequently recorded more than one symptom on a single day. [b] Difference between mean and mean for control group significant ($P < 0.05$).

TABLE 2
Duration and number of episodes of illness

No. of episodes	Males			Females			Combined		
	Synthetic drink	Orange juice	Synthetic drink	Synthetic drink	Orange juice	Synthetic drink	Synthetic drink	Orange juice	Synthetic drink
	Vitamin C (mg/day)			Vitamin C (mg/day)			Vitamin C (mg/day)		
	0	80	80	0	80	80	0	80	80
A. Distribution of short episodes (1–2 days)									
0	19	27	38[a]	20	15	14	39	42	52
1	23	25	22	19	24	17	42	40	39
2	9	7	7	6	12	15	15	19	22
3 and more	10	3	4	6	5	3	16	8	7
B. Distribution of longer episodes (3–5 days)									
0	20	29[a]	37[b]	29	22	22	49	51	59
1	18	23	23	15	26	16	33	49	39
2 and more	23	10	11	7	8	11	30	18	22

[a] Difference between group and control for total episodes in each group, significance $P < 0.05$. [b] Difference between group and control for total episodes in each group, significance $P = 0.01$.

TABLE 3
Symptom-free days during period of trial

	Males			Females			Combined		
	Synthetic drink	Orange juice	Synthetic drink	Synthetic drink	Orange juice	Synthetic drink	Synthetic drink	Orange juice	Synthetic drink
Vitamin C (mg/day)	0	80	80	0	80	80	0	80	80
Total number of symptom-free days	3257 (61)[a]	3526 (62)	4084 (71)	2760 (51)	3129 (56)	2673 (49)	6017 (112)	6655 (118)	6757 (120)
Mean symptom-free days per participant	53.4	58.9	57.5	54.1	55.9	54.6	53.7	56.4	56.3
percentage increase		6.6	7.7		3.3	0.9		5.0	4.8

[a] Figures in parentheses are the numbers in each group.

TABLE 4
Absences from school/college during period of trial[a]

No. of absences (days)	Males			Females			Combined		
	Synthetic drink	Orange juice	Synthetic drink	Synthetic drink	Orange juice	Synthetic drink	Synthetic drink	Orange juice	Synthetic drink
Vitamin C (mg/day)	0	80	80	0	80	80	0	80	80
0	41	45	57	24	30	20	65	75	77
1–2	10	9	7	14	18	13	24	27	20
3 or more	10	8	7	13	8	16	23	16	23
χ^2		0.49	2.86		7.38	5.25		7.24	4.54

[a] More than 50% of the subjects had no absences for illness; a frequency distribution was formed for days off and analyzed by χ^2, combining adjacent frequencies where necessary.

in males ($P < 0.05$ for orange juice, $P < 0.01$ for synthetic drink).

The apparent increase in symptom-free days associated with supplementation did not attain statistical significance (Table 3). "Days absent" (Table 4) were only included in the analyses if a concomitant respiratory condition was clearly indicated. As more than 50% of the participants recorded no absences during the period of the study the frequency

distribution of absences was analyzed by χ^2, combining, where necessary, adjacent frequencies. However, there was no significant difference associated with AA supplementation. There is some evidence that a period of 3 weeks elapses before tissue "saturation equilibrium" of AA is attained with a daily intake of 80 mg (9). The data used in Tables 1 to 4 were therefore reanalyzed by omitting the results for the first 3 weeks of the trial; the results were not significantly different from those obtained over the full 10-week period.

Discussion

The percentage of the participants who completed the trial (97%) was substantially higher than that reported in earlier surveys where percentage withdrawals of up to 25% have been reported (13, 14). The structure of the survey ensured that the supplements were taken regularly and at the correct level. Previous surveys have often relied heavily on participants receiving sufficient supplement for the whole study at the beginning.

The overall reduction in symptoms associated with a dietary AA supplement is quantitatively similar to that reported in a number of earlier studies, in some of which considerably larger intakes of AA were used (2, 13–15). Males appeared to benefit more than females for supplementation, particularly when the results were analyzed in terms of episode duration. Clegg and Macdonald (13) reported that males benefited more than females from AA supplementation. Females, have, in general, higher blood AA levels than males and may respond less clearly to supplementation with AA.

The essential difference between the "natural" (i.e., fruit juice) and synthetic forms of AA is that natural sources of AA contain flavonoids that can potentiate the activity of AA in experimental animals. However, previous clinical studies have indicated that flavonoids, either alone or in combination with AA, fail to modify the onset and course of the common cold (16, 17), and this was confirmed in the current study. The reduction in total symptoms and other benefits of AA supplements occurred independently of the source of the AA.

The results of the present study indicate only a small effect of AA supplementation on the symptoms of the common cold, which barely attains statistical significance. It is possible that AA is effective against only a small proportion of common cold viruses; or there may be genetic or population factors resulting in a partial response to AA prophylaxis. AA breakdown products or metabolites may be more important in prophylaxis than AA itself. Such a secondary relationship could produce a variable and poorly defined response to any AA treatment. It is also possible that only subjects who are deficient of ascorbic acid in a population would respond clearly to AA supplementation.

A combination of these factors could explain the poorly defined general response to AA treatment and the inconsistencies reported sometimes by the same groups of workers (12, 18). The significance of AA catabolites and possible AA-virus relationships require further investigation. Patients with altered immune mechanisms, in whom the prophylaxis of the common cold is critical, may also respond more clearly, as ascorbic acid is known to induce a rise in IgG and IgM levels (19). The results do not appear to support the widespread use of prophylactic AA supplements in the well-nourished young adult; careful attention to diet, and perhaps the use of moderate supplementation of fruit juice, would appear to supply the required AA intake.

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