High dose ascorbic acid in Nigerian asthmatics

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Summary. Forty-one asthmatic patients in remission were randomly allocated to two treatment groups in a double-blind trial. One group took 1 g of ascorbic acid as one effervescent tablet once daily and the second group took a matching placebo. The asthmatics were selected from those attending the Asthma Clinic. One criterion for selection was the increase in exacerbation during the rainy season. These exacerbations were precipitated by respiratory infection.

After 14 weeks, an assessment of the severity and rate of attacks showed that those on ascorbic acid suffered less severe and less frequent attacks of asthma during the study period. Plasma ascorbic acid estimations showed a significant rise in the level in those taking ascorbic acid over those on placebo ($P < 0.01$). Cessation of ascorbic acid in the group taking it increased attack rates.

It is concluded that high dose ascorbic acid is probably a good prophylaxis in some bronchial asthmatics.

Introduction

Large doses of ascorbic acid have been shown to be effective prophylaxis against the common cold (Wilson and Loh, 1973; Pauling, 1970; Anderson *et al.*, 1972). Linus Pauling (1971) summarised the evidence in favour of this contention. Some workers have not confirmed this (Walker *et al.*, 1967; Schwartz *et al.*, 1973). Coulehan *et al.* (1974, 1976) got conflicting results in their studies in Navajo school children. Ascorbic acid has also been used with some benefit in the management of wounds and bed sores (Taylor *et al.*, 1974 a & b).

Physiologically, ascorbic acid has some effect on connective tissues (Hume and Weyers, 1973) collagen and cell membrance (Boyd, 1970). It has been demonstrated to have anti-histaminic effect in man; broncho-constriction induced by histamine was significantly reduced by a previous administration of ascorbic acid (Zuskin *et al.*, 1973).

On pharmacological and physiological considerations, therefore, a role can be found for ascorbic acid in asthma. This can either be a prophylactic role or even as part of the therapy of an attack.

Respiratory infections are known to precipitate asthmatic attacks in predisposed persons. Most respiratory infections start as an upper respiratory tract infection. Viruses of the upper respiratory tract have been found associated with pneumonia in children (Clarke, 1973) and exacerbation of chronic bronchitis (Eadie *et al.*, 1966; Stenhouse, 1976). These facts made it appear possible that ascorbic acid could have a role in the prophylaxis and/or therapy of

asthma. It was on the basis of these considerations that a study was undertaken to determine the value of ascorbic acid, in large doses, in asthma.

Materials and Methods

The subjects were asthmatics attending the asthma clinic run by one of us (C.O.A.). They were all known asthmatics who had had the disease for at least four years. They were all in remission at the time they entered the study. Clinical examination at this time showed clear lung fields. Most were on maintenance therapy with bronchodilators. One was on a small dose of steroids (5 mg of prednisolone daily) on entry into the study. They were all left on whatever drugs sustained their remission. New asthmatics were admitted only after they had been treated for the exacerbations and had gone into remission. They had previous histories of increased attacks during the rainy season. Their attacks were precipitated, in all cases, by respiratory infections. These started as sore throat and a dry cough.

The study was done as a double-blind trial. Two identical effervescent tablets were provided for the trial (by courtesy of Roche (Nig.) Limited) and labelled A or B. Selection of subjects for the study was simple. Any person who agreed to participate after a full explanation of the procedure, was accepted, unless he/she lived outside the city. If he could attend at regular intervals, including reporting to the hospital emergency service in the event of a severe attack at any time of the day or night, he was accepted. Those with complicating bronchitis and/or emphysema were not admitted into the study group.

Two groups were established on the basis of what they were taking - Groups A and B. Admission to the group was done randomly. They were not matched for age or sex. Visits to the clinic were arranged at 4 weekly intervals, except the last visit, but each patient was encouraged to visit the hospital emergency service (which was open 24 hours a day) in the event of a severe attack. They were also told to take note of the frequency of attacks in the interval between attendances at the clinic. The tablets were to be dissolved in a small quantity of water and taken once daily. The study lasted 14 weeks. It was conducted during the rainy season when all the subjects usually experienced more frequent attacks.

Each patient had the following investigations done on admission to the trial. Haemoglobin or Packed Cell Volume (PCV), white blood cell count (WBC) with eosinophil count (%), stool miscroscopy, Peak Expiratory Flow Rate (PEFR), Plasma Ascorbic Acid.

The PEFR was estimated at the onset of the study; this was not repeated at monthly visits for the purpose of the study. The PEFR was used instead of FVC for convenience. The plasma ascorbic acid was done by the dye method (2-6 dichlorophenol indophenol titration as described by Varley (1964) using trichloroacetic acid as a precipitant). The plasma ascorbic acid was repeated at every visit till the termination of the trial. The estimation was done within 2 hours of drawing blood. It was not a fasting blood sample though all patients had not eaten anything for at least 2 hours by the time of venepuncture.

The patients were assessed clinically. Patients were asked about attacks in between attendances at the clinic and these attacks were recorded, according to patients' description, as mild, moderate or severe. The severe attacks were those that necessitated emergency attendance at the hospital. The mild ones consisted of some increase in wheezing and breathlessness or where there was no wheeze or breathlessness before, the development of the same. The moderate attacks were those that necessitated the use of inhalers more frequently - more than three times a day, in addition to regular medications, if they were on any medication. The introduction of previous medication on a regular basis put the attack as moderate in those who were not on any medication in remission.

Results

There were 41 patients in the study, 22 males and 19 females. Of the patients 22 were in group A and 19 in group B. The average age for the patients was 27.1 years. The average age for group A was 26.5 with a range of 15-42. The average age for group B was 27.8 with a range of 15-46. The male: female ratio in the two groups A & B was 12:10 and 10:9 respectively. The PEFR was similar in both groups with a mean of 274.1 in A (range 200-340) and 279.2 in B

Table. Plasma ascorbic acid in groups A & B

Sample	*Ascorbic acid (mg%)*		*Statistical significance of rise of AA in groups A & B (student T-test)*
	Group A	*Group B*	
1st sample pre-study	0.9 ± 0.37	1.18 ± 0.44	$0.10 < p < 0.20$
2nd sample 4 weeks from onset of study	2.16 ± 0.62	1.24 ± 0.4	$p < 0.01$
3rd sample 8 weeks from onset of study	2.36 ± 0.69	1.47 ± 0.7	$p < 0.01$
4th sample 12 weeks from onset of study	2.62 ± 0.76	1.52 ± 0.6	$p < 0.01$
5th sample 14 weeks from onset of study	2.72 ± 0.64	1.5 ± 0.52	$p < 0.01$

(range 200-325). The genotype and the stool microscopy were also done but results could not be obtained for all patients especially for stool microscopy. The eosinophil count was abandoned at the early stages of the study because results were thought to be unreliable. The plasma ascorbic acid estimations are shown in the table. The values represent the mean of the values for all patients in each group as checked on first admission to study and 4,

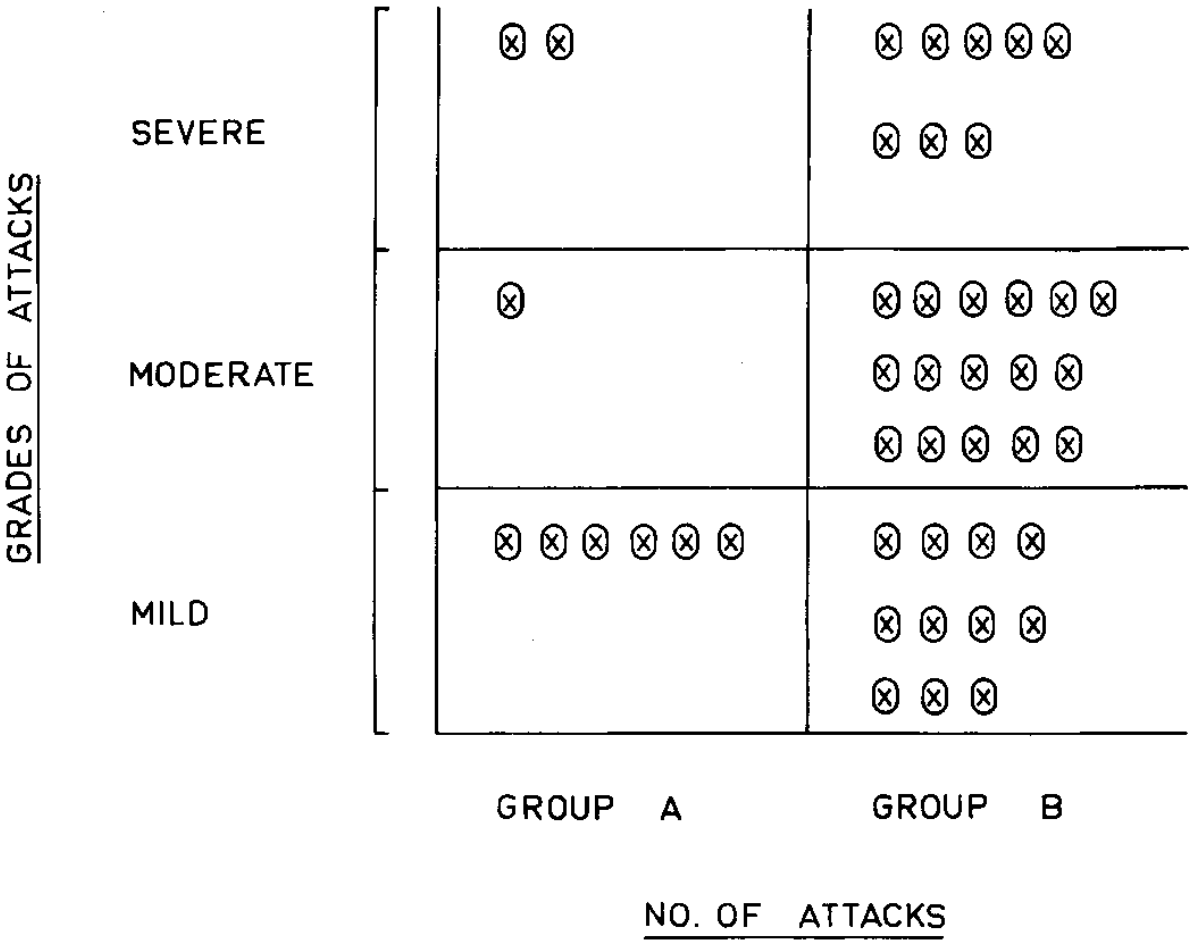

Figure. Frequency and severity of attacks in patients studied.

8, 12 and 14 weeks later. On average, there was a rise in plasma ascorbic acid in group A, after the commencement of therapy, which was maintained throughout the period of study. Group B showed no significant rise in the plasma ascorbic acid level throughout the period of study. It was concluded that A was Ascorbic Acid and B the placebo; this corresponded with the key when broken.

The figure shows the attacks experienced by individual patients throughout the study; the attacks have been represented according to severity. An attempt has been made to show the number of attacks experienced by each group, but not by individual patients. The two in group A who had severe attacks had one severe attack each. One did not have any further attack moderate or mild, while the second one had two more mild attacks during the period of study. Those in group B who had mild or moderate attacks had more than three such attacks each. The severe ones occured more than once in each case and one had to be admitted. On the whole, there were 9 attacks in Group A and 35 attacks in Group B. The occurrence of attacks in Group A patients on cessation of therapy at the end of the study has not been shown. This occured in all those in Group A who did not have any attack during the period when they took ascorbic acid. By the second visit after the cessation of therapy, all the patients in group A had suffered at least one mild to moderate attack. No patient in either group suffered any side effects from ascorbic acid or placebo.

Discussion

Several reports have appeared in the literature on the use of ascorbic acid (in high dose) in the prophylaxis against the common cold. Chalmers (1975) evaluated the evidence in his summary of the trials. Hunt (1938) reported on a trial on 25 asthmatic patients. Another report was quoted by Zuskin *et al.* (1973). Any study on asthma has to take into consideration the variability of the condition, spontaneous relief in some cases and the multifactorial nature of the precipitating factors. Some attempts were made to counter some of these factors in this study. For example, those selected were those who admitted and were known to having more attacks during the rainy season. This is during the months of April to September. Other factors remained the same.

From the results of the study, it is reasonable to conclude that ascorbic acid in the dose given (1 g daily) has been effective in sustaining remission. The plasma ascorbic acid level in those taking ascorbic acid was higher than in those taking placebo. Both groups started at about the same ascorbic acid plasma level. The normal value of the plasma level in the Nigerian adult is 1.22-1.40 mg/100 ml (Nutritional Survey, Republic of Nigeria, 1961). The difference between the two groups at the 4 dates on which estimations were done (excluding pretrial estimation) were statistically significant ($P < 0.01$).

The question that could be asked was whether the rise in plasma ascorbic acid level could be correlated with maintenance of remission and lack of attacks. The study was designed in such a way there that were only two obvious variables - precipitating factors in attacks and ascorbic acid levels in the blood. In the selection of patients, only those who had frequent attacks during the rainy season and whose attacks were preceeded by respiratory infection were selected. Respiratory infection was inferred if patient had a sore-throat and cough before onset of tightness in the chest. By doing so, a deliberate selection criterium was built into the study.

This allowed the ascorbic acid level as the one variable which could be manipulated. If this design was accepted, then the changes in the rate of exacerbation, if any, could be ascribed to any changes in the plasma level of ascorbic acid. A cross-over trial could have given more meaning to the results but this could not be carried out as the seasonal criterion would have ceased to operate: the period covered by the trial would have exceeded six months. It was therefore decided to observe Group A subjects during the period after cessation of therapy with ascorbic acid. There was a remarkable recurrence of attacks within eight weeks of

cessation of administration of ascorbic acid. This recurrence could not be attributed, solely, to withdrawal of ascorbic acid; it can only be said to have probably contributed to it. Ascorbic acid in large doses, up to 1 g daily, as used in this study, was without any important side effect. Its administration in asthma could therefore be recommended. In fact workers using same for common cold research gave as much as 2-4 g daily. The long term effect of ascorbic acid is not yet known, thought its acidification of urine and possible mobilization of calcium from bone could result in renal stones (Thornton and Omdahl, 1969). It appears that once daily dose regime can maintain a rise in the plasma level even though any high dose of ascorbic acid is known to be largely excreted in about five hours (Grollman, 1960). The peak flow rates were all above 200 litre/min. except in two cases; these were amongst the oldest (ages 35 and 46 years). Elebute and Femi-Pearse (1971) found the values in normal Nigerians to be 482 ± 83.3 for males and 385.6 ± 65.7 for females. It is known that asthmatic have lower levels of respiratory function than normals even when they are in remission (Palmer and Kelman, 1975). This could account for the values obtained. The other factor is lack of experience on the part of patients in the use of the peak flow metre. All patients were non-smokers.

The estimation of the haemoglobin genotype in the patients was undertaken as a routine exercise. The significance of the findings cannot be easily explained. It is interesting to note that none was homozygous for the S haemoglobin and that only four were heterozygous. The ratio for the heterozygous S haemoglobin in Nigerians is about 20% (Evans 1944).

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