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Brief Communication

OXYRADICALS AND MULTIVITAMIN TABLETS

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Abstract—Ingestion of a single multivitamin tablet leads to hydroxyl radical production equivalent to a radiation dose rate of 53 Gy/h.

Keywords—Vitamin C; Ascorbic acid; Salicylic acid; Hydroxyl radical; Hydroxyl radical scavenger; Free radicals

Antioxidants, such as vitamins C and E, are important for the prevention or termination of oxyradical reactions implicated in many diseases.[1] Vitamin C plays a paradoxical role in that it both inhibits and promotes oxyradical reactions. On the one hand, it reacts very rapidly with the hydroxyl radical,[2] such that small concentrations scavenge the hydroxyl radical effectively. On the other hand, in the hydroxylating Udenfriend system[3] ascorbate reduces ferric to ferrous ion, which autoxidizes and forms superoxide. Via dismutation and the one-electron reduction of hydrogen peroxide, the hydroxyl radical is produced, as suggested nearly four decades ago.[4]

The presence of both iron and ascorbate in multivitamin tablets might lead to hydroxyl radical production in the stomach. In this brief communication we attempt to estimate how much of this radical is formed. The conversion of salicylic acid to dihydroxybenzoic acids is used to estimate hydroxyl radical production.[5–7] As shown in Fig. 1, a considerable flux of this radical is observed upon dissolution of a single tablet in 100 ml dilute hydrochloric acid, pH 2, the approximate acidity of the empty stomach. While it would be more realistic to have various proteins present, none were added. At low pH, Fe(II) is not bound to proteins and these have, therefore, no influence on the formation of hydroxyl radicals. However, proteins would interfere with the determination, due to their diffusion-limited rate of reaction with the hydroxyl radical.[2] Surprisingly, a tablet supposedly without iron produced nearly identical amounts of hydroxyl radicals. This is most likely due to contamination by iron or other redox-active metals. Without oxidants, two hydroxyl radicals are required to form one dihydroxybenzoate, whereas in the presence of oxidants, such as oxygen, the number is closer to one.[7] For a conservative estimate we assume that one hydroxyl radical yields one dihydroxybenzoic acid. The changes in concentrations of 2,3- and 2,5-dihydroxybenzoic acid with time suggest a rate of more than 16 μM/h at the beginning of the experiment. This rate of hydroxyl radical production is equivalent to that produced by ionizing radiation at a dose rate of 53 Gy/hr. In the absence of food in the stomach hydroxyl radicals will react with the mucosal lining, pepsin, and pepsinogen. A well-characterized hydroxyl radical scavenger, 1.0 M ethanol, greatly reduced the rate of formation of dihydroxybenzoates (see Fig. 1). Production of hydroxyl radicals is likely to diminish when, upon ingestion of food, the pH rises and iron becomes bound to proteins and forms inactive hydroxo-complexes. Similar considerations apply to the intestine.

The results presented here indicate that (a) harmful oxyradicals may be generated during a process that is not associated with a disorder or a disease, but that is considered necessary to maintain good health, and (b) that the stomach can tolerate a high flux of oxyradicals. Nevertheless, intake of vitamin C should be combined with food to limit or prevent injury.

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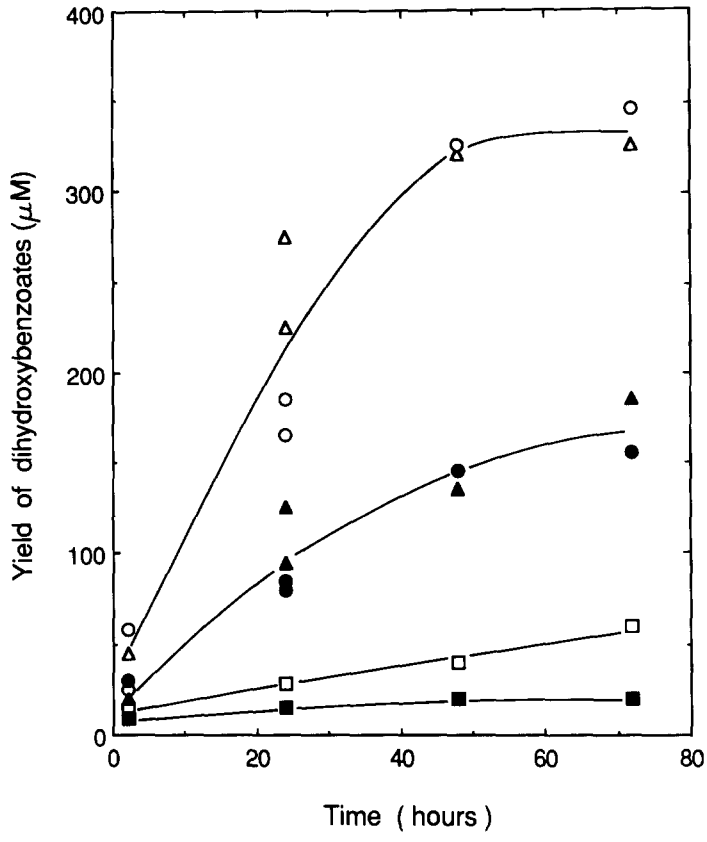

Fig. 1. Hydroxyl radicals were measured by their ability to hydroxylate salicylic acid, which leads to 2,3- and 2,5-dihydroxybenzoic acid. (△, -Fe; ○, +Fe; □, +Fe, +1 M ethanol.) Open symbols pertain to 2,3-dihydroxybenzoate, and closed symbols to 2,5-dihydroxybenzoate. One generic multivitamin tablet, with or without 18 mg iron in the form of Fe(II) complexed to fumarate was dissolved in 100 mL of an air-saturated 10 mM salicylate (Sigma) solution acidified to pH 2 with hydrochloric acid (Baker, analyzed reagent quality). The tablets contain 60 mg ascorbate. As shown, there is not much difference in hydroxyl radical production between iron-free and iron-containing multivitamin tablets, and a single line was drawn. The determination of dihydroxybenzoates by high-pressure liquid chromatography has been described earlier.[7] No dihydroxybenzoate products were observed when vitamin tablets were omitted (not shown).

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