



## Client Information Resources

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### **Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues**

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Human pharmacokinetics data indicate that i.v. ascorbic acid (ascorbate) in pharmacologic concentrations could have an unanticipated role in cancer treatment. Our goals here were to test whether ascorbate killed cancer cells selectively, and if so, to determine mechanisms, using clinically relevant conditions. Cell death in 10 cancer and 4 normal cell types was measured by using 1-h exposures. Normal cells were unaffected by 20 mM ascorbate, whereas 5 cancer lines had EC50 values of <4 mM, a concentration easily achievable i.v. Human lymphoma cells were studied in detail because of their sensitivity to ascorbate (EC50 of 0.5 mM) and suitability for addressing mechanisms. Extracellular but not intracellular ascorbate mediated cell death, which occurred by apoptosis and pyknosis/necrosis. Cell death was independent of metal chelators and absolutely dependent on H<sub>2</sub>O<sub>2</sub> formation. Cell death from H<sub>2</sub>O<sub>2</sub> added to cells was identical to that found when H<sub>2</sub>O<sub>2</sub> was generated by ascorbate treatment. H<sub>2</sub>O<sub>2</sub> generation was dependent on ascorbate concentration, incubation time, and the presence of 0.5-10% serum, and displayed a linear relationship with ascorbate radical formation. Although ascorbate addition to medium generated H<sub>2</sub>O<sub>2</sub>, ascorbate addition to blood generated no detectable H<sub>2</sub>O<sub>2</sub> and only trace detectable ascorbate radical. Taken together, these data indicate that ascorbate at concentrations achieved only by i.v. administration may be a pro-drug for formation of H<sub>2</sub>O<sub>2</sub>, and that blood can be a delivery system of the pro-drug to tissues. These findings give plausibility to i.v. ascorbic acid in cancer treatment, and have unexpected implications for treatment of infections where H<sub>2</sub>O<sub>2</sub> may be beneficial.