Modeling and Kinetics of Gastric Nitrosation

by

William Robert Licht

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Abstract

It has been suggested that the formation of N-nitroso compounds in the stomach, from nitrite and various amine or amide precursors may be important in the etiology of cancer in the stomach, liver, and perhaps other organs. The overall objectives of this research were to develop a mathematical model to predict the gastric rates of formation of N-nitroso compounds under various experimental or environmental conditions, and to use this model to examine factors which might increase or reduce the exposure to carcinogens formed in the stomach.

The reaction between nitrite and proline to form N-nitrosoproline (Npro), a non-carcinogenic N-nitrosamino acid, was studied in vitro and in the canine stomach. The catalytic effects of SCN^- and Cl^- and the inhibitory effects of ascorbic acid (ASC) were examined. Kinetic studies demonstrated that the stoichiometry of the reaction between nitrite and ASC is not fixed (as previously suggested), but is determined by competition between oxidation of NO by dissolved oxygen (recycling the nitrite into a reactive form) and physical removal of NO from the system (mass transfer across the gas-liquid interface or the gastric mucosa). At lower mass transfer rates, at lower pH, and/or in the presence of SCN^- or Cl^-, more ASC is consumed by a given amount of nitrite. A kinetic model was developed to describe each of these features. Experiments in the dog showed that nitrite is rapidly lost from the stomach and that adsorption is the primary mechanism responsible for the drop in the nitrite concentration. Adsorption was shown to be first order in total nitrite, weekly dependent on pH, and unaffected by SCN^- or Cl^-. A model was developed to describe the concentrations of nitrite and other species in the stomach as a function of time, including the effects of absorption, reaction, dilution and secretions. This model was combined with the kinetic model to accurately describe NPro formation in the canine stomach without adjustable parameters. Experiments with added ASC showed that the effective permeability of NO and O_2 is the same as that for total nitrite.

The gastric nitrosation model was adapted to humans by developing, from the literature, descriptions of human physiologic features which affect gastric nitrosation: gastric volume, pH, $[SCN^-]$, dilution, nitrite absorption, and nitrite secretion. The sensitivity of the model to each of these features was tested by describing a range of physiologically realistic values. In agreement with published values, the model predicts that 89 nmol of $[^{15}N]$Npro are formed in the stomach following an experimental protocol in which individuals consume 3.5 mmol $[^{15}N]$nitrate followed 1 hour later by 4.3 nmol proline. When 500 mg of ASC is included with the nitrate dose, for these same types of

experiments, ~0.6 nmol of [^{15}N]Npro are predicted to be formed, in agreement with experimental resuls. Secretion of ASC is not necessary to explain this finding. Under "typical" conditions (precursors not administered, but present at common dietary levels), the model predicts <nmol/day of intragastric Npro synthesis, an order of magnitude smaller than typical levels of NPro excretion. This demonstrates that Npro excretion is not a good marker of gastric nitrosation. The model predicts that 14 pmol/day of N-nitrosodimethylamine (NDMA) is formed in the stomach of an indviudual consuming a diet that is high in dimethylamine (DMA) but otherwise "typical". This is two orders of magnitude smaller than the estimated dietary exposure, and suggests that gastric NDMA synthesis is not important in the etiology of gastric or other cancer. Due to the lack of information about the concentrations of amine and amide substrates in the diet and secretions which enter the stomach, the model cannot be used to predict the amount of intragastric synthesis of other N-nitroso compounds. However, the model results are presented in a form, which will facilitate estimates of intragastric synthesis of other N-nitroso compounds, as this information becomes available.

Thesis Supervisor: William M. Deen
Title: Professor of Chemical Engineering