Pseudosepsis Syndrome, Multiple-System Organ Failure, and Chronic Salicylate Intoxication

Inhibition of Regulatory Eicosanoids?

In the quest to ameliorate the cardinal effects of inflammation, Americans consume up to 16,000 tons of aspirin per year in transactions involving 80 million tablets and $2 billion.1 Acetylsalicylic acid (ASA) is the gold standard against which nonsteroidal anti-inflammatory drugs (NSAIDs) are compared. Although highly effective in modulating inflammation, the exact mechanisms of action of ASA remain unclear. However, such an understanding is central in determining how ASA intoxication paradoxically induces inflammatory processes that escape host regulatory control to enhance tissue injury.2,3

Many forms of tissue damage are due to production of cyclooxygenase pathway metabolites.4 Most mammalian cells possess the requisite microsomal enzymes for prostaglandin (PG) biosynthesis. By acetylyating a serine residue, ASA inhibits cyclooxygenase-mediated transformation of arachidonic acid to PGG$_2$. The causal role of PGs in inducing inflammation supports the hypothesis that suppression of excessive PG production by ASA or NSAIDs is beneficial during pathologic conditions ranging from rheumatic disorders to septic shock.5,6 Both ASA and NSAIDs may have anti-inflammatory effects by additional mechanisms, including binding to cell membranes1 and receptor-linked G proteins.6 Why, then, is salicylate intoxication associated with proinflammatory effects?

In contrast to the reversible toxicity associated with acute ASA overdose, chronic salicylism is characterized by protean clinical manifestations, frequent delayed diagnoses, and significant morbidity and mortality.5,8 In this issue, Leatherman and Schmitz (see page 1391) retrospectively document the clinical course of five patients in whom chronic salicylate intoxication strongly simulated a sepsis syndrome. As acknowledged, certain features of this symptom complex (eg, fever, ARDS, and acute renal failure) have been characterized previously.2,3 However, attention is drawn to the leukocytosis, shock, and multiple organ failure.

By what mechanisms can these observations be explained? Exclusion of sepsis is problematic, since sepsis syndromes can arise and resolve with antimicrobial treatment in the absence of microbiologic proof of infection.7 Furthermore, high levels of salicylates increase endothelial permeability, as typified by salicylate-induced pulmonary edema.3 Therefore, one cannot exclude ASA-induced increases in gastrointestinal mucosal permeability generating an endogenous endotoxemia. Assuming that salicylate did not interfere with cytokine measurements, the increased serum levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 in two patients deserve comment.

First, while recognized as mediators of Gram-negative sepsis,8-10 these cytokines can be released in response to tissue injury.11 Second, eicosanoids act as second messengers for several tissue-specific effects of TNF-α, IL-1β, and IL-6. Pharmacologic inhibition of the cyclooxygenase pathway blocks cytokine-eicosanoid interactions and blunts several pathophysiologic effects of cytokines.12 However, such inhibition augments circulating cytokine levels.13 Spinazi et al14 found increased TNF-α and IL-6 concentrations after endotoxin challenge in ibuprofen-pretreated humans despite amelioration of clinical responses. Similarly, a 4.2-fold increase in TNF-α occurred in other ibuprofen-pretreated subjects following endotoxia.15 This appears secondary to interruption of dose-dependent inhibitory feedback of PGE$_2$ on cytokine gene expression.16-18 The clinical consequences of altered cytokine responses by anti-inflammatory agents are incompletely understood. Conceivably, sustained suppression of regulatory eicosanoids, such as PGE$_2$, by chronically elevated ASA levels partially accounts for the clinical manifestations of salicylate toxicity described in the current report. For example, elevated plasma cytokine concentrations are found in Reye’s syndrome.19 Sustained alterations in cytokine responses during chronic salicylate intoxication and transient changes during therapeutic inhibition of the cyclooxygenase pathway may thus represent two different points along an immunophysiologic continuum. Both phenomena clearly require more investigation.

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Aerosolized Pentamidine Prophylaxis

Several years ago, oral trimethoprim-sulfamethoxazole prophylaxis was shown to prevent Pneumocystis pneumonia in AIDS patients with Kaposi’s sarcoma. Prophylaxis became standard for human immunodeficiency virus-infected patients with low CD4 lymphocyte counts (eg, <200/cu mm). However, frequent adverse reactions attributed to trimethoprim-sulfamethoxazole invited searches for other agents and methods of prophylaxis. Administration of pentamidine by aerosol inhalation was found to produce concentrations of pentamidine in bronchoalveolar lavage fluid much higher than those obtained after intravenous administration. Low plasma levels indicated little systemic absorption, which appeared to account for the lack of systemic toxicity. Aerosolized pentamidine has become the prophylactic method of choice at some centers, further justified by recently reported randomized studies which found that aerosolized pentamidine prevented both relapse of Pneumocystis pneumonia and the first episode of Pneumocystis pneumonia in patients with CD4 counts lower than 200/cu mm.

Advantages of administering pentamidine by aerosol include (1) documented effectiveness; (2) lack of serious toxicity for the large majority of patients; (3) easy assessment of compliance; and (4) cost-effectiveness when compared to the costs of treating Pneumocystis pneumonia.

Aerosolized pentamidine has not proved to be a panacea, however, as observations of an adverse nature have either suggested or demonstrated problems with prophylactic aerosolized pentamidine. Limitations and complications include (1) failure rates in the range of 5 to 30 percent when patients were followed up for 6 to 18 months, compared with rare failures in patients who received a systemic prophylactic agent (eg, trimethoprim-sulfamethoxazole); (2) extrapulmonary Pneumocystis disease; (3) doubts concerning efficacy in patients with frequent relapses or with altered pulmonary anatomy or physiology that might result in ineffective delivery of aerosolized pentamidine to parts of the lung (eg, in patients with chronic obstructive lung disease); (4) clinical and radiographic alterations in the presentation of Pneumocystis pneumonia to “atypical” forms (eg, pleural and upper lobe disease); (5) potentially life-threatening pneumothoraces, which might also reflect active Pneumocystis disease and thus failure of aerosolized pentamidine; (6) difficulty in diagnosing relapses of Pneumocystis pneumonia by examination of bronchoalveolar lavage specimens and transbronchial biopsy specimens from patients who received aerosolized pentamidine; (7) high cost of pentamidine, especially in comparison with oral agents, such as trimethoprim-sulfamethoxazole; (8) need for special facilities and trained personnel to administer aerosolized pentamidine; (9) potential that aerosolized pentamidine administration will promote spread of respiratory pathogens, especially Mycobacterium tuberculosis; environmental exposure of health-care workers and others to pentamidine with the possibility of untoward reactions or consequences (eg, teratogenicity); and (11) involvement of regulatory agencies in the administration of aerosolized pentamidine, with encroachment of attendant bureaucratic duties on professional time, threat of fines, and unfavorable publicity. Some of these problems, such as pneumo-