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Antipyretic Therapy, ibuprofen, and acute viral infection

Aspirin, ibuprofen, and NSAID may increase severity and infectivity of viral respiratory infection.

Paul Bergner
Editor, *Medical Herbalism*

Controversy arose last month after a French health minister advised that patients with suspected COVID-19 infection not take ibuprofen or other non-steroidal-anti-inflammatory-drugs (NSAID), because it may promote more severe infection. This was soon criticized, and the World Health Organization and Centers for Disease Control issued statements saying there was no data to support the assertion, and that people should consult with their doctor if they have questions about their medications.. Some front line clinicians are paying attention however. The continuously updated online *Internet Book of Critical Care (IBCC),* in its chapter on COVID-19 advises critical care physicians to avoid all non-steroidal anti-inflammatory drugs (NSAID) in COVID-19 infection, because of their potential to up regulate the virus-binding receptors on cells and worsen the infection. Front-line clinicians do not always wait for big data from researchers before making clinical decisions that may minimize harm. NSAID may also cause kidney toxicity, with kidney complications common in serious COVIC-19 infection. Even if slam-dunk science specifically on NSAID and COVID-19 is not to be had, there is at least some scientific basis to avoid the use of NSAID in viral infections. NSAID in general, and in some cases, ibuprofen specifically, promote the worsening of respiratory and other infections. Each trial identified here showed the same trend toward longer duration of infection, more severe symptoms, increased viral shedding, or a more lethal outcome in animals or humans who took NSAID during experimental viral infection. These drugs suppress inflammation, one expression of immunity, and in doing so they suppress immune resistance to viral infection.

Basic Science

NSAID and cyclooxygenase

NSAID inhibit the enzyme cyclo-oxygenase (COX) which mediates the production of immune-enhancing Series 2 prostaglandins. These in turn promote immunity through effects on the antigen-recognizing B-Lymphocytes, and on antibody production. COX also promotes the production of interferon, one of the body's chief methods of detecting virally-infected cells. (Pottahill et al.)

In-vitro research

NSAID and reduced antibody production

The theoretical effects of NSAID on immune function were affirmed in lab dish studies, which found that ibuprofen and other widely used NSAID inhibited the production of antibodies from human immune cells. They conclude: “The implications of this research are that the use of widely available NSAIDs after infection or vaccination may lower host defense.” (Bancos et al.)

In-vivo animal trials

NSAID reduce humoral immunity and interferon production

The same researchers as above then tested for the effect of NSAID on an experimental virus infection in mice. They found that in mice with drug-suppressed COX, the number of B-lymphocytes competent to recognize the infection was reduced, and corresponding antibody production was reduced. The virus titers in the medicated mice were 70-times higher than in the control mice. Interferon-secreting T-helper lymphocytes were likewise reduced. The authors conclude: “chronic use of NSAIDs . . . blunt the ability of B cells to produce anti-viral

antibodies, thereby making vaccines less effective and possibly increasing susceptibility to viral infection. (Bernard et al.)

Aspirin and NSAID may promote mortality in pneumonia
Rabbits infected with *Pasteurella* a common cause of pneumonia, had a 29% mortality rate. One group had their fever lowered by 1.5 degrees with salicylates, and had 100% mortality. Salicylates alone in uninfected rabbits caused no mortality. Treated rabbits had a lower white blood cell count than their infected but untreated counterparts, and their lung and liver bacterial counts were higher. (Vaughn et al 1980, 1981)

Influenza mortality increased
On meta-analysis of 8 trials in animals, the use of aspirin, acetaminophen, or diclofenac increased mortality from experimental influenza infection by 34%. (Eyers et al.)

Pneumonia mortality doubled
In a meta-analysis of 3 animal studies, antipyretic therapy in pneumonia doubled mortality rate. The *Pneumococcus* bacterium is temperature sensitive, and lowering temperature can facilitate survival and infection by the bacterium. (Jeffries et al.)

Viral shedding increased
A group of cows were artificially infected with the RSV respiratory virus. Half were given ibuprofen. The researchers noted a increase in viral shedding, indicating the possibility of increased infection and also increased transmission to other cows. At peak of viral shedding on days 6-8 it was increased by a statistically significant 50%. The researchers said that lung pathologies were not different between the two groups, but noted that one cow in the ibuprofen group had to be euthanized due to the severity of its infection. (Walsh et al.)

Human trials

Antibody response in humans
Human trials of experimental rhinovirus infection treated with salicylates and NSAID. Lowering the fever with aspirin and acetaminophen suppressed antibody response and increased the severity of subjective symptoms. Ibuprofen had a strong similar trend (worse than placebo on every measure) but which did not reach statistical significance. Trends for all medications were for worsening symptoms, decreased antibody response, and increased viral shedding. (Graham et al.)

Duration of illness
In a retrospective observational study, some patients infected with *Influenza* or *Shigella* were given aspirin or acetaminophen. The researchers conclude “There was a striking correlation between antipyretic therapy and duration of illness in subjects infected with influenza A and Shigella sonnei.” Patients who got antipyretics were sick 3.5 days longer than those who did not (8.8 ± 2.3 days vs 5.3 ± 3.0 days) The patients infected with Shigella who took antipyretics had a trend towards prolonged duration of illness (4.6 ± 2.1 days with antipyretics vs 1.9 ± 1.6 days without). (Plaisance et al.)

Viral shedding
In 2 double-blind trials, 45 adults infected with rhinovirus were given aspirin or placebo for 5 days, beginning on the day after viral exposure (as opposed to the typical use in response to the development of symptoms). Aspirin increased the amount of viral shedding by 36% in 1 trial and 17% in the other ($P<.01$), potentially increasing the infection and also risk of spread. (Stanley et al.)

Time to healing in Varicella infection
In a randomized controlled trial evaluating antipyretic effects on the duration or severity of childhood Varicella, 31 children received placebo and 37 received acetaminophen for 4 days. Children treated with acetaminophen took 1.1 days longer to total scabbing.

Summary
Although we do not have data showing that ibuprofen, aspirin, or other NSAID will specifically worsen the course of covid-19 infection, we have plenty of data suggesting that these drugs inhibit anti-viral defenses.

Paul Bergner is director of the North American Institute of Medical Herbalism and editor of the *Medical Herbalism* journal. He has practiced nutrition and medical herbalism since 1973. He has trained more than 400 student residents in teaching clinics for clinical nutrition and medical herbalism since 1996. He has taught both medical herbalism and clinical nutrition at both the undergraduate and graduate levels of the university, and has developed and delivered more than 500 hours of Continuing Education for herbalists, nutritionists, acupuncturists, nurses, and naturopathic physicians. He is author of the *Healing Power of Garlic*, the *Healing Power of Echinacea, Goldenseal and the Immune Herbs*, *The Healing Power of Minerals and Trace Elements*, and four other books on herbalism, nutrition, ethnobotany, Chinese medicine, and naturopathic medicine.

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