Analgesic Therapy of Rheumatoid Arthritis
Part I: The Problems of Conventional Therapy

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Abstract

Although allopathic drugs such as cortisone, methotrexate, gold, sulfasalazine, and nonsteroidal anti-inflammatory drugs (NSAIDs) are effective treatments for the acute phase of rheumatoid arthritis, the therapeutic outcome remains unsatisfactory. Long-term treatment with such preparations often fails to alleviate symptoms, especially pain, and causes numerous adverse effects. The newest of these drugs, classified as selective cyclooxygenase-2 (COX-2) inhibitors, are no exception. At high doses, their selectivity declines and they begin to inhibit cyclooxygenase-1 (COX-1), which is needed to protect the lining of the stomach and small intestine. Thus, complementary therapies with more favorable or nonexistent adverse effect profiles are needed, especially since NSAIDs become ineffective against pain if taken for long periods.

Introduction

Despite application of allopathic therapy and intensive research efforts, patients with rheumatoid arthritis (chronic polyarthritis) still experience pain, premature disability, and substantial economic losses. In addition to classic corticosteroids, medications used to treat rheumatoid arthritis include antimalarial drugs such as chloroquine, sulfasalazine, oral or parental gold therapy, and methotrexate, a cytostatic agent better known for its use in cancer therapy. Experience confirms the value of early and aggressive treatment of acute-stage rheumatoid arthritis. As the illness progresses, however, initially successful therapies often are abandoned due to adverse sequelae that affect primarily the organs of hematopoiesis and/or the liver.[1-3] Nonsteroidal anti-inflammatory drugs (NSAIDs), which may not totally eliminate pain but at least reduce it, are often prescribed in addition to corticosteroids when increasing pain causes a decline in the patient's quality of life.

Adverse Effects of Corticosteroid and NSAID Therapy

Unfortunately, NSAIDs and, to a still greater extent, corticosteroids can cause severe adverse effects, especially if taken for long periods. Many patients turn to pain specialists in the hope of avoiding the adverse effects associated with such therapy (osteoporosis, Cushing's syndrome, diabetes mellitus). Prolonged treatment with only 5 mg of prednisolone is associated with an almost 50% risk of fractures of the neck of the femur. Vertebral body fractures occur five times as frequently in patients taking corticosteroids on a long-term basis.

Worldwide, NSAIDs are among the most frequently prescribed medications. They also head the list of medications with the most adverse effects. As a matter of principle, NSAIDs should be prescribed for rheumatic pain only in cases of primary or secondary inflammatory rheumatic diseases, and medications such as ibuprofen and diclofenac, which have a low risk profile for ulcers, are preferred. NSAIDS should not be prescribed in combination with high doses of steroids, however, because the anti-inflammatory effect of high-dose steroids is so great that supplementary treatment with NSAIDs is redundant. Also, treatment with steroids alone does not increase the risk of ulcers. An NSAID should be prescribed only when the steroid dose is less than the equivalent of 10 mg of prednisolone.

Risk Profile

The risk of adverse effects varies among NSAIDs. The gastrointestinal tract is affected in 90% of cases (Table 1). Potentially serious gastrointestinal complications such as gastric ulcers, bleeding, and perforations are not rare. Lesions of the mucosae are found in up to 65% of patients, erosions in up to 54%, and bleeding in up to 45%, while ulcers affect 15% to 45% and indigestion 30% to 50%. In the

Table 1. Potential Adverse Effects of NSAIDS

Gastrointestinal tract	indigestion, erosions, ulcers, hemorrhaging, perforation
Kidneys	kidney disease due to acute reduction in the rate of glomerular filtration, interstitial nephritis, nephrotic syndrome
Skin	eczema, erythema
Liver	increased liver enzymes and bilirubin, hepatitis
Organs of hematopoiesis	anemia, leukopenia, thrombocytopenia, agranulocytosis
Central nervous system	affective, cognitive, and memory disorders, double vision, tinnitus, hearing disorders
Type B adverse effects	Lyell's syndrome, Stevens-Johnson syndrome, inflammation of the optic nerve, pancreatitis, sialadenitis

United States, at least 80,000 patients are hospitalized each year due to adverse effects of NSAIDs, and approximately 10,000 to 20,000 die from sequelae of such therapy. Risk factors for gastrointestinal complications include age older than 40 years, serious rheumatic disease, high doses of NSAIDs, prior history of ulcers, smoking, and concomitant cortisone therapy.[4-6] Approximately 40% of patients affected do not experience pain that would alert them to the beginning of ulceration in the gastrointestinal tract.

The most frequent renal adverse effect of NSAIDs is interstitial nephritis, because NSAIDs not only inhibit prostaglandin biosynthesis and therefore also vasodilation, but also the simultaneous release of renal leukotrienes causes further vascular constriction. The second most frequent vascular adverse effect of NSAIDs is kidney disease due to disturbed T-lymphocyte functioning, which results in increased cell infiltration into interstitial tissue and a subsequent reduction in glomerular filtration.

Acetaminophen, an aniline derivative, is considered a liver toxin. Normally, highly reactive acetaminophen metabolites are broken down through conjugation with glutathione, but when glutathione conjugation is exhausted, these metabolites damage liver cells. Hence, children who take more than 2 g run the risk of acute liver necrosis.

Contrary to earlier assumptions, the frequency of gastric lesions is the same in male and female patients, and for both sexes not all NSAIDs are equally toxic. A toxicity index established by the ARAMIS study (Arthritis, Rheumatism, and Aging Medical Information System), a databank that has documented long-term results and consequences of treating rheumatic diseases for 20 years, gives information on patient tolerance of individual substances (Table 2).

Symptomatology of Rheumatoid Arthritis

The characteristic symptoms of rheumatoid arthritis are:

- Symmetrical joint swelling (especially in the metacarpophalangeal joints of the fingers and toes) that obscures the contours of the joint
- Permanent pain in the joints
- Morning stiffness and exhaustion

Generic NSAIDS	Number of Cases treated (n)	Risk Exposure (years)	GI Toxicity index (average value=SD)
Aspirin	1516	3056	1.06 ± 0.16
Salasate	187	241	0.87 ± 2.24
Ibuprofen	577	826	1.16 ± 0.17
Naproxen	1062	1801	1.78 ± 0.25
Piroxicam	814	1167	2.07 ± 0.24
Tolmetin	243	306	2.16 ± 0.50
Fenoprofen	158	221	2.48 ± 0.63
Diclofenac	415	337	2.17 ± 0.38
Ketoprofen	259	253	3.09 ± 0.54
Indomethacin	418	613	2.40 ± 0.42
Meclofenamate	165	1798	4.03 ± 0.78

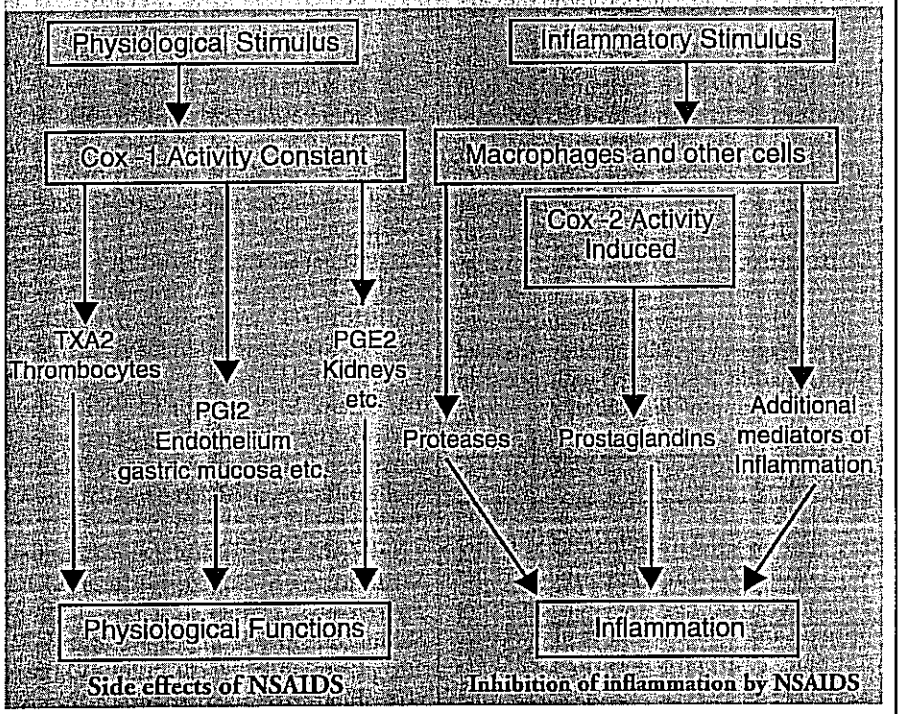
Table 2: Overview of the toxicity of frequently used NSAIDs (according to the ARAMIS study). Relatively good tolerance of aspirin is due to the low dosages used in outpatient treatment.

Figure 1: The different stages of rheumatoid arthritis as shown in the finger joints; (c) Mardeno Inc.

- Rheumatic nodules
- Elevated erythrocyte sedimentation rate
- Elevated serological antibody titers (IgG, IgA, IgM), elevated antistreptolysin and C-reactive protein
- Indirect radiological evidence (collateral phenomenon: decalcification of the bone near the joints) appears only after weeks or months
- Direct radiological evidence (narrowing of the joint cavity, cysts, bone lesions, malpositioning, ankylosis, deformation) appears only after months or years

Serological findings are poor predictors because many infections are endemic and the available tests are of limited reliability due to cross-reactions. Likewise, elevated antistreptolysin titers are predictive only when they change in the course of the illness. There is still no definitive diagnostic test for rheumatoid arthritis. Although the disease is presumed to be caused by an infectious agent and/or triggered by abortive defense reactions on the part of the immune system (autoaggressive immune responses), no agent has yet been discovered.

Figure 2: The significance of cyclo oxygenase-1 (Cox-1) and cyclo oxygenase -2(Cox-2) in mediating inflammatory processes.
PGE =Prostaglandin E; TXA=Thromboxan A; PGI=Prostacyclin



To date, immunological research on the pathogenesis of rheumatoid arthritis has discovered that macrophages play a central role. Consequently, the current school of thought tends to assume that a regulatory cycle responsible for macrophage activation is disturbed in patients with rheumatoid arthritis. This assumption is supported by results showing that tumor necrosis factor (TNF-α) is responsible for all of the effects of rheumatoid arthritis, from inflammation to joint destruction, and that TNF-α can be blocked by monoclonal antibodies.

The course of the disease is similar in all cases of rheumatoid arthritis (Figure 1):

1. Inflammation of the synovium eventually spreads to the joint capsules, ligaments, and tendons.
2. Gradual destruction of the articular cartilage with narrowing of the joint cavity is visible on X-rays; atony of the joint capsule and ligaments.
3. Macrophages attack the bone, causing partial breakdown.
4. Loss of function and stiffening of the joint.

The Neurophysiological Basis of Rheumatic Pain

The so-called pain-triggering substances released when synovial cells become inflamed or are damaged or destroyed include prostaglandin E, kinin, histamine, bradykinin, and H^+ and K^+ ions. Prostaglandin E plays a key role, because peripheral pain receptors are not stimulated unless it is present. The neurotransmitters acetylcholine and serotonin can also trigger a sensation of pain at a nociceptor. Histamine triggers sensations of pain only at relatively high concentrations. In contrast, even low concentrations of acetylcholine sensitize pain receptors to other mediators; that is, acetylcholine readily triggers pain in association with other mediators that are ineffective on their own. Serotonin is another substance of central importance in the group of pain-triggering mediators. Formation of prostaglandins increases during both rheumatic inflammation and direct tissue damage, with prostaglandin E_2 playing a particular role. Prostaglandins are an essential factor in chronic pain. Prostaglandins do not stimulate nociceptors directly but make them more sensitive to the effects of other mediators. Therefore, the use of NSAIDs to inhibit prostaglandin synthesis is an important principle of analgesic therapy. NSAID action is dosage-dependent and individual substances belonging to this group differ in potency.

The effect of all NSAIDs is due to inhibition of the enzyme cyclooxygenase, which in turn restricts prostaglandin synthesis. Acetylsalicylic acid is thought to cause an irreversible change in the enzyme, while other NSAIDs compete with arachidonic acid, keeping it away from the enzyme's active linkage site.

According to the latest scientific studies, the undesired adverse effects of NSAIDs are also due to cyclooxygenase inhibition. The two isomers of this enzyme are coded by different genes.[7] Cyclooxygenase-1 (COX-1) catalyzes prostaglandin synthesis in the stomach and kidneys. NSAIDs decrease renal perfusion because COX-1 inhibition prevents the formation of vasodilating prostaglandins. In patients whose kidney perfusion is already limited due to coronary insufficiency, hypovolemia, etc., NSAID use can cause conditions ranging from fluid retention to kidney failure. In contrast, production of cyclooxygenase-2 (COX-2) is stimulated by inflammatory processes (Figure 2). Massive concentration of prostaglandins in the synovia is characteristic of rheumatoid arthritis and is due to proinflammatory cytokines such as interleukin-1, TNF-α, etc. In experiments, interleukin-1 has been shown to stimulate the expression of COX-2 mRNA in synovial fibroblasts. Thus, the therapeutic effects of NSAIDS are based on COX-2 inhibition while their undesired effects are due to COX-1 inhibition. Hence, the risk-benefit profile of an NSAID can be gauged by its relative inhibition of COX-2 and COX-1.

Allopathic Treatment of Rheumatic Pain: Treating Pain With Opiates

Long-term treatment of rheumatic pain with NSAIDs, corticosteroids, gold, or methotrexate is often either ineffective in controlling chronic benign pain in the motor apparatus or characterized by severe adverse effects. Because pain prevents patient rehabilitation, pain specialists must have alternative therapies available. As rated according to World Health Organization guidelines, low- to high-potency opiates (such as dihydrocodeine, tramadol, dextropropoxyphene, and MST) have proved eminently suitable when administered either alone or in combination with a low-dose NSAID. A 50/50 combination of aspirin and dextropropoxyphene has been shown to be more effective in relieving pain than aspirin alone.[8]

Although opiate therapy for nonmalignant pain is still controversial and the subject of ongoing discussion,[9-13] protocols that include opiates are indicated for the treatment of nonmalignant pain if the pain persists when all other established therapies have failed. In such cases, as in opioid therapy for cancer pain, these principles apply:

- Therapy according to a fixed schedule
- Ongoing monitoring, so that the dosage can be adjusted at any time
- Intensity of pain, rather than diagnosis, determines whether opioids are prescribed
- Initial treatment with less potent opioids
- Opiate therapy in conjunction with other medications
- Prophylactic therapy for constipation

In general, pain specialists agree that severe, therapy-resistant pain due to a benign underlying illness must be considered malignant and merits opioid therapy.

As in the treatment of tumor pain, the objection that chronic administration of opioids can lead to addiction is clearly not valid. Opiate therapy has proved especially effective in treating the symptoms triggered by the most serious degenerative joint diseases and the pain of deafferentiation.[11,14]

(Part II, "Implementing Complementary Therapies: Combining Allopathic and Homeopathic Treatment," will appear in the next edition of *Biomedical Therapy*.)

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