The Clinical Pharmacology of Anti-Inflammatory Agents

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To our wives,
Helen, Mary and Margaret

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graduated from Glasgow University in 1972 and moved to Canada where he studied internal medicine and rheumatology before moving to McMaster University, Hamilton, Ontario in 1980. Walter Kean has a major research interest in the mechanism of action of gold-thiol complexes and the pharmacokinetics of NSAIDs in the elderly. He has edited a book on rheumatic diseases in the elderly and is coauthor of other rheumatology texts. He is presently an Associate Professor of Medicine and Co-Director of the Laboratory for Inorganic Medicine at McMaster University.

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has made a number of important contributions to rheumatology during his years as Physician-In-Charge of the Centre for Rheumatic Diseases in Glasgow where he was also Titular Professor of Medicine at the University of Glasgow, Scotland and as Professor of Medicine and Chief of Rheumatology, McMaster University, Hamilton, Ontario, Canada. Dr. Buchanan has a major interest in measurement of disease activity in inflammatory joint disease. With Dr. James A. Boyle he coauthored a textbook of Clinical Rheumatology, as well as other textbooks on multiple choice questions, clinical examination of the locomotor system and critical review of clinical trials of anti-rheumatic drugs.

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Contents

Introduction

Inflammation is one of the basic pathological processes producing tissue damage. It is the cause of joint destruction in the rheumatic diseases where it leads to significant pain and disability.

In this book we have attempted to review the process of inflammation and look at some of the pharmacological methods used to control the inflammatory process. Following a description of the pathogenesis of inflammation and its assessment, the different classes of anti-inflammatory and anti-rheumatic drugs are reviewed. Each chapter is concerned with a particular group of anti-inflammatory agents, reviewing their chemistry, pharmacology, toxicology and pharmacokinetics, and providing a brief description of their clinical effect.

A broad classification of anti-inflammatory, analgesic agents is shown in table 1. Pure analgesic agents, such as paracetamol (acetaminophen), codeine derivatives, pentazocine, propoxyphene and the opioids, will modulate pain perception, but do not influence inflammation. However, it is thought that many of the non-steroidal anti-inflammatory drugs (NSAIDs) may have a primary analgesic effect when used in low dose.

The largest group of anti-inflammatory analgesic agents comprises the NSAIDs. The best known of these are the salicylates, but over the last 60 years many new drugs have been produced. Although the NSAIDs share a common mechanism of action, interfering with the activity of cyclo-oxygenase and thus reducing prostaglandin formation, they have many other biochemical and immunological effects. However, some of the newer drugs seem to have a lower incidence of side-effects and may act specifically on certain inflammatory pathways.

The slow-acting anti-rheumatic drugs (SAARDs) affect the cellular aspects of inflammation. They work over a prolonged period of time and clinical responses to them are delayed. They comprise the anti-malarials, gold compounds, D-penicillamine, other thiol drugs and sulphasalazine.

Corticosteroid agents are potent inhibitors of the inflammatory response and may be given orally, by intravenous injection or by injection into inflamed areas in or around the synovial tissues.

The major immunosuppressive agents used in rheumatic disease are azathioprine, methotrexate, chlorambucil and 6-mercaptopurine. These drugs

Table 1. Anti-inflammatory analgesic agents.

Pure analgesic agents
Non-steroidal anti-inflammatory drugs (NSAIDs)
Slow-acting anti-rheumatic drugs (SAARDs)
Anti-malarials
Gold compounds
D-penicillamine and other thiol drugs
Sulphasalazine
Corticosteroids
Immunosuppressive agents
Anti-gout preparations
Colchicine
Uricosuric agents
Allopurinol

suppress cellular elements of the inflammatory response, but major side-effects are encountered with their long-term use.

Three major groups of anti-gout preparation are available including anti-inflammatory agents, such as NSAIDs or colchicine, the uricosuric agents, sulphinpyrazone and probenecid, and the xanthine-oxidase inhibitor allopurinol.

All anti-inflammatory, analgesic agents may be used alone or in combination, depending on the nature of the inflammatory response. However, owing to the complicated nature of inflammation it is likely that better control will be achieved by using a combination of drugs from different groups, particularly when they have different spectra of activity or side-effects, or drugs from within the same group.

> "Hear the rest, and you will marvel even more at the crafts and resources I've contrived. Greatest was this: in the former times if a man fell sick he had no defence against the sickness, neither healing food nor drink, nor unguent; but through the lack of drugs men wasted away, until I showed them the blending of mild simples wherewith they drive out all manner of diseases."
>
> Aeschylus (525–456 BC)

1. Inflammation

The rheumatic diseases are among some of the most common complaints affecting mankind. There are at least 150 different types of arthritis ranging from transient, post-traumatic, soft-tissue rheumatism to severe, destructive, rheumatoid arthritis. The basic pathological process in all these conditions is inflammation.

The inflammatory response is determined by a variety of factors which follow the primary event, producing immunological and pharmacological responses. These 'responses' are transferred via the body fluids (usually the blood) to the effector cells (the white cells, platelets etc.), where activation occurs. The subsequent release of a number of destructive molecules—arachidonic-acid metabolites and oxygen radicals—results in tissue damage. All stages of this process are regulated by positive- and negative-feedback loops.

The basic principles of inflammation, as they apply to rheumatic disease, are discussed in this chapter. The same principles may, however, pertain to other diseases in which inflammation plays a key role.

Inflammation in rheumatic disease is best exemplified by rheumatoid arthritis. In other types of inflammatory joint disease, such as the seronegative spondyloarthropathies, the pathology is similar, although the initiating factor or factors may be different. In osteoarthritis the primary event would seem to be cartilage breakdown and the secondary event, mild inflammatory synovitis.

More and more evidence is being obtained to support a genetic basis for rheumatic diseases. The association of the human leucocyte antigen HLA–B27 with ankylosing spondylitis and a variety of reactive arthropathies, is now well established. Recent work has demonstrated an association between rheumatoid arthritis and a number of histo-compatibility antigens in the D-related (DR) locus of the major human histo-compatibility complex. The DR4 antigen, for example, is more prevalent in patients with rheumatoid arthritis, particularly in those who have rheumatoid factor in their serum.

Microbial factors

Although the relationship of microbial agents to rheumatoid arthritis remains

hypothetical, many pyogenic bacteria, mycobacteria, fungi and viruses can multiply within the synovial cavity. Other micro-organisms may localise in the joint space (rubella) or become associated with immune complexes which are taken up by the joint (e.g., the immune complexes associated with hepatitis B). Bacteria, such as the streptococcus, may produce cross-reacting antibodies which give rise to synovitis, their cell walls acting as initiating agents in this process. Indeed, streptococcal peptido-glycans have been shown to remain within macrophages for long periods of time and are strongly arthritogenic in a variety of animal models.

Many viruses, including adenovirus and Coxsackie virus, are associated with polysynovitis. The arbovirus, Ross river virus, is carried by mosquitos and is associated with an epidemic polyarthritis and a maculo-papulo skin rash. Other viruses, such as the Epstein–Barr virus, have been accorded an aetiological role in rheumatoid arthritis. Epstein–Barr virus is particularly interesting as it is a polyclonal B-cell activator and more than 90% of adults show serological evidence of having been infected with it. However, the development of rheumatoid arthritis is complex, possibly depending on a number of viruses as well as genetic and environmental factors.

Pathology

In the normal diarthrodal joint (figure 1.1) articular cartilage covers the bone ends and the joint capsule is lined by a thin layer of synovial tissue. Articular cartilage is a dense matrix of collagen and proteoglycans containing the occasional chondrocyte. It is divided into four zones, superficial, intermediate, deep and calcified. The superficial zone is at the surface of the articular cartilage. Here, the collagen fibres are orientated at a tangent to the surface and contain little proteoglycan. In the intermediate or transitional zone the collagen fibres are randomly orientated and, in the deep or radial zone, collagen fibres are found perpendicular to the surface and fixed firmly to the sub-chondral bone plate. The collagen fibre and proteoglycan matrix retains a large amount of water and this provides the cartilage with many of its elastic properties. As the cartilage is devoid of blood vessels, chondrocytes deep in the matrix must obtain nutrients from the synovial fluid by diffusion, intermittent compression of cartilage or by active transport. Changes in the water content of cartilage lead to alterations in its elasticity and the development of degenerative joint disease. Although, in the past, it was felt that cartilage was unable to repair itself, there is evidence that the chondrocytes can proliferate and enable some healing to occur.

The synovial membrane which lines the joint capsule is made up of synovial lining cells overlying fatty and fibrous tissue. These cells, which produce hyaluronic acid, the major constituent of synovial fluid, can be classified into three different types. Type A cells (prominent Golgi apparatus, vesicles and vacuoles) have a major phagocytic (macrophage-like) function; type B cells,

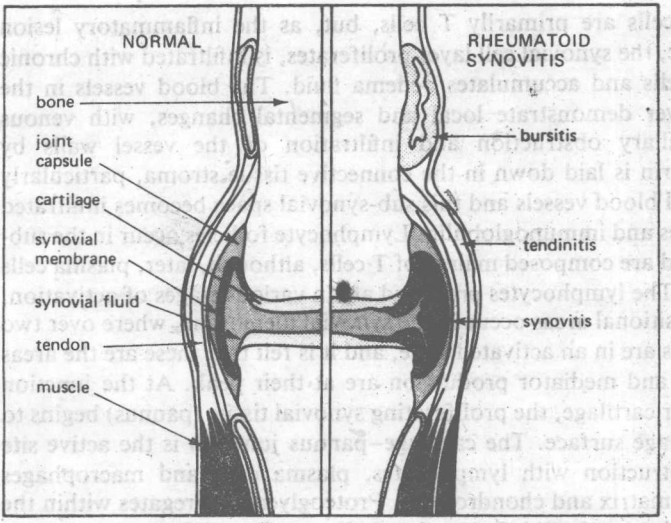

Figure 1.1. Diagram of normal and inflamed diarthrodal joint.
Adapted from *Atlas of Clinical Rheumatology*, by P. A. Dieppe, P. A. Baçon, A. N. Bamji and I. Watt (Gower Medical Publishing).

with prominent endoplasmic reticulum, act as fibroblasts; and C (or intermediate) cells have features of both fibroblast and macrophage and may represent an early stage of differentiation. The synovial lining is normally no more than three to four cells in thickness. However, some synovial blood vessels are present and the whole is surrounded by fibrous tissue and fat. The synovial membrane does not have a basement membrane and, thus, no anatomical barrier exists between the synovial fluid and synovial blood vessels.

Synovial fluid, which aids the movement of cartilage surfaces over each other during normal joint motion, is a filtrate of plasma from the sub-synovial capillaries, to which hyaluronic acid, secreted by the synovial cells, is added. Normal synovial fluid contains a few cells, a number of proteins and hyaluronic acid. Under normal conditions, large molecules such as alpha-2 macroglobulin (the principal proteinase inhibitor of plasma), fibrinogen and IgM are almost totally excluded from passing through the synovial interstitium by hyaluronic acid. However, once the joint is inflamed, this barrier breaks down and larger proteins can pass through.

In rheumatoid joint inflammation the earliest changes are seen in the small blood vessels of the sub-synovial connective tissues. These become dilated and a proliferation of vascular tissues occurs. Careful examination of the vascular endothelium reveals gaps which allow fluid and cells to leave the intravascular compartment, producing interstitial oedema. At an early stage, the blood vessels become obliterated by platelet thrombi and attract mononuclear cells.

Initially, these cells are primarily T cells, but, as the inflammatory lesion becomes chronic, the synovial cell layer proliferates, is infiltrated with chronic inflammatory cells and accumulates oedema fluid. The blood vessels in the sub-synovial layer demonstrate local and segmental changes, with venous distension, capillary obstruction and infiltration of the vessel walls by neutrophils. Fibrin is laid down in the connective tissue stroma, particularly around the small blood vessels and this sub-synovial space becomes infiltrated with lymphocytes and immunoglobulin. Lymphocyte follicles occur in the sub-synovial area and are composed mainly of T cells, although, later, plasma cells start to appear. The lymphocytes produced are in various stages of activation, but specific transitional areas occur in the synovial membrane, where over two thirds of the cells are in an activated state, and it is felt that these are the areas where antibody and mediator production are at their peak. At the junction with the articular cartilage, the proliferating synovial tissue (pannus) begins to invade the cartilage surface. The cartilage–pannus junction is the active site of cartilage destruction with lymphocytes, plasma cells and macrophages interacting with matrix and chondrocytes. Proteoglycan aggregates within the cartilage are broken up both by neutral proteinase released from the synovial cells and by chondrocytes. The small proteoglycans are then further degraded by enzymes such as cathepsin D and sulphatase. Elastase cleaves the cross-linked regions from collagen fibrils while collagenase cleaves the helical regions. The remaining collagen fragments spontaneously denature and are further metabolized by neutral proteinases and collagenolytic cathepsins. Fragments of collagen are strongly chemotactic for monocytes as well as fibroblasts. Finally, the absorption of bone mineral occurs, as osteoclasts are activated by arachidonic-acid metabolites or cytokines.

Lymphocyte infiltration

The majority of lymphocytes in the inflamed synovium are T cells. Careful histological studies have shown a marked variation in T-cell population throughout the rheumatoid synovium, but cells of the OK T4 (helper/inducer) series are seen primarily in the small lymphocyte collections, while those of the OK T8 cytotoxic drug suppressor series predominate in the active 'transitional areas'. T-cell proliferation, in these immunologically active areas, occurs as a result of macrophage interaction and leads to the secretion of a variety of biologically-active, soluble substances that stimulate antibody production by B cells.

In contrast to the large numbers of T cells, there is a small but significant number of B lymphocytes, which mediate local antibody production. Immunoglobulin synthesis occurs in the synovial tissue and large amounts of IgG and IgM, either alone or in combination, are found in the cells of the synovial lining, in the sub-synovial connective tissue, and around the synovial blood vessels. The lymphocytes of the rheumatoid synovium seem to be attracted to

different antigens than the peripheral blood lymphocytes. In rheumatoid arthritis the most common immunoglobulin product is rheumatoid factor, which is directed against IgG.

The role of rheumatoid factor in the genesis of rheumatoid arthritis is still unclear. While patients with hypogammaglobulinaemia and negligible circulating IgG can develop rheumatoid arthritis, there is a strong association between the presence of serum rheumatoid factor and extra-articular manifestations of the disease. Approximately 70% of patients with rheumatoid arthritis are positive for IgM rheumatoid factor and it is likely that many patients with sero-negative disease have IgG rheumatoid factor, but that it is masked by other serum proteins. The role of genetic factors in the production of rheumatoid factor is unclear, but family studies suggest that they are important. Within the synovium high concentrations of antibody, together with low concentrations of antigen, lead to the production of intermediate-size immune complexes which fix complement and are highly immunogenic. In serum, small complexes are often formed. These are usually stable and not capable of fixing complement. However, in certain situations, large or intermediate-size complexes form and cause immune-complex-mediated vasculitis.

Macrophages

Macrophage-like cells are found in the synovial lining and in the pannus, which invades the cartilage in chronic rheumatoid arthritis. They are activated by a variety of factors, including chemicals known as cytokines, which may be released from T lymphocytes. A variety of cytokines and other inflammatory substances, such as the complement component C5a, denatured protein and collagen, may be chemotactic to macrophages, attracting them to the sites of inflammation. Once activated, the macrophages undergo a burst of metabolic activity, which may involve phagocytosis and the release of a variety of soluble mediators including neutral proteinases, such as plasminogen activator and collagenase, acid hydrolases, complement components, arachidonic-acid metabolites, and reactive metabolites of oxygen such as the superoxide radical. Oxygen radicals are also released from a variety of other cells during inflammation and play a very important role in activating enzymes, destroying proteins, and causing extensive tissue damage.

Macrophages induce vascular proliferation within inflamed connective tissues and promote fibroblast proliferation. They have a large number of surface receptors, including Fc, complement, and glycoprotein receptors, which play an important role in their anti-microbial and immunoregulatory functions. The interaction between T lymphocytes and macrophages is important to inflammation and gives credence to the theory that rheumatoid arthritis results from a delayed-type hypersensitivity reaction. Antigen-stimulated lymphocytes release cytokines which activate macrophages, but macrophages may modify antigen recognition by T lymphocytes through immune-response

genes found on the macrophage membrane. In addition, macrophages may process antigen and present it to the lymphocyte, stimulating the release of cytokines.

The pannus

The pannus is vascular granulation tissue and is made up of proliferating fibroblasts, blood vessels and a variety of inflammatory cells. Three types of pannus have been described. The first is known as the cellular pannus, being synovial-like in appearance and infiltrating the cartilage with new blood vessels and perivascular mononuclear cells. Enzymes are released from the mononuclear cells and destroy the cartilage. The second type of pannus is composed of fibroblasts and monocytes, around which cartilage degradation occurs, but the third type of pannus is avascular and seems to occur as a result of tissue injury. It is composed of dense acellular fibrous tissue which may interfere with cartilage nutrition.

Polymorphonuclear leucocytes

Although polymorphonuclear leucocytes (PMN) are not found to any great extent in the synovial lining, they are the major cell in inflammatory synovial fluid. It is thought that the PMNs migrate from the intravascular compartment and are trapped in the synovial fluid. A number of chemotactic factors are released during the inflammatory process (e.g., complement components, histamine, and arachidonic-acid metabolites), which are chemotactic for human PMNs. Within the inflamed joint PMNs are involved in phagocytosis causing tissue damage by releasing large numbers of oxygen radicals and a variety of lysosomal enzymes. In addition, they can aggregate and cause microvascular occlusion within the synovial tissue, precipitating ischaemic tissue damage. The activation of PMNs is associated with the internal release of the lipoxygenase metabolite, leukotriene B4.

Platelets

The potential contribution of the platelet to inflammation and, in particular, rheumatoid arthritis, is considerable. The fact that platelets accumulate intravascularly at sites of tissue injury, and specifically within thrombosed synovial vessels, has been clearly demonstrated. However, they do tend to remain within the vascular compartment. Platelets can also adhere to other inflammatory cells, and may act as inflammatory mediators. During activation, they release serotonin, arachidonic-acid metabolites, acid hydrolases and factors which stimulate the proliferation of vascular smooth muscle cells. However, it has yet to be determined whether platelet aggregation occurs as a secondary event in inflammatory reactions or plays a more pivotal role.