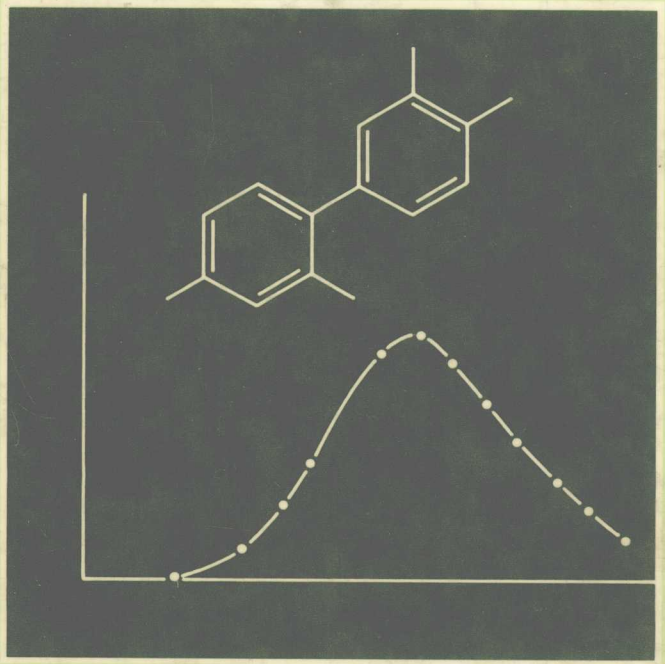
Anti-rheumatic Drugs

Edited by Edward C. Huskisson



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Anti-Rheumatic Drugs

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Anti-Rheumatic Drugs

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Preface

Anti-rheumatic drugs are becoming more and more important. They are likely to become still more important since the solution to many rheumatic diseases is likely to be a drug rather than an exercise or an operation. And drug therapy has taken great strides forward during the last few decades, in rheumatic diseases as well as in infections and other areas of medicine. The increasing number of anti-inflammatory drugs represents an advance in treatment. Individual variation in response ensures the success of each new compound, which will always be dramatically effective for a small group of patients. A glimpse of the future is provided by drugs such as penicillamine and allopurinol which are directed at particular diseases. We have many new drugs but we have also developed a greater expertise in the use of older drugs and in the management of their toxicity. All this is a healthy sign of the state of the art. Infections are treated exclusively by chemical means, and most successfully: why not arthritis and rheumatism?

I wish to recall my sincerest gratitude to the contributors to this volume, who have put forward their arguments with skill and with appropriately balanced judgement. As well as calling upon contributors from academic medicine, I have asked colleagues in the pharmaceutical industry for a number of chapters. I make no apology for this since a large repository of information, in part often unpublished, exists within the companies which market particular compounds. The pharmaceutical industry is the origin of most of our current treatments and the likely source of our future advances.

While drugs are clearly not the only way to treat arthritis, they are widely used and often appropriate. I hope the information in this book will help to bring together the right drug and the right patient.

EDWARD C. HUSKISSON

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Classification of Anti-rheumatic Drugs

EDWARD C. HUSKISSON

Classification of anti-rheumatic drugs has never been more important or more difficult. It is important because of the increase in the number of drugs available, which presents the physician with a bewildering choice. It is difficult because differences between drugs are not always clearly defined. Time will inevitably clarify the situation and any classification now will only be temporary.

The major classes of drugs used to treat rheumatic diseases are shown in Table 1. One must first distinguish the non-specific or symptomatic remedies from specific drugs for particular diseases. Aspirin relieves pain in a proportion of patients regardless of the nature of the disease which caused it. The action of aspirin is independent of the nature of the disease

Table 1. *Major classes of anti-rheumatic drugs*

Non-specific or symptomatic therapy
Simple analgesics
Paracetamol (acetaminophen), aspirin in small doses, dextropropoxyphene, codeine and dihydrocodeine
Non-steroidal analgesic anti-inflammatory drugs
Aspirin, indomethacin, phenylbutazone, oxyphenbutazone
Propionic acid derivatives—fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, indoprofen, suprofen, fenbufen
Drugs whose clinical effects resemble those of propionic acid derivatives—sulindac, tolmetin, azapropazone, diflunisal, flufenamic and mefenamic acid, diclofenac, piroxicam, fenclofenac, zomepirac
Pure anti-inflammatory drugs
Corticosteroids, ACTH, orgotein
Adjuvants
Anti-depressants, tranquillizers, hypnotics, haematinics
Specific therapy for particular diseases
Rheumatoid arthritis
Gold, penicillamine, chloroquine, levamisole, immunosuppresive drugs
Gout
Colchicine, allopurinol, uricosuric agents
Paget's disease
Calcitonin, mithramycin, EHDP

process and can therefore be called 'non-specific'. Penicillamine, on the other hand, is effective only in rheumatoid arthritis and some related conditions. Its action is disease dependent or 'specific'. A number of properties distinguish these major classes of drugs, apart from their disease specificity. 'Specific' drugs in general work slowly. They act on features of the disease other than pain and swelling, removing for example gouty tophi or rheumatoid nodules. Some alter the course of the disease for which they are given, improving the ultimate prognosis.

ANALGESICS

Analgesics relieve pain and do nothing else. Their action begins within an hour of administration of the drug, reaches a peak after a few hours, and is finished after a few more hours. Two classes of compound have this type of action. The term 'simple analgesic' is used to describe compounds like dihydrocodeine which have no additional anti-inflammatory action. Such compounds are to be distinguished from the non-steroidal anti-inflammatory drugs, which also have an analgesic action. In inflammatory disorders like rheumatoid arthritis, drugs with additional anti-inflammatory activity are likely to be more effective. Thus aspirin has been shown to be more effective than even narcotic analgesics (Fremont-Smith and Bayles, 1965). Similarly, anti-inflammatory drugs are more effective than simple analgesics in osteoarthritis (Doyle et al, 1981). Inflammation plays some part in most musculoskeletal disorders, which suggests that anti-inflammatory compounds will usually be preferable to simple analgesics. There are two other advantages for the anti-inflammatory drugs. Many are safer and better tolerated than the simple analgesics, especially in overdosage. The traditional analgesics – aspirin, paracetamol and centrally-acting compounds like dextropropoxyphene and dihydrocodeine – are all dangerous in excess. Overdoses of aspirin cause potentially fatal metabolic acidosis, paracetamol may cause hepatic necrosis and centrally-acting compounds may cause respiratory depression. The dangers of dextropropoxyphene-containing compounds taken with alcohol have recently been emphasized (Carson and Carson, 1977). In therapeutic doses, paracetamol is very well tolerated and aspirin causes much fewer side effects in the doses required for a simple analgesic effect than in the heroic doses recommended for anti-inflammatory therapy in rheumatoid arthritis. There are important interactions and contraindications to be remembered. Anti-inflammatory analgesics have one disadvantage: most are considerably more expensive than simple analgesics like paracetamol. Some are longer acting, like diflunisal, which can be given twice daily for pain, an additional advantage in the treatment of chronic disease.

Analgesics are used either for patients with mild or intermittent symptoms who do not need regular therapy or as a supplement to regular treatment with drugs of other types. Many patients with rheumatoid arthritis like to have a supply of pain killers on hand to take when times are bad.

Available simple analgesics include paracetamol (acetaminophen),

aspirin in small doses, codeine, dihydrocodeine and dextropropoxyphene. There are also many combinations including the widely used 'Distalgesic' ('Darvocet N') containing paracetamol and dextropropoxyphene. This combination is more effective than either dextropropoxyphene or paracetamol alone (Hopkinson et al, 1973; Huskisson, 1974; Messick, 1979) and patients appear to like it. It is wise to remember the hazard of taking an overdose of dextropropoxyphene and alcohol, and patients should be warned. Agonist–antagonist compounds like pentazocine or butorphanol can be used in rheumatic diseases, though the central nervous system side effects of pentazocine are a distinct disadvantage. Pentazocine is much less effective taken orally than parenterally and in one study was no more effective than paracetamol (Huskisson, 1974). In a multiple-dose study in rheumatoid arthritis, it was not superior to placebo (Nuki et al, 1973). Nefopam is a new centrally-acting analgesic whose site of action is not the opiate receptor. It is no more effective than aspirin, but seems to be well tolerated.

The non-steroidal anti-inflammatory drugs also have an action of this type when given in single doses. They can therefore be used in the same way as simple analgesics, prescribed to be taken 'on demand'. Clear differentiation of the analgesic and anti-inflammatory actions of aspirin was first achieved by Boardman and Hart (1967). These authors showed that reduction in joint swelling was achieved with high-dose aspirin but not with low-dose aspirin or paracetamol. It is now agreed that while analgesic effect can be achieved with a dose of 600 mg of aspirin taken four times daily, at least 3.6 g daily are required for an anti-inflammatory effect. There are other drugs with this type of profile. Fenoprofen is an effective analgesic in single doses of 200 mg (Gruber, 1976), while doses used in rheumatoid arthritis are around 2.4 g daily (Huskisson et al, 1974). On the other hand, diflunisal shows little difference between analgesic and anti-inflammatory doses. A single dose of 500 mg is required for optimal pain relief, while maintenance doses in rheumatic patients lie between 250 and 500 mg twice daily.

Some non-steroidal anti-inflammatory drugs are more suitable than others for use as simple analgesics and some have been developed as analgesics rather than as anti-inflammatory drugs. Zomepirac just happens to have more analgesic activity, just as there are compounds like indomethacin and flubiprofen with more anti-inflammatory activity. It is probably the most effective analgesic of this class and the only one whose efficacy is clearly superior to that of aspirin (see Chapter 22). Many compounds are comparable in efficacy to aspirin, including mefenamic acid, fenoprofen, ibuprofen, indoprofen, naproxen or naproxen sodium, azapropazone and piroxicam. Compounds with short plasma half-lives and more frequent dosing schedules are particularly suitable for use as simple analgesics. A compound with a very long half-life, like piroxicam, is less suitable though it is as effective as aspirin, because the 20 mg dose cannot be given more than once a day except for short periods of time. There is evidence to suggest that a frequent dosing schedule (three or four doses daily) is more appropriate for patients with severe pain, requiring

analgesia, while a once or twice daily schedule is more appropriate for those requiring an anti-inflammatory effect (Huskisson, Scott and Christophidis, 1981).

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

There is no entirely satisfactory way of classifying the subgroups of this class of drugs and it could be argued that the attempt is not worthwhile. The drugs have much in common. All are analgesics when given as a single dose. When given regularly in sufficient dosage they have an anti-inflammatory effect which develops over the course of a few days. Not only is there relief of pain, but also a reduction in the duration and severity of stiffness in the morning or after sitting, a reduction in the number of tender joints, a reduction in the swelling of joints (Boardman and Hart, 1967), a reduction in joint temperature and improvement in function – changes in all the cardinal features of inflammation. Reduction in swelling of the proximal interphalangeal joints was at first regarded as the hallmark of this type of drug, but some drugs, such as propionic acid derivatives, achieve this effect slowly. Similarly, joint temperature is reduced slowly by anti-inflammatory drugs, whereas pain and stiffness are relieved almost at once. Inflammation is a complex phenomenon and one must assume that different measurements reflect different aspects of it.

Though all the drugs show these properties, it would be misleading to suggest that they are all the same. The effects of propionic acid derivatives are very different from those of aspirin. The biggest difference is in their side effects, for those of propionic acid derivatives are enormously less frequent than those of aspirin. Some propionic acid derivatives have less anti-inflammatory effect than aspirin but some are at least as effective and it is therefore misleading to call them 'minor' anti-inflammatory drugs.

A historical classification is perhaps the most appropriate at the present time. In the beginning there was aspirin. Its early mimics, indomethacin and phenylbutazone, shared its ability to cause gastric and other side effects and did not challenge the view that aspirin was the first line of treatment. But propionic acid derivatives were clearly different. Their large advantage in safety and tolerance led to their use as first-line treatment for a wide range of rheumatic disorders. Since the introduction of propionic acid derivatives, a number of compounds of other chemical types have appeared which share with them a large advantage in safety and tolerance over aspirin. Many of these are derivatives of older drugs. Sulindac is an indene derivative related to indomethacin, but its clinical properties resemble those of naproxen. Tolmetin is also related chemically to indomethacin. Azapropazone is a pyrazole, but does not resemble phenylbutazone – it is well tolerated and does not cause blood dyscrasias. Diflunisal is related to aspirin and is perhaps the most difficult to classify. Like aspirin, it has both analgesic and anti-inflammatory properties, but other similarities are hard to find. It is safe and well tolerated, can be given twice daily and lacks a number of aspirin side effects such as tinnitus and