Drug Treatment of Rheumatoid Arthritis

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Inflammation is the central and essential component of rheumatoid arthritis, and control of inflammation by various drugs is paramount to the success of treatment of the disease. No specific cure is available for rheumatoid arthritis, but judicious and individualised treatment regimes can relieve symptoms, if not modify the disease process. A number of different types of drugs are available and will be discussed under the following headings:

- Analgesic agents
- Non-steroidal anti-inflammatory drugs (NSAID)
  - Specific anti-arthritic preparations:
    - Gold
    - D-penicillamine
    - Anti-malarials
    - Corticosteroids
  - Immunosuppressive agents

Agents from a number of groups are often used together in an attempt to control different features of the disease process.

Analgesics

The evidence that pure analgesic agents alone are useful in the management of pain in rheumatoid arthritis is poor. Controlled clinical trials show no benefit of paracetamol\(^1\) and pentoazoline\(^2\) over placebo for a two-week period, though these drugs have been shown to be analgesic compared to placebo over a six-hour period.\(^3\) A number of prescribing studies\(^4\) have shown that analgesics are used widely together with other agents in the routine management of rheumatoid arthritis. Moertel\(^5\) has shown that aspirin is the best analgesic available and that this should be the drug of choice, followed by paracetamol, and combinations of these drugs with codeine or pentoazoline. Doloxene, though used extensively, has still not been demonstrated to have significantly better analgesic effect than placebo. The important thing when considering the use of an agent for rescue analgesia is to make sure that NSAID are being taken in maximum tolerated doses by the patient before adding an analgesic agent. Paracetamol is possibly the analgesic of first choice because of the interaction of aspirin with other NSAID.

Non-Steroidal Anti-Inflammatory Drugs

The concept that NSAID act purely by inhibition of prostaglandin synthetase is now under review and it seems that NSAID have a number of actions on constituents of the inflammatory cascade including kininogens and the complement system. NSAID will often reduce the cardinal signs of inflammation, and though there is no formal long term study to show that these agents have any effect on the prognosis of rheumatoid arthritis, it seems reasonable to surmise that a reduction of synovial swelling will reduce the tendency to deformity, and possibly cartilage and bone destruction by the inflammatory process. In this regard, adequate doses of NSAID should be used as early as possible in the disease process.

Salicylates. Aspirin is still the drug of first choice in the treatment of rheumatoid arthritis because none of the other available NSAID have yet been shown to be superior to it in relieving pain. The problem with aspirin is one of patient tolerance. Firstly, patients have often had aspirin before in an inadequate dose or side-effects have occurred. An explanation about the action and side-effects of aspirin and the use of newer slow release preparations with individualisation of dose will often reduce the drop-out rate of aspirin treated arthritis. Patients are often concerned about the renal effects of aspirin and should be reassured that long-term studies on aspirin treated rheumatoid arthritis indicate a minimal relationship between analgesic nephropathy and aspirin,
Ingestion. Aspirin is also associated with increased gastrointestinal blood loss and increased incidence of peptic ulceration and hence should probably not be given to patients who have had a recent (6-month) history of active peptic ulceration.

Given that aspirin is the drug of first choice, which preparation should one use? The major types of salicylate preparations are plain, soluble, buffered, enteric-coated, slow-release, aloxiprin and benorylate.

Plain aspirin is notorious for its effect on gastric mucosa and the soluble or buffered tablets are more rapidly absorbed and cause less bleeding. The problem with these preparations is that to maintain plasma salicylate levels, frequent administration is essential.

Enteric-coated or slow-release preparations show less side effects of gastric intolerance and microbleeding, and have the advantage of less frequent administration. Aloxiprin, an aluminium and aspirin polymer, also produces less gastric bleeding than plain aspirin, but constipation can be troublesome.

Benorylate is a paracetamol ester of aspirin and has been shown to be effective in rheumatoid arthritis, and along with the slow release preparations has the advantage of twice daily dosage.

As an anti-inflammatory activity has been demonstrated at doses of 3.6 g aspirin daily, treatment should be started at this level and the dose altered according to efficacy, development of tinnitus (care should be taken in elderly patients), or to maintain plasma salicylate levels between 1.0–2.0 mg/L.

Indomethacin. Indomethacin, an indole derivative has proved extremely useful in the rheumatic diseases, especially taken orally in doses of 75–200 mg per day or as a suppository (100–200 mg per day). It is particularly useful for relieving morning stiffness when taken at night. Dyspepsia is relatively common in patients receiving indomethacin, and asymptomatic precordial ulcers may occur. Headache and other mild CNS disturbances are other major reasons for ceasing the drug, though these can sometimes be circumvented by gradually increasing the dose of indomethacin. Marked individual variations occur in indomethacin pharmacokinetics and plasma levels are not clinically helpful.

Ibuprofen. Ibuprofen is the first of the phenylalkanoic acid derivatives to be released in Australia. It is rapidly absorbed and has a short (6-hour) half-life. Clinical trials using up to 3-2 g daily have shown its efficacy in relieving pain of rheumatoid arthritis and have demonstrated a low incidence of gastric side effects.

Phenylbutazone and oxyphenbutazone. Phenylbutazone has been shown to be efficacious in rheumatoid arthritis and equipotent to oxyphenbutazone (its major metabolite). Phenylbutazone is used in daily doses of 200–300 mg, and with a half-life of 72 hours can be given once a day. The optimum dose of phenylbutazone is still not known, but in practice one uses the lowest effective dose to control pain. Peptic ulceration can occur and an entericoated preparation will reduce dyspepsia.

Haematological side effects of agranulocytosis, thrombocytopenia and aplastic anaemia may be fatal; agranulocytosis tends to occur early in a course of treatment and aplastic anaemia late and in elderly patients. Phenylbutazone can also cause fluid retention, and because of this and aplastic anaemia, should be used with care in the elderly. Though phenylbutazone is an extremely potent anti-inflammatory drug, it must be used with caution in the long term management of rheumatoid arthritis.

The fenamates. Mefenamic acid (Ponstan) and flufenamic acid (Arlief) are equivalent to the standard doses of other NSAID, but are not used widely in long term treatment. The reason for this is unclear, because although diarrhoea, dyspepsia and rashes occur, they seem to be no more frequent than with other non-steroidal anti-inflammatory drugs.

New NSAID. The propionic acid derivatives including fenoprofen, flurbiprofen, ketoprofen and naproxen, have all been demonstrated to be equivalent to aspirin in double-blind clinical trials. Significant differences between these agents are hard to demonstrate, but they seem to be less toxic than aspirin though they are more expensive and their long term effects have
yet to be assessed. There is no doubt that they will be useful in certain patients.

Azapropazone is a phenylbutazone-like agent which seems to be as effective as other NSAID in short term trials: it achieves another interesting drug which has been shown to be efficacious with fewer side-effects, and seems to have some long term effect in rheumatoid arthritis. Most of these new NSAID are not yet available in Australia.

Specific Anti-Arthritic Agents

Gold salts. Gold salts have been used for nearly 50 years to treat patients with rheumatoid arthritis, and controlled studies have shown that they are effective in suppressing activity of the disease. The mechanism of action is still unclear, though gold is concentrated in synovial tissues where it stabilises lysosomal membranes and inhibits sulphhydryl dependent enzymes. No consistent pattern has emerged between the metabolism of gold and the outcome of therapy or toxic reactions. The indication for gold is failure of response to NSAID with continuing active synovitis. Standard practice is to introduce gold slowly, increasing to 50 mg of sodium aurothiomalate over a period of 3-4 weeks and continuing with 50 mg injections at weekly intervals until 1 g has been given. The answer to the question of what to do at 1 g is still not clear. Continued monthly injections of 50 mg in responders is usual since relapse occurs if gold is ceased. A recent report suggests that by increasing the weekly dose of gold after one gram has been given in non-responders, a significant increase in the therapeutic response can be seen without an increase in the incidence of side effects. This study also showed that gold thiolglucose was more efficacious than sodium aurothiomalate (Myocotrin). The present worry with gold therapy is the incidence of side effects such as thrombocytopenia, aplastic anaemia, dermatitis, proteinuria, enterocolitis and pulmonary fibrosis. Cessation of gold therapy is necessary in 15-30% of patients in reported series, the major reasons being dermatitis, proteinuria and occasionally myelotoxicity. Thrombocytopenia may occur suddenly and after only a small amount of gold while total aplasia tends to occur after a progressive drop in neutrophil count. Eosinophilia may be useful in heralding a skin reaction, but also occurs in rheumatoid arthritis per se. When gold treatment is prescribed a full blood count should be done before each injection, and the urine tested for protein. If proteinuria of 100 mg% or dermatitis of a pruritic nature occurs, then gold is ceased, but can be restarted in a smaller dose if the proteinuria or rash disappear rapidly.

D-penicillamine. The exact mode of action of D-penicillamine in rheumatoid arthritis is not known, though it chelates heavy metals, prevents reduction of mature, insoluble collagen fibres and reduces levels of rheumatoid factor and levels of immunoglobulins. D-penicillamine has been shown to be better than placebo and equal to gold over an 18 month period, side effects being more common with D-penicillamine, but necessitating cessation of therapy more often in the gold treated patients. This drug seems particularly useful for vasculitis and other severe extra-articular manifestations of rheumatoid arthritis. Most authors agree that about 25% of patients fail to respond to D-penicillamine, and there is no evidence yet that D-penicillamine alters the course of the disease. Side effects occur in up to 50% of cases, and include rash, proteinuria, thrombocytopenia, gastrointestinal upsets and loss of taste. These side effects may be dose-related, but published series show that up to 50% of patients on D-penicillamine had ceased the drug after 18 months. The dose of D-penicillamine should be increased slowly over an eight week period up to a maximum of 1 g per day and continued for at least three months. Some patients will require higher doses, but this is often associated with an increased incidence of side effects. As with gold therapy, platelet counts, white cell counts and urine tests should be done at weekly intervals for the first two months and then at monthly intervals. D-penicillamine is still too toxic to use as a first-line drug for rheumatoid arthritis, but it is of importance in pointing the way for the development of other drugs having the same specific effect in rheumatoid arthritis.

Anti-malarials. Studies in the early 1960s suggested that these agents were better than placebo in rheumatoid arthritis, but little assessment has been done since. Clinical improve-
ment occurs slowly with these agents, but because of toxic effects particularly on the retina they are now rarely used in the treatment of rheumatoid arthritis.

**Corticosteroids**

There is no doubt that corticosteroids are effective agents in reducing inflammation in rheumatoid arthritis,22 but the potential side effects restrict their routine use. Despite some evidence that corticosteroids have some advantage over oral corticosteroids in the maintenance of the hypothalamic-pituitary-adrenal axis23, oral prednisolone, prednisone or prednisolone stearoyl glycolate24 are preferred because of convenience of administration. The indications for steroids are uncontrolled disease, vasculitis or socio-economic factors. The smallest dose of corticosteroid to control symptoms should be used and given in a single morning dose not exceeding 7.5 mg. In those patients on long term therapy an attempt should be made to withdraw steroids—sometimes at a rate no faster than 1 mg per month.25

**Immunosuppressive Agents**

The accumulating evidence of abnormal immune mechanisms in rheumatoid arthritis has led to the use of immunosuppressive agents in this disease. Controlled clinical trials have shown the efficacy of azathioprine23 and high dose cyclophosphamide23 and a combination of low dose cyclophosphamide with prednisolone. At present, these agents have to be reserved for severe cases of rheumatoid arthritis because of toxicity and the still undetermined effect of long term immunosuppressive therapy on the development of neoplasms.

**Conclusions**

Because patients with rheumatoid arthritis may respond differently to the medications used, treatment must be individualised. Therapy is most effective if the groups of drugs are used in combination and, when combined with physiotherapy, occasional therapy and surgery, aggressive drug treatment is the key to optimum management.

**References**


**Discussion**

**Macaulay:**

Do you use alternate day steroids in rheumatoid arthritis?

**Brooks:**

I find it difficult to control adult rheumatoids on alternate day therapy. If steroid therapy...
is necessary in children with Still's disease. Alternate day treatment helps to overcome the problem of growth suppression.

Dieppe:
Could I comment on levamisole? It is effective treatment but we are having increasing problems with toxicity. Of 60 patients treated with the traditional dosage six have developed severe agranulocytosis; consequently we feel its use is unacceptable although different dose schedules may possibly reduce this toxicity.

There is an argument in favour of the use of drugs like ibuprofen and naproxen before aspirin since they are effective and have less toxicity. I think this is a matter of individual choice.

Brooks:
I would accept that. I use aspirin first because it is cheaper and has been used for much longer. We still do not know about the long term effects of the other agents.

Boyden:
Could you comment on the use of low dose gold?

Brooks:
You mean 10 mg per week? There has been some work on this but I have no personal experience. It has been suggested that low dose gold has fewer side effects and equal efficacy to standard regimes. Other workers have shown that high dose regimes have equivalent side effects but better efficacy than the standard dosage. I do not think we know the final answer yet.

Howe:
Rothermuck has implied that loss of anti-rheumatic control occurs more commonly if maintenance injections are given less frequently than every three weeks.

Brooks:
This seems true for some patients and I think that as with other drugs gold therapy must be individualised. A good relationship between efficacy, toxicity and pharmacokinetics has not been demonstrated.

Grigor:
Levamisole is widely used in cattle and sheep in New Zealand; is there any evidence that as a result of this we are not all on levamisole?

Brooks:
I do not know but it is a good point.

Macauley:
Patients with rheumatic diseases apparently have a higher incidence of side effects of levamisole than do patients with other diseases. Is there any explanation for this?

Whitehouse:
We do not think that these drugs have an absolute toxicity per se but rather that it depends on the disease being treated. It is a case of disease/drug interaction and generalities about the drug per se should not be made.

Champion:
Would you comment on Lorber's work claiming greater efficacy if gold plasma concentrations are kept above 300 micrograms/ml?

Brooks:
Lorber's work has not been confirmed by other workers who have found no relationship between efficacy and pharmacokinetics, excretion or plasma levels.

Johnston:
An apparently effective oral gold preparation has recently been mentioned. Could you comment?

Champion:
Oral gold (Auranofin) exhibits pharmacokinetic and pharmacological properties which differ from myocrisin. Early human studies indicate reasonable efficacy and lower "allergic" side effects but there is some gastrointestinal toxicity.