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Report of the  
FOURTH JOINT WHO/ILAR TASK FORCE  
MEETING ON RHEUMATIC DISEASES  
8-10 July 1991, Geneva



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## 1. INTRODUCTION

The meeting was opened by Dr Hu Ching-Li, Assistant Director-General. Dr Hu welcomed the members of the task force to Geneva. Dr Hu also noted that rheumatic diseases were important to world health because they were more prevalent in the elderly and the proportion of elderly persons throughout the world was increasing rapidly. In terms of lifetime risk, rheumatic diseases were noted to be of similar importance to breast cancer and ischaemic heart disease.

Dr Hu then referred to the statements made by Dr Hiroshi Nakajima, Director-General of the World Health Organization, at the Forty-fourth World Health Assembly and the sixteenth session of the Programme Committee of the Executive Board. The Director-General called for a "new paradigm for health" to enable the Organization's 168 Member States to achieve the goal of health for all, in the face of rapid changes taking place in the world's political, social and economic climate.

Dr Hu pointed out that increasing urbanization and life expectancy also implied a significant increase in the incidence of disability, particularly in developing countries. Rheumatic diseases would be one of the health issues resulting from rapid changes in life-style and socioeconomic situations.

Dr K.D. Muirden, President of ILAR, was elected Chairman; Dr J.P. Edmonds, Secretary General of ILAR, was elected Vice-Chairman, and Dr P.M. Brooks and Dr C.H. Goldsmith were elected Rapporteurs.

The list of participants is contained in Annex I.

This meeting, the fourth WHO/ILAR task force, extended the work of a meeting chaired by Dr L. Shulman, held in Geneva 2 years previously, which surveyed the status of rheumatic diseases, their pathogenesis and treatment in general. The current meeting was designed to focus on certain aspects of antirheumatic therapy and to develop guidelines for the use and evaluation of antirheumatic therapies in Rheumatoid Arthritis, Osteoarthritis and Gout. It did not deal specifically with disseminated connective tissue disease and some other areas.

## 2. ANTIRHEUMATIC DRUG USE BY COUNTRY

Various participants presented drug use from their countries and regions. The issues considered were of a non-steroidal anti-inflammatory drug (NSAID) use by rheumatologists and other health professionals, etc., ability of patients to afford antirheumatic drugs, the impact of patents on the development of a new drug and whether subsidies were available to help segments of the population to afford rheumatic drugs, whether there were patents to protect the developer of a new drug, and whether there were regulations governing the use and marketing of generic preparations. Drug distribution and over the counter (OTC) regulations were discussed, as well as the drug registration/approval process. The issue of drug 'dumping' and the sale of expired medications was noted and the place of natural/herbal remedies was mentioned. Whether there was a requirement for Quality Assurance/Quality Control on the local producer and importer of medications was noted. Attention was drawn to the degree of overuse and misuse of NSAIDs medications particularly in OA and soft tissue rheumatic diseases. (See recommendations.)

## 3. USE OF GUIDELINES FOR ANTIRHEUMATIC DRUGS

The indications for use of these agents in the Rheumatic Diseases follows these general criteria.

A. Indications for use  
Relative/Absolute  
Contraindications

B. Usage  
Dose - Starting  
- Continuing  
- Specific Situations: Pregnancy, Elderly, Lactation  
- Social and Cultural Variations

**Administration**

Route: Oral, Suppository, IM, IV

Formulation

**Interactions**

Other Drugs

Food

**Measures of Efficacy****C. Toxicity**

Major Adverse Reactions

Monitoring for toxicity

**D. Reasons for stopping therapy****E. Advice to patients****3.1 Non-steroidal anti-inflammatory drugs (NSAIDs)****A. Indications for use**

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be used for the treatment of generalized inflammatory rheumatic diseases: i.e. Rheumatoid Arthritis, Gout, Seronegative Arthritis, or Systemic Connective Tissue Diseases. They should not be used as initial therapy for degenerative diseases or soft tissue rheumatic diseases. It was felt in general that there was overuse of oral NSAIDs and that more emphasis should be made of nonpharmacological therapies in OA and soft tissue rheumatism. With increasing use of NSAIDs given transdermally, there is a need for appropriate evaluation of this route.

**B. Usage**

Individual variability in response to these agents should be appreciated. The recommended daily doses are seen in the accompanying paper. Once symptomatic relief has been achieved the dose should be reduced and in some situations can be ceased. Prescribing of NSAIDs in pregnancy and lactation should be reduced to a minimum. NSAIDs are best taken with food to reduce gastric intolerance. NSAIDs may interfere with the hypotensive effects of beta blockers, ACE inhibitors and vasodilators as well as the diuretic effects of thiazides and other 'loop' diuretics.

The major measures of efficacy are: reduction in pain, stiffness and joint swelling, and if these do not respond within 10-14 days, at appropriate dosage, then the NSAID should be changed.

**C. Toxicity**

NSAIDs should be used with great care in the elderly or those with a history of renal impairment. The issue of ulcer prophylaxis may be considered in those patients requiring NSAIDs who fulfil the following criteria: age > 65 years, female, previous peptic ulcer, significant disability or concomitant steroid treatment. Further work needs to be done in this area to identify those at risk from significant gastrointestinal toxicity with NSAIDs and the exact role of ulcer prophylaxis.

**D. Therapy cessation**

NSAIDs should be ceased if major adverse reactions occur, if the disease for which the NSAID is being prescribed goes into remission or if the NSAID does not seem to be providing relief of symptoms.

**E. Patient advice**

Patients should cease NSAIDs and report to their health care adviser if gastrointestinal or other serious untoward events occur when taking NSAIDs.

### 3.2 Slow-acting antirheumatic drugs (SAARDs)

#### A. Indications for use

Chronic inflammatory rheumatic diseases such as Rheumatoid Arthritis or seronegative arthritis. Treatment should be initiated only by a medical practitioner with special training in the use of these agents. Slow-Acting Anti-Rheumatic Drugs (SAARDs) should not be used for the treatment of soft tissue rheumatic disorders or osteoarthritis.

#### B. Usage

Treatment with SAARDs should be initiated as soon as possible after diagnosis of chronic inflammatory arthritis before significant damage to the joints has taken place. Choice of the individual agents to be used depends on the prescriber but should take into account the therapeutic ratio of the SAARD in that particular clinical situation. The health care worker monitoring a patient on a SAARD should be fully conversant with the known adverse reactions to that particular SAARD. Criteria for response to a SAARD include a decrease in clinical features (joint count, pain, duration of stiffness) and blood tests such as ESR, C reactive protein and other acute phase reactants. SAARDs are used in an attempt to prevent progressive disability and the development of cartilage and bone erosions.

#### C. Toxicity

Toxicity monitoring will depend on the SAARD used - refer to the background paper. Further studies looking at the cost-effectiveness of various drug monitoring regimens need to be carried out. Studies reviewing differences in patient response and adverse reactions between different countries should be encouraged.

#### D. Therapy cessation

Patients on SAARDs need frequent review to assess efficacy of therapy. If the SAARD is not working, or if side-effects occur, treatment should be reviewed.

#### E. Patient advice

Patients should be provided with a list of the common side-effects and should be encouraged to report to their health care worker if they have concerns about their treatment.

### 3.3 Corticosteroids

#### A. Indications for use

Corticosteroids are extremely useful to control severe systemic connective tissue disease and vasculitis and may be used in active inflammatory joint diseases. They should not be prescribed for patients with osteoarthritis or soft tissue rheumatic diseases. They should always be used in the lowest dose possible to control disease and particularly in children where growth can be significantly retarded.

#### B. Usage

Corticosteroids can be given orally (prednisilone or prednisone) or parenterally (IV, IM, IA or intralesionally). Oral preparations with 1 mg tablets should be used to allow for small reductions in dose. Sale of preparations containing corticosteroids with other agents (i.e. NSAIDs) should not be allowed. Control of severe connective tissue diseases (SLE, Vasculitis) may require high doses of oral or intravenous steroids initially. Dose should then be reduced to the lowest dose required to control the disease.

#### C. Toxicity

Corticosteroids are a major cause of adverse drug reactions when prescribed long term or in high doses. Particular care should be exercised with the use of steroids in the young and in the elderly. Consideration should be given to use of calcium supplementation and hormone

replacement therapy for those at particular risk of osteoporosis. Those patients on long-term corticosteroids should be given steroid support in emergency situations, trauma or surgery.

Further studies identifying those at particular risk of corticosteroid side-effects and strategies to reduce these should be considered.

#### D. Therapy cessation

The doses of corticosteroids should be tapered as the disease process is controlled. Other SAARDs or immunosuppressive agents should be used as 'steroid sparing' agents where steroid dose produces unacceptable side-effects without disease control.

#### E. Patient advice

Patients should be warned regarding side-effects of steroids, the dangers of suddenly altering the dose and the need for frequent re-evaluation of disease activity and dose.

### 3.4 Hypouricaemic agents

#### A. Indications for use

Recurrent gouty arthritis, renal calculi, and tophaceous gout. Drug treatment of asymptomatic hyperuricaemia is not usually necessary.

#### B. Usage

Nonpharmacological methods (diet, weight reduction, stopping thiazide diuretics, etc.) should be pursued in addition to hypouricaemic therapy. Allopurinol can be used as a single daily dose. Uricosurics may require alkalinization of the urine. Cost factors in long-term therapy need to be appreciated. When commencing treatment with drugs which alter plasma urate concentration, patients should always be given colchicine (0.5 mg, BD) or an NSAID for at least 4 weeks to prevent acute attacks of gout.

#### C. Toxicity

Dosage of allopurinol should be reduced in patients with significant renal disease.

#### D. Therapy cessation

Therapy should be reviewed if significant reduction in serum urate is not achieved.

#### E. Patient advice

Patients should be advised that lifetime therapy is probably required. Further studies on intermittent dosage regimens should be pursued.

### 3.5 Analgesics

#### A. Indications for use

Analgesics should be used to relieve pain, one of the main objectives in the treatment of rheumatic diseases. Health care workers should be aware that many of their patients will self-medicate for pain.

#### B. Usage

Analgesia is achieved by narcotics, non-opiate analgesics including aspirin (acetyl salicylic acid), acetaminophen (paracetamol), small doses of NSAIDs, traditional and herbal medicines, transcutaneous nerve stimulation, massage, manipulation, ultrasound, heat, cold, and psychotropic drugs. These drugs are commonly taken orally, however, suppositories, transdermal patches and injections are also used.

C. Toxicity

Analgesic drugs can cause anaphylactoid attacks, liver problems, and gastrointestinal bleeding - analgesic nephropathy can be associated with compound analgesic usage over long periods of time. Tinnitus is often a side-effect of the high doses used to treat some rheumatic diseases.

D. Therapy cessation

Analgesics should be ceased if major adverse reactions occur. Patients, particularly those who self medicate, should be encouraged to seek the help of health care workers if these side effects occur.

E. Patient advice

Patients with rheumatic diseases should be counselled as to the common side-effects of analgesic therapy. Some side-effects such as tinnitus can be handled by dose reduction, however, serious side-effects such as blood in the stool, blackened stools, gastrointestinal pain and anaphylactoid reactions should be brought to the immediate attention of a health care worker.

4. REGULATORY ASPECTS OF ANTIRHEUMATIC DRUGS

Drug regulatory practices vary greatly across countries. The IFPMA and WHO have standards for drug approval and drug regulation that can be adapted to developing countries. (See Annex III.) Those countries with no or limited drug regulatory practices should consider adopting these guidelines for the production, marketing and distribution of antirheumatic drugs.

Countries must adopt quality assurance and quality control practices for the production and distribution of generic medications to ensure that patient safety is a prime consideration.

5. TESTING PROTOCOLS FOR ANTIRHEUMATIC DRUGS

5.1 NSAIDs

The principle effect of an NSAID is to produce symptomatic relief. This occurs relatively rapidly and usually within 2 weeks. Minor modifications of the EULAR Guidelines (Annex III) on testing NSAIDs were made and were adopted. Discussion stressed the importance of continuing to include placebo in early trials of efficacy. Early pharmacokinetic studies will allow development of appropriate dosing schedules and long-term studies should be directed at assessment of the important adverse reactions. The importance of including functional indices and quality of life measures as end-points in these trials emphasizes the requirement for validation of these instruments in different clinical and geographic situations.

5.2 Antirheumatic drugs

A new classification for antirheumatic drugs was proposed.

- A. Symptomatic or Ameliorative: NSAIDs, SAARDs, Steroids
- B. Disease Modifying

Features of a disease modifying ARD would include the ability to reduce the erosion rate and to diminish functional deterioration by decreasing inflammatory synovitis over a prolonged period of time. Speakers stressed the need to develop better methods of detecting cartilage deterioration including MRI, ultrasound, and microfocal radiography. Functional indices were also emphasized as important end-points. Further studies needed to be carried out to identify those patients likely to develop erosive disease. It was pointed out that since most patients with RA who develop erosions will do so within 2 years of disease onset, it is these patients in whom it is most likely to be able to demonstrate the ability of a drug to reduce the development of erosions.

Further standardization of trial methodology, end-point development and evaluation is required and this should be continued in concert with other interested groups such as the EC concerned action programme in Rheumatology and the EULAR studies group.

### 5.3 Drugs acting in osteoarthritis

Although it was recognized that some drugs have the potential to reduce cartilage degeneration or enable cartilage repair, there are few validated human studies to support these concepts. Methods for assessing cartilage degeneration include a variety of imaging techniques such as MRI, ultrasound and plain radiography as well as biochemical markers in blood, synovial fluid and urine. None of these methods have been adequately assessed and a great deal of work is required to develop useful ways of measuring disease progression in OA. Issues such as the natural history of OA and the long duration of follow-up needs to be considered when designing clinical trials for these drugs. Certain groups of patients were identified for particular study (Annex IV). However, it was felt that a great deal more preliminary work on developing valid end-points was required before clinical trial guidelines could be developed.

## 6. REGISTRY OF THERAPEUTIC EVALUATIONS IN RHEUMATIC DISEASES

The concept of a registry of therapeutic studies in rheumatic diseases was discussed and generally recommended for consideration by ILAR. This registry ought to be located in Geneva and based at WHO. Coronary heart disease, Diabetes, AIDS are diseases with study registries. The benefits of a registry would be to encourage collaboration amongst investigators, manufacturers, regulatory agencies and patients interested in therapies in rheumatic diseases. Such a registry would permit the survey of studies worldwide on a rheumatic disease therapy, enhance the ability to access studies that should be considered for meta-analyses, enhance the study of long-term exposure, permit the identification of the risk to subsets of patients not heavily represented in original trials, and generally encourage scientific improvement of rheumatic disease therapies.

A committee to prepare a specific report for ILAR was formed by Dr K.D. Muirden, President, ILAR. The committee was charged with the task of preparing a specific proposal for a registry by considering registries in other disease areas, proposing a format for the registry and drafting a budget for the first five years of support. Various mechanisms for financing such a registry were discussed: access charges, grants from governments and industry, WHO and ILAR.

## 7. RECOMMENDATIONS

1. Important differences exist between ILAR countries in regulatory control, clinical use and monitoring of antirheumatic drug therapies. Studies should be conducted into the sources of these variations.
2. Departments of Health should be made aware of the problems with quality control and marketing of OTC preparations for use in the rheumatic diseases, and in particular the combinations of corticosteroids in these preparations.
3. NSAIDs are overused in non-inflammatory rheumatic disease. In general, the primary indication for their use is inflammatory arthritis. They should be used with great care in the elderly, in those with a previous history of peptic ulceration and those with cardiac, renal or liver disease. In patients with osteoarthritis their use should be restricted to short-term treatment with the lowest dose required to suppress symptoms.
4. SAARDs may be used both early and late for treatment of chronic inflammatory arthritis but should only be initiated by a medical practitioner with special training and experience in their use. SAARDs have serious and special side-effects requiring regular clinical and laboratory monitoring by a health care worker aware of the potential adverse effects.

5. Corticosteroid therapy should only be initiated on recommendation of a medical practitioner with special training and experience with their use. Patients prescribed corticosteroids should be made aware of the adverse effects of long-term therapy and the importance of regular review by a medical practitioner with special training in management of rheumatic diseases.
6. Asymptomatic hyperuricaemia does not require hypouricaemic drug therapy. If hyperuricaemia requires treatment, measures may include weight reduction, diet modification, reduced alcohol consumption and where necessary appropriate drug therapy.
7. Governments should be encouraged to adhere to IFFMA and WHO (see Annex III) guidelines for the manufacture, distribution and marketing of antirheumatic drugs and to develop methods for enforcement of these guidelines.
8. Governments and individuals should be informed of antirheumatic drugs withdrawn from sale and the reasons for this withdrawal. It is recommended that one of the ILAR Standing Committees (the ILAR Standing Committee on Clinical Studies) be responsible for developing (along with WHO) a mechanism for effective exchange of information on restrictive decisions relating to antirheumatic drugs. The Pharmaceutical Programme can be instrumental in this activity.
9. That the guidelines for testing of NSAIDs (Annex IV) be adopted and that promulgation be discussed by the ILAR Executive.
10. That the classification of antirheumatic drugs outlined in Annex IV be adopted, and that the ILAR Standing Committee on Clinical Studies with the help of Drs J. Smollen and D. Scott be asked to review protocols for testing of Disease Modifying Antirheumatic drugs.
11. That the guidelines for testing drugs for use in osteoarthritis be further developed by the ILAR Standing Committee on Clinical Studies.
12. That on currently available data in humans, there is no evidence to suggest that any particular NSAID is chondroprotective and that the term 'Chondroprotective' should be used with caution.
13. That a register of therapeutic interventions in rheumatic diseases be established as a joint WHO/ILAR initiative.
14. That the Secretary-General of ILAR be asked to prepare a position paper on the establishment and funding of such a registry, to be presented to the ILAR executive at its meeting in Cairo in September 1991.
15. That the WHO publication on Essential Drugs be reviewed by Drs J. Darmawan and P.M. Brooks with regard to the inclusion of a specific section on antirheumatic disease drugs in the next edition.
16. That ILAR assist WHO to produce a booklet on antirheumatic drugs for their series on model prescribing.



FOURTH JOINT WHO/ILAR TASK FORCE  
MEETING ON RHEUMATIC DISEASES

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\* \* \* \*



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LIST OF WORKING PAPERS

1. Survey of Antirheumatic Drug Use and Availability in Argentina. An Introduction, O. Hubscher
2. Survey of Antirheumatic Drug Use in Australia, P.M. Brooks
3. Antirheumatic Drug Use Practice in Brazil, W.H. Chahade
4. Survey of Drug Use Practice: A Canadian Experience, A.S. Russell
5. Antirheumatic Drugs in The Mainland of China, Zhang Nai Zheng
6. Drug Use (Practice) in Indonesia and the Asia Pacific Countries, J. Darmawan
7. Survey of Antirheumatic Drug Use in Japan. M. Nobunaga
8. Survey of Use of Drugs for Rheumatic Disease in Sweden. In "Regulation of use of drugs for rheumatic disease", A. Bjelle
9. Drugs for Rheumatic Diseases: Use and Practice in the United States. A Brief Report, H.E. Paulus
10. The Main Aim of the Drug Treatment of Rheumatic Diseases in the USSR, V.A. Nassonova
11. Guidelines for Use of NSAIDS, G. Mintz
12. Guidelines for the Safe Use of NSAIDS in Developing Countries, J. Darmawan
13. Background Paper for ILAR/WHO Meeting, D.L. Scott
14. Testing of Drugs for Rheumatic Disease, Development of testing protocols for slow-acting anti-rheumatic drugs, H.E. Paulus
15. Problems in the Design and Interpretation of Trials of Second-Line Agents, K.J. Bulpitt and H.E. Paulus
16. The Use of Surrogate Markers in Clinical Trials of SARDS, H.E. Paulus
17. Development of Guidelines for Use of Corticosteroids in Rheumatic Diseases, P.M. Brooks, V.A. Nassonova, M. Nobunaga
18. Hypouricaemic Agents in Rheumatic Diseases, O. Hubscher
19. Hyperuricaemic Agents, Proposals and Discussions, A. Bjelle
20. Development of Guidelines for Use of Antirheumatic Drugs: Analgesics, G.E. Ehrlich, A.S. Russell & Zhang Nai Zheng
21. Regulations for the Use of Drugs in Rheumatic Diseases - Development of Guidelines for use of antirheumatic drugs - Experimental and chondroprotective, M. Lequesne
22. Distribution of Anti-Rheumatic Drugs and Availability in Indonesia and the Asia Pacific Countries, J. Darmawan
23. Regulatory Aspects of Antirheumatic Drugs: Advertising, G.E. Ehrlich, M. Cone & A. Tyndall

24. Regulatory Aspects of Antirheumatic Drugs - Educational Aspects, R. Grahame
25. Educational Aspects - Patients and Health Professionals, A. Bjelle
26. Ethical Issues on Drug Trials and Regulation of Drug Availability in Developing Countries of the Asia Pacific, J. Darmawan
27. Ethical Issues for Drug Trials in Developing Countries, O. Hubscher
28. Ethical Issues for Drug Trials in Developing Countries and Regulation of Drug Availability, J.M. Mbuyi-Muamba
29. Development of Testing Protocols for NSAIDS, P.M. Brooks, J. Boyle, C.H. Goldsmith
30. Testing Protocols for Slow-Acting Antiosteoarthrotic Drugs ("Chondroprotective Agents" included), M.G. Lequesne
31. Trial Registers, Industry and Government Regulatory Efforts and Meta-analysis of Results, C.H. Goldsmith
32. Access and Confidentiality in "Establishment of Clinical Trials Register", A. Bjelle
33. The Establishment of a Clinical Trial's Register. Site, Staffing, Funding, K.D. Muirden
34. Recommendation for Registry
35. Generic versus patented drugs, M. Nobunaga
36. Generic versus patented drugs, W.H. Chahade



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LIST OF WHO, IFPMA AND OTHER DOCUMENTS

1. IFPMA Code of Pharmaceutical Marketing Practices, 1989, IFPMA, Geneva.
2. Ethical Criteria for Medicinal Drug Promotion, 1988, WHO, Geneva.
3. Structure and Activities, Revised Version, September 1989, IFPMA, Geneva.
4. Training in Quality Control, IFPMA, Geneva.
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11. WHO Model Prescribing Information: Drugs Used in Anaesthesia, 1989, WHO, Geneva.
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WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

FOURTH JOINT WHO/ILAR TASK FORCE  
MEETING ON RHEUMATIC DISEASES

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ANNEX IV

FINAL RECOMMENDATIONS FOR:

1. GUIDELINES FOR USE OF ANTIRHEUMATIC DRUGS
2. DEVELOPMENT OF TESTING PROTOCOLS FOR ANTIRHEUMATIC DRUGS

## 1. GUIDELINES FOR USE OF ANTIRHEUMATIC DRUGS

### NSAIDs - Goals of these guidelines

- A) - To improve the therapeutic benefits of this group of medications, measured by:
- improvement in patient's well-being,
  - improvement in physician assessment of patient's condition,
  - improvement in function,
  - improvement in the "natural history" of the disease.
- B) - To identify the risk of potentially dangerous side reactions, measured by:
- patients tolerance to medication,
  - absence of symptoms and signs of intolerance or toxicity,
  - patients compliance to the prescription.
- C) - To increase physicians' awareness of important drug interactions.

### Indications

In principle NSAIDs are not curative medications. They may be useful in the treatment of minor musculoskeletal problems and a variety of nonrheumatic diseases. In some acute conditions, like acute gout, they may seem to "cure" the patient, but they are only interfering in the inflammatory process and shortening the duration of that particular manifestation of the disease, and not curing the gout. In chronic illnesses, like rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, etc. the expected effects of NSAIDs are:

1. to decrease inflammation;
2. to decrease pain;
3. to improve function.

NSAIDs may vary in pharmacological properties and individual patients vary in their responsiveness to different drugs. The potential toxicity should be kept in mind and careful consideration given to safety and long-term administration. A list of common rheumatic diseases where NSAIDs may be indicated:

- rheumatoid arthritis
- ankylosing spondylitis
- other seronegative spondylarthropathies
- gout and pseudogout
- osteoarthritis
- non-articular rheumatism
- back pain
- sports injuries and trauma

### Dosage

Clinically some patients respond to one NSAID and not to another. Some have toxic reaction to one, not to another. Therefore when patients fail to respond to one drug or develop an adverse reaction, it may be worthwhile to try another.

The philosophy of treatment should always be to start with a low dose of an NSAID and to try to avoid progressing to higher doses.

NSAIDs should in general be used one at a time and not in combination because of the risk of increased adverse reactions.

### Toxicity

The main toxicity of these medications is in the gastrointestinal tract. Epigastric distress, nausea, vomiting, peptic symptoms are universally reported in studies of all the NSAIDs. Occult blood in the stools is usually found, however, more serious side effects like severe upper gastrointestinal bleeding or ulcer perforation are infrequent except in the frail elderly. Reactivation of peptic ulcer can occur.

Patients on continuing medication of NSAIDs should be regularly reviewed.

Some clinicians recommend the ingestion of medications with meals and antacids. Some physicians recommend H2 blockers (such as cimetidine or ranitidine), prostaglandin analogues (such as misoprostol) or proton pump inhibitors (such as omeprazole) or mucosal protectors (such as sucralfate), however this area requires further studies.

Diarrhoea, lower intestinal bleeding, pancreatitis, low white blood cell count, agranulocytosis and hepatic toxicity may rarely occur.

Local prostaglandin synthesis in the kidney is inhibited by NSAIDs. This may produce water and salt retention and, in some patients, can lead to acute renal failure. Recently reports have appeared of NSAID-induced immune mediated nephritis. Analgesic nephropathy can be found after large and prolonged doses of combined aspirin and phenacetin.

Skin reactions or allergy are a potential side-effect of all NSAIDs, from morbilliform rash to toxic epidermal necrolysis. Anaphylactic reactions have also been reported.

#### Duration of use and special precautions

Duration of administration will depend on the therapeutic indication in the specific patient.

None of the NSAIDs have been studied in pregnancy. Efforts should be made to avoid their use during the first trimester because of the possibility of teratogenesis and in the last prepartum weeks because of the potential of diminished uterine activity, increased postpartum bleeding, and premature closure of the ductus arteriosus.

They should be avoided if possible during lactation since small amounts of NSAID can be secreted in the maternal milk.

NSAIDs should be used with caution in the elderly because of possible GI side effects. Smaller daily doses should be prescribed initially and changes made according to the patient's response.

#### Monitoring

In all patients receiving NSAIDs the practitioner should ask about skin rashes, abdominal symptoms, bleeding from the GI tract and central nervous system symptoms as well as other history as appropriate at regular intervals. In higher risk patients, a baseline complete blood count, liver function tests and renal function tests (blood urea or blood urea nitrogen plus creatinine) should be obtained and monitored appropriately.

#### Interactions

Anticoagulants. Patients receiving these drugs should have frequent monitoring of coagulation parameters.

Oral hypoglycaemics. Patients receiving these should be followed closely in respect of the control of diabetes.

Antihypertensives and diuretics. NSAIDs may alter renal function and control of blood pressure in patients taking antihypertensive drugs. These patients should be carefully followed.

#### High Risk Patients.

Elderly & frail  
History of peptic ulcer:  
History of upper GI bleeding:  
Advanced cirrhosis with ascites:  
Impaired renal function  
Previous aspirin or NSAID  
hypersensitivity

#### Recommendation

Avoid use if possible  
Avoid use if possible  
Avoid use if possible  
Avoid use if possible.  
Avoid use if possible  
Avoid use

Guidelines for the use of slow-acting antirheumatic drugs (SAARDs) in rheumatoid arthritisBackground

This is a diverse group of therapeutic agents traditionally classified together. The drugs in this class include injectable gold and oral gold, D-penicillamine, sulphasalazine, hydroxychloroquine, chloroquine, azathioprine, and methotrexate. There is debate about the most suitable terminology for these drugs; in this document they will be referred to as SAARDs.

Initiation and supervision

These drugs should be initiated by a medical practitioner with special training and experience in their use. Patients receiving these agents require regular monitoring, primarily for safety, which should be supervised and arranged by the initiating clinician. However safety monitoring can be delegated to various health care providers as appropriate to the setting. Monitoring must be individualized for each SAARD.

Indications for initiation

These drugs are appropriate in both early and late rheumatoid arthritis in patients with persistently active disease.

Indications for discontinuation

The drugs should be stopped if there is a clinically significant adverse reaction or persistent lack of effect. The detection of adverse reactions should include assessment of the patient and laboratory and urine testing as individualized for different drugs. For significant adverse reactions the drug should be withheld and the supervising clinician consulted. Many patients have an incomplete clinical response and the drugs should be given for an appropriate length of time in appropriate dose before they are stopped because of lack of effect. Usually discontinuation for lack of effect should only be done following consultation with the medical practitioner initiating and supervising therapy.

These drugs have many serious adverse effects and these should be familiar to the initiating clinician and to the health care worker monitoring the treatment. They should be avoided, if possible, in pregnancy. Studies to ascertain cost effectiveness of monitoring regimens should be carried out.

Specific drugs

Injectable gold: given intramuscularly, initially 15-50 mg weekly, increasing the interval between dosages after optimal improvement has been attained and sustained regularly. Safety monitoring, including full blood count with assessment of platelets and urine testing for proteinuria, is required. Significant adverse reactions include a major rash, severe stomatitis, proteinuria, low white cell count, and thrombocytopenia.

Oral gold: given orally, 3-9 mg daily. Safety monitoring, includes full blood count with assessment of platelets and urine testing for proteinuria. Significant adverse reactions include major rash, diarrhoea, proteinuria, low white cell count, and thrombocytopenia.

D-Penicillamine: given orally, initially 125-250 mg daily, slowly increasing if desired to a maximum dose of 750 mg daily. Safety monitoring, includes full blood count with assessment of platelets and urine testing for proteinuria. Significant adverse reactions include major rash, proteinuria, low white cell count, and thrombocytopenia.

Sulphasalazine: given orally, initially 500 mg daily, increasing every 1-2 weeks to 2-3 gm daily. Safety monitoring includes full blood count with assessment of platelets. Significant adverse reactions include major rash, nausea and other gastrointestinal symptoms, low white cell count, and thrombocytopenia. Liver function may be adversely affected. This agent should be avoided in patients with G-6-P deficiency.

Hydroxychloroquine and chloroquine: given orally, with maximum doses of 4 mg/kg/day lean body weight for chloroquine and 6 mg/kg/day for hydroxychloroquine. Safety monitoring requires preliminary and regular ophthalmic examination with assessment of the visual fields. Significant adverse reactions include ophthalmic toxicity and myopathy.

Azathioprine: given orally, 1.25-2.5 mg/kg/day. Safety monitoring requires full blood count with assessment of platelets. Significant adverse reactions include gastrointestinal symptoms, fever and other allergic reactions, low white cell count, and thrombocytopenia. It should be avoided in patients with previous or current malignant disease.

Methotrexate: given orally or intramuscularly, usually 2.5-15 mg weekly, with a low initial starting dose. Safety monitoring includes full blood count with assessment of platelets. Significant adverse reactions include stomatitis and other gastrointestinal symptoms, teratogenesis, low white cell count, and thrombocytopenia. Hepatic and pulmonary adverse reactions may also occur. Trimethoprim and alcohol should be avoided.

Other drugs: cyclosporin, chlorambucil, cyclophosphamide, levamisole and dapsone are given occasionally but their use is not routine and should be restricted.

#### Guidelines for use of corticosteroids in rheumatic diseases

- a. Indications
- b. Dosage
- c. Toxicity monitoring
- d. Duration of use
- e. Special precautions, e.g. pregnancy, lactation and the elderly

#### Introduction

Corticosteroids remain one of the most powerful agents for control of inflammation in the rheumatic diseases.

The basic mechanisms of action of corticosteroids include:

1. Increase in production of lipocortin and subsequent inhibition of phospholipase A2.
2. Reduced production of cytokine in inflammatory enzymes.
3. Alteration in T & B cell function.
4. Reduction in Fc receptor expression.
5. Changes in white cell traffic.

The principal glucocorticoid hormone of the human adrenal cortex is cortisol (hydrocortisone). There are a number of synthetic corticosteroid preparations which tend to have greater glucocorticoid activity and less mineralocorticoid activity.

The commonly used glucocorticoids are shown in Table 1.

Corticosteroids may be given orally, intramuscularly, intravenously or intra-articularly. These various routes of delivery are used in specific situations as outlined below.

#### Indications

The major indication for use of corticosteroids is for severe inflammatory joint disease or systemic connective tissue disorders. These include:

- Systemic connective tissue diseases (SCT)
- Systemic vasculitis
- Systemic Juvenile Chronic Arthritis
- Rheumatoid arthritis (RA)
- Seronegative Spondyloarthropathies

Table 1

Duration of Action	Equivalent Oral or Intravenous Doses (mg)	Relative Sodium Retaining Action
Short (T <sub>1/2</sub> 8-12 hours)		
Cortisone	25	0.8
Cortisol	20	1.0
Intermediate (T <sub>1/2</sub> 12-36 hours)		
Prednisone	5	0.8
Prednisolone	5	0.8
Methylprednisolone	4	0.5
Triamcinolone	4	0
Long (T <sub>1/2</sub> 36-52 hours)		
Paramethasone	2	0
Dexamethasone	0.75	0
Betamethasone	0.6	0

In theory, short courses of prednisolone in a fairly rapidly decreasing dose can be used in acute inflammatory synovitis or exacerbations of chronic synovitis in rheumatoid arthritis and seronegative inflammatory arthropathies. Unfortunately, patients started on corticosteroids tend to stay on them. Continuous doses of IV or oral steroids may be used with other immunosuppressive or slow acting antirheumatic drugs in an effort to suppress inflammation and maintain function in SCT and in chronic inflammatory rheumatic diseases.

Intramuscular or intravenous doses of corticosteroids can be used intermittently for induction and maintenance therapy in SCT and inflammatory rheumatic diseases together with immunosuppressive drugs or slow-acting antirheumatic drugs. Further studies need to be done to determine relative efficacy of IV or oral pulse steroid regimens and to determine the most appropriate dose for induction regimens.

Intra-articular injection of corticosteroids can be extremely useful in relieving inflammation in single or multiple joints in inflammatory arthritis, including the crystal arthropathies.

Dosage

- a. Oral - Prednisolone or prednisone should be taken as the prototype compounds. Their great advantage is that they are available in tablets of 1, 2.5 and 5 mg strength. This allows much smaller adjustment in dosage increment or decrements than if the other synthetic steroids such as triamcinolone, paramethasone, dexamethasone or betamethasone are used. Adverse reactions are also more common with fluoridated corticosteroids. Patients may be extremely sensitive to dosage alterations as little as 0.5-1 mg of prednisolone, particularly in conditions such as polymyalgia rheumatica. Alternate day regimens may reduce side effects and still maintain disease control. Preparations of corticosteroids with other drugs such as NSAIDs should not be used.
- b. Parenteral (IMI or IVI) - The commonly used preparations include methylprednisolone and ACTH. Studies to ascertain the appropriate dose and route of administration should be encouraged.
- c. Intra-articular and intralesional injections - Injection of corticosteroids into or around inflamed joints might provide prolonged relief from pain and swelling, improve function and allow physiotherapy to be continued. There is conflicting evidence as to whether these injections actually affect the progression of the rheumatic disease. The doses of intra-articular steroids vary from 5-10 mg for small joints (MCPs, PIPs, DIPs) to 40 mg for moderate sized joints (wrists) to 80-120 mg for larger joints (knees, hips, etc.). Again there is little scientific evidence to show that higher doses are harmful.

### Side effects

The adverse reactions of systemic corticosteroid therapy are listed in Table 2.

Table 2

#### Adverse effects of systemic corticosteroid therapy

Metabolic	- Obesity, Glucose/protein metabolism, electrolyte balance, enzyme induction.
Predisposition to infection Musculoskeletal	- Myopathy, osteoporosis, avascular necrosis, tendon rupture, steroid withdrawal syndrome.
Gastrointestinal	- Peptic ulcer disease (high dose) and pancreatitis.
Ophthalmological	- Cataract and glaucoma.
Central nervous system	- Psychosis depression, benign intercranial hypertension.
Dermatological	- Acne, striae, alopecia, bruising and skin atrophy.
Growth retardation Hypothalamic/pituitary/adrenal axis suppression Impaired wound healing and subcutaneous tissue atrophy Suppression of the immune response	- Secondary infection with bacterial, fungal, viral and parasitic organisms.

The major problems with long-term corticosteroids are those of cushingoid features, obesity and metabolic effects which will occur in about half of the patients treated for five years or more. The risk of osteoporosis from long-term corticosteroids is still not completely delineated but recent studies would suggest that, at doses of 7.5 mg Prednisolone daily or less, the risk of osteoporosis is relatively low as long as mobility is maintained. Thinning of the skin in elderly patients on long-term corticosteroids poses a major problem with skin trauma, infection or after surgery. Patients at particular risk of adverse reactions to steroids may require osteoporosis prophylaxis with hormone replacement therapy or peptic ulcer prophylaxis. Studies to identify those groups particularly at risk should be encouraged. Particular care should be taken to provide mineralocorticoid support during surgery or severe illness.

Adverse reactions can be kept to a minimum if the steroid dose can be reduced or ceased. Once the inflammatory disease has been controlled with steroids or other means, the dose should be reduced slowly and persistently. Patients with polymyalgia rheumatica might need a reducing regimen of not more than 1 mg daily every two months while patients with other conditions might have their steroids reduced more rapidly. The key to successful steroid reduction is to make sure that patients do not manipulate their own dose of steroids (upwards) and that recurrence of musculoskeletal pain is not necessarily considered as an exacerbation of inflammatory disease and, therefore, treated with increased steroid dosage.

### Duration of use

This will depend on the disease treated, i.e. polymyalgia rheumatica or temporal arteritis may require corticosteroids for years, acute exacerbations of rheumatoid arthritis may require corticosteroids for weeks while chronic inflammatory joint disease or connective tissue diseases might require corticosteroids in stable dosage over long periods of time.

### Special precautions

Pregnancy - although corticosteroids have been associated with cleft palate formation in mice and rabbits, there does not seem to be any significant instance of teratogenesis at standard therapeutic doses in humans. Mothers taking corticosteroids are at slightly greater risk of infection or of developing diabetes and foetal adrenal suppression has resulted in babies of mothers on high doses of corticosteroids. Certain corticosteroid preparations (prednisone/prednisolone) seem not to cross the placenta and may therefore be more appropriate for use during pregnancy.

Lactation - corticosteroids are found in small amounts in breast milk with milk prednisolone concentrations of between 5 - 25% of maternal serum concentrations. This means that the baby will only be exposed to small amounts of corticosteroids. Infant exposure to significant corticosteroid dosage will only occur in women taking more than 20 mg or equivalent of prednisolone and these women should avoid breast feeding during the four hours after each dose.

The elderly - corticosteroids might be more likely to produce side effects in the elderly if there is a reduced serum albumin concentration.

### Advice to patients

Patients should be informed as to side effects of corticosteroids and the significant risks of long-term use. Dose of corticosteroids should not be altered without reference to a health care worker with special training in the use of these drugs.

### Guidelines for use of hypouricaemic agents in rheumatic diseases

These guidelines are specifically for the use of hypouricaemic agents in rheumatic disorders and not for the treatment of gout *per se*. However, one must consider gout as a metabolic disorder characterized by hyperuricaemia as a result of the overproduction of uric acid in relation to the patient's ability to excrete it. Hyperuricaemia in gouty patients provokes deposition of urate in the tissues, particularly in joints and kidneys leading to acute gouty attacks and urinary calculi. To prevent or reverse this precipitation, serum uric acid levels should be reduced below the saturation point. This is normally accomplished by a detailed explanation to the patient about the natural history of the disease and by the permanent administration of agents which reduce the production of uric acid (allopurinol) or which increases its urinary excretion (uricosuric agents). In some patients, however, all that may be required is reduction of alcohol intake, treatment of obesity, a low purine diet and avoidance of factors such as use of thiazide diuretics that trigger the occurrence of acute gouty attacks.

The majority of patients with hyperuricaemia do not require long-term drug treatment and there is no role for hypouricaemic drug therapy in the maintenance of asymptomatic hyperuricaemia.

### Allopurinol

This inhibitor of xanthine oxidase (the enzyme that converts hypoxanthine to xanthine to uric acid) is rapidly oxidated to oxipurinol, also an inhibitor of the enzyme, which has a much longer plasma half life. Consequently, an effective xanthine oxidase inhibition is maintained over a 24-hour period with a single dose of allopurinol.

### Indications and dosage in gouty patients

Effective reduction of serum and urinary uric acid concentrations can usually be achieved with 100-800 mg/day in the management of patients with primary or secondary gout presenting:

- . recurrent attacks;
- . tophi;
- . joint destruction;
- . uric acid lithiasis or nephropathy.

In a high percentage of patients a single daily dose of 300 mg is sufficient to achieve normal serum urate levels within a few weeks. Dosage in excess of 300 mg/day should be given in divided doses. Serial (not single) uric acid determinations are normally used to adjust the appropriate daily dose of allopurinol. While adjusting the dosage, concomitant administration of colchicine or NSAIDs are recommended until serum uric acid has been normalized and gouty attacks have been stopped for several months. This is because an increase in acute attacks of gout may occur during the early stages of allopurinol administration. For the same reason it is wise to start with a low dose (100 mg/day) and increase at weekly intervals by 100 mg.

Because it is not an innocuous drug, allopurinol is not indicated for the treatment of asymptomatic hyperuricaemia. An exception to this is the prevention of uric acid nephropathy during therapy of neoplastic disease. Treatment with 600-800 mg/day for two or three days prior to antineoplastic therapy is advisable, together with a high fluid intake.

#### Precautions during allopurinol therapy

- Allopurinol and oxipurinol are primarily eliminated by the kidney. Therefore, the dose should be reduced in patients with decreased renal function. With a creatinine clearance of 20 ml/min or less, 100 mg/day may be adequate. Even lower doses are recommended in patients with extreme renal impairment.

- Skin rashes or other signs or symptoms of an allergic reaction is a formal indication for discontinuation of allopurinol. These hypersensitivity reactions may be increased in patients with decreased renal function and may be followed by severe cutaneous and systemic toxicity and even death.

- An increase in the frequency of skin rashes may occur among patients receiving ampicillin, amoxicillin and thiazides.

- It has been reported that allopurinol may prolong the half life of dicumarol and chlorpropamide. Clinical significance of these findings may be higher in the presence of renal insufficiency.

- Since allopurinol also inhibits the enzymatic oxidation of mercaptopurine (MP), patients receiving this drug or azathioprine (AZA) in addition to allopurinol will require a reduction in dose of MP or AZA to approximately one third to one quarter of the usual scheme.

- Therapy with allopurinol should not be started until a gouty attack has subsided. Toxicity.

The most frequent adverse reactions are skin reactions of various types. An infrequent syndrome consisting of desquamative skin rash, fever, hepatitis, eosinophilia and worsening renal function has been described in several patients receiving standard doses of allopurinol. A high percentage of these patients had evidence of renal insufficiency and one fifth have died as a result of this reaction.

#### Uricosuric agents

These drugs exert their hypouricaemic action by inhibiting the tubular reabsorption of urate. Thus, they may precipitate urolithiasis and renal colic, especially in the initial stages of therapy. Therefore, an adequate fluid intake and alkalization of the urine are recommended. As allopurinol they are also indicate for the treatment of:

- . recurrent gouty attacks;
- . chronic tophaceous gout.

Salicylates antagonize the uricosuric action of these agents (Probenecid, Sulfipyrazone and Benzbromarone are the most commonly used) and for this reason their concomitant prescription is contraindicated in gouty patients. This nullifying effect is not observed on allopurinol. Uricosuric agents should not be started until a gouty attack has subsided and then the

suitable daily dose should be reached gradually. It should be noted that these drugs may not be effective in chronic renal insufficiency particularly when the glomerular filtration is 30 ml/min or less.

Uricosuric agents are not indicated for the treatment of asymptomatic hyperuricaemia.

#### Concomitant use of allopurinol and uricosuric agents

The clearance of oxipurinol is increased by uricosuric drugs. Consequently, the addition of a uricosuric reduces the inhibition of xanthine oxidase by oxipurinol and increases to some degree the urinary excretion of uric acid. In every day practice the effect of this combined therapy may be useful in some patients (particularly in those with large tophi) in achieving minimum serum acid levels.

#### Guidelines for use of analgesics

Pain relief is one of the major objectives in the treatment of arthritis/rheumatic diseases. To achieve this aim, a variety of approaches needs be addressed. Some are administered by physicians and healers, others are self-initiated by the patient or sufferer and may not be known to the physician (or bypass appropriate medical care entirely).

The treatments consist of narcotics, which should generally be avoided in chronic disease and are available predominantly by prescription; non-opiate analgesics, most available without prescription, and including aspirin, acetaminophen (paracetamol), and small doses of nonsteroidal anti-inflammatory drugs (NSAIDs); traditional medicine, including herbal remedies; acupuncture, and moxibustion; and physical approaches, including transcutaneous nerve stimulation, massage, manipulation, ultrasound, heat, and cold, including freezing. The effects of some are central, of others peripheral. And in certain rheumatic syndromes, analgesia is achieved by psychotropic drugs, usually mood elevators, that also regulate non-REM sleep.

Although most analgesics are self prescribed or obtained from sources other than the physician, they should also be considered as adjunctive therapy in rheumatic syndromes while waiting for more definitive therapy to become effective. The physician may be able to reduce doses of more potent and potentially more toxic medications through the judicious use of simple analgesics.

The guidelines should emphasize: awareness on the part of the treating health professionals that their patients are treating themselves or being treated by others; awareness that these various treatments may have unfavourable consequences; awareness that these measures could interfere with assessment of prescribed treatments. Among the unfavourable consequences are anaphylactoid attacks during intermittent administration (e.g. aspirin, zomepirac); possible interference with liver metabolism of NSAIDs (paracetamol); delay in applying definitive treatment or diagnosing the disorder because of self-induced suppression of symptoms for a time. Analgesic medications, whether pharmaceuticals or herbals, often are formulated in combinations (with corticosteroids, with potent NSAIDs, or with decongestants and antihistamines in medications against the common cold). These preparations are not recommended.

Pharmaceutical analgesics are administered chiefly by oral route, but are popular also as creams and gels for topical administration aiming at transdermal transfer. Suppositories, transdermal patches, and injections are additional modes of administration.

Because the main modes of administration are under the control of the sufferer, factors such as weight, age, renal and hepatic function, pregnancy, and previous intolerance of related compounds cannot be monitored in advance. Therefore, education of the public becomes an all-important factor. This must emphasize the precautions and the need to inform the health professional and, as a corollary, emphasize potential consequences and interactions to the health professional. Quality assessment, as in the book, Guidelines médicaments vendue sans ordonnance by J.P. Giroud and C.G. Hagège, would also help patients make informed choices. Traditional medicine must substitute for pharmaceuticals in much of the developing world, for economic, social, and cultural reasons.

Thus, guidance to the consumer is the paramount need, especially in self medication, because the ready availability of the medications or the bypass of standard medicine by unscrupulous promoters make it appear that such approaches are harmless. They're not.

Pain is a subjective symptom. Labelling drugs as useful in mild, moderate, or severe pain fails to recognize the imprecision of these terms and the cultural factors that govern, not pain perception, but pain reporting. It would thus be best to agree on labels for pharmaceuticals that indicate rapidity of onset of pain relief, peak effect, and duration of effect. That would permit informed choices for the treatment of acute, self-limited pain and chronic pain. Addictive or habituating potential of the various treatment must be taken into account.

## 2. DEVELOPMENT OF TESTING PROTOCOLS FOR ANTIRHEUMATIC DRUGS

The principal effect of a non-steroidal anti-inflammatory drug (NSAID) is analgesic and anti-inflammatory and the response is, therefore, symptomatic. Most of the end-points to be used are subjective and it may be difficult to discriminate between the analgesic and anti-inflammatory effect. NSAIDs are quick acting and maximum efficacy is usually obtained within two weeks. Some of the long half-life NSAIDs might, however, take a little longer to reach steady state (particularly in joint tissues) and, therefore, sufficient time should be given to take this into account when assessing efficacy.

NSAIDs may be tested in the following groups of rheumatic diseases:

- a. Inflammatory diseases of the joints of the extremities and spine including rheumatoid arthritis, ankylosing spondylitis and related conditions, other systemic connective tissue disorders.
- b. Certain metabolic joint diseases, e.g. gouty arthritis or chondrocalcinosis.
- c. The degenerative arthropathies, involving the joints of extremities and spine.
- d. Soft tissue or non-articular rheumatism, including diseases of muscles, tendons, tendon sheaths, painful conditions of muscles caused by postural, occupational or other factors.
- e. Pain models to investigate analgesic effect, i.e. dental pain, post-episiotomy or other post-operative pain and pain of osteoarthritis.

### Principles to be considered:

#### Ethics

All drug trials should be conducted in accordance with the Declaration of Helsinki (British Medical Journal, 1964; 2:177). Before undertaking a trial of a new drug for the treatment of rheumatic diseases, it is important to consider whether the drug in question is likely to offer any advantage over drugs already available. This applies particularly to NSAIDs as there are already a considerable number.

#### Objectives

Studies of NSAIDs should be planned to establish in the short and long term:

1. Efficacy (relief of pain and stiffness and improvement in function).
2. Safety.
3. Relative efficacy in safety, the trial drug being compared to at least one reference drug.
4. The mode of action.

### Type and design of trials

The characteristics of the disease to be treated should be considered in the design of the clinical trial, i.e. rapid fluctuations in disease activity, slow progressive disease, stable disease, etc., or acute arthritis, e.g. gout, or chronic disease, e.g. osteoarthritis. Studies can be conveniently classified into phases - the phases recognized for the purposes of this document are:

- a. Initial studies in man (human pharmacology).
- b. Pilot therapeutic trials and dose finding studies.
- c. Main therapeutic trials.
- d. Long term studies (for safety) or special investigations - extremes of age, interactions, etc.

Background information on the trial drug and its anticipated relevance in treatment, as well as the objectives and anticipated problems of the trial, should be set out when a study is designed.

The patient sample should be as homogeneous as possible, if subgroups can be identified they should be stratified. There must be a requirement for drug treatment. The possible effects of non-drug therapy (physiotherapy, surgery, immobilization, etc., or changes in life-style with possible therapeutic influence) should be taken into account in the design of the studies.

### Initial studies in humans

These usually comprise initial investigations on a few healthy volunteers or on a small number of hospital patients in order:

- to confirm the findings of animal experiments;
- to obtain initial data on pharmacokinetics; and
- to determine the approximate dose.

### Pilot therapeutic trials and dose finding studies

These investigations involve a larger number of patients that are often carried out as open studies on patients in hospital. They are designed to obtain reliable basic data on matters which include the following:

- \* Pharmacokinetics - dynamics.
- \* Presence of a therapeutic effect - this might involve the first comparison with a placebo. These early placebo controlled trials should be of at least six weeks duration and the use of acetaminophen (paracetamol) should be allowed, recorded and used as a measure of efficacy.
- \* Dose response and dose ranging studies - these should be:
  - a. Placebo controlled.
  - b. Involve cohorts of patients who are assigned a particular dose and either stay on it for the duration of the trial or drop out.
  - c. Not involve complex dose titration regimens which are difficult to interpret or analyse.
- \* Elderly patients might be included if the drug is likely to be used in this age group.
- \* An impression of the potential indications for the use of the drug.

- \* Principal short-term adverse reactions to the drug. These should include blood loss studies using labelled chromium and endoscopic studies.
- \* Major reasons for non-response.
- \* Possible interaction with other drugs particularly anticoagulants, anticonvulsants and antihypertensive agents.

#### Main therapeutic trials

Before starting these trials, there should be a critical appraisal of work in the earlier phases to ensure that there is a therapeutic effect and that this (and the effects observed on laboratory variables) justify further studies.

The main trials involve:

- \* Controlled studies with a sufficient number of patients to reach statistical significance and avoid a type 2 error (i.e. the risk that a difference which is indeed present between two groups with fail to be demonstrated). The dose range of the trial drug believed to be optimal should be employed.
- \* Comparison with active reference drugs (and perhaps further placebo trials) within appropriate dose ranges in relation to the dose response curve of the trial and the reference drug.
- \* Study of individual preferences (in cross-over studies only).
- \* Controlled withdrawal studies (where appropriate).
- \* Long-term studies (provided a reasonable number studied, i.e. 100 for 1 year and 500 for 6 months) and special studies.
- \* Further studies (including post-marketing evaluation and surveillance).
- \* Continued controlled trials to broaden knowledge of the therapeutic effect, indications and adverse reactions.
- \* Trials for new indications.
- \* Studies in special subgroups of patients, e.g. elderly patients (>65 years), diabetics, children and other groups at special risk. This may include pharmacokinetic and pharmacodynamic studies in patients with renal, hepatic, cardiac insufficiency.
- \* Long-term efficacy - safety studies which, in chronic disease, are of particular importance in view of possible fluctuations in the disease and the long-term effects (wanted or unwanted) of prolonged drug treatment. Long-term safety studies can be open, but it is obviously of medical importance to determine how safe a drug is as compared with others of its type.
- \* Benefit-risk and benefit-cost analysis where these are required.

#### Selection of patients

Clear diagnostic criteria of the conditions under study should be set out and fulfilled by patients entering into the trial should include age, sex, weight, height and the main characteristics of the disease. Disease complications and concurrent treatment should be recorded such that their effects, if any, on the results of treatment with the new drug may be determined. In view of the age structure of the rheumatic population, it is particularly important that elderly patients be studied from an early phase, both in kinetic and therapeutic investigations.

#### Clinical trial design

The nature and specific uses of various study designs are summarized below:

1. Open study - both the patient and the doctor know which drugs are in use throughout the trial. These studies are of limited value for demonstrating efficacy, primarily because of the subjective influence on assessments.
2. Single blind study - either the doctor or the patient knows which drugs are being used in each case. An alternative is the use of an independent blinded observer.
3. Double blind study - neither patient nor doctor know which drug, active or placebo or reference, is given during the various phases of the trial. An alternative is the use of an independent blinded observer.

### Controls

In all comparative studies, patients should be randomly allocated to receive the active compound or the placebo. Special tables for randomization are available. The randomization should take place after the patient is accepted for inclusion into the trial. Stratification may also be required if there is wide variation in the patient material. When choosing treatment for the control group, it should be decided whether it is desirable or ethically justifiable to use a placebo or whether another active (reference) drug should be used for comparison.

Controls can, in principle, be of two types:

- a. Controlled trials with a parallel group - random allocation is essential and double blinding techniques should be applied.
- b. Cross-over designs in which patients serve as their own controls.

Cross-over trials are mainly useful for drugs with a short half-life or a short duration of effect and where the effect is reversible. If this is not the case, carry-over effect might invalidate the results. Consideration should also be given to the possibility of the difference in the carry-over effect between the two drugs. The desirability or necessity for a washout period before entering into the trial and between the different phases of the cross-over study will depend on the carry-over effect of the drugs involved in the trial and of any drugs taken in advance. In cross-over studies, the order of administration of drugs should be randomized since it might affect the outcome, e.g. if the first drug given produces a greater placebo effect.

Where the above-mentioned criteria for performance of a valid cross-over trial cannot be met, preference should be given to comparative parallel between patient studies.

### Importance of selecting patients with responsive (to NSAIDs) disease

In inflammatory forms of arthritis such as rheumatoid arthritis or the seronegative arthropathies where patients are already taking NSAIDs, a flare in disease (pre-determined increase in clinical parameters such as joint count, pain score or duration of morning stiffness) should be demonstrated by substituting placebo for their usual NSAID therapy prior to entering the trial. Only patients who demonstrate a flare in disease activity should be admitted to the study and, therefore, randomized to received placebo or active compounds. In the ideal situation, a similar substitution of placebo should be carried out at the end of the trial to demonstrate that the patient has had responsive disease throughout the study period. Timing of the placebo flare should be organized so as to minimize the duration of the flare.

### Multicentre trials

These are often necessary to obtain a sufficiently large number of patients within a short period. In a multicentre trial, the selection of patients and the collection of data are carried out by a number of physicians. The number of patients from each centre should be fairly similar and should be sufficient to exclude potential biases. A multicentre trial introduces certain difficulties regarding the comparability of patients as well as introducing observer differences. But these failure can be compensated for in the design.

### Treatment schedules and dosage

The dosage schedule to be employed should be specified and explained in advance. Detailed instructions should be given. There should be a well defined design for changes in doses during the trial if indicated. Fixed dose increments or individual dose titration may be necessary in pilot studies or even in major clinical trials. The time of intake of the drug in relation to meals should be known and recorded. Any reference drug (used as a control) should be given at the accepted therapeutic dose so that comparisons of efficacy and safety can be valid.

### End-points

There are a wide variety of clinical end-points that can be used in trials of NSAIDs. They should, however, fulfil the following criteria (from Bellamy, Baillieres Clinical Rheumatology, 1988;2:page 339).

### Criteria for evaluative indices for musculoskeletal clinical trials

1. The index should be designed for a specific purpose.
2. The index should have been validated on individuals or populations of patients having similar characteristics to future study populations.
3. Reliability should be adequate for achieving measurement objectives.
4. Validity (face, content, criteria and construct) should be adequate for measurement objectives.
5. The index must be responsive (i.e. able to detect significant change in the underlying variable).
6. Index performance should be maintained in subsequent applications under similar study conditions.
7. The method of deriving scores, particularly in composite indices, should be both credible and comprehensible.
8. The feasibility of data collection and instrument application should not be constrained by time or cost.
9. The measurement process must be ethical.
10. Utilization of the index should have been adopted by other clinical investigators.
11. The influence of language, cultural differences and other factors on the end-points should be appreciated.

The following end-point measurements can be used:

- a. Pain - Likert scale, visual analogue scale, numerical rating scale, graphic rating scale, continuous chromatic analogue scale and pain face scale. Behavioural observation methods can also be used as well as pain questionnaires (McGill or analgesic consumption).
- b. Joint count - articular index (Lansbury index, ARA Cooperating Clinics index, Ritchie index for RA, Doyle index).
- c. Global assessment, use of signal measurements, i.e. signal joints or signal functions.
- d. Functional indices and quality of life measures, arthritis impact measurement scales (AIMS), functional status index (FSI), health assessment questionnaire (HAQ, Mactar and the WOMAC).
- e. Joint stiffness - duration or visual analogue.

f. Performance tests - grip strength, duration of 50 foot walking time.

The preferred outcome measures in clinical trials in rheumatoid arthritis and osteoarthritis have been noted by workers in this field (Bellamy, Clinical Rheumatology; 1982;2:739-862).

a. Rheumatoid arthritis: (top 11 ratings)

- Joint count
- Pain (change)
- Global activity (change)
- Pain (absolute)
- Global activity (absolute)
- Joint stiffness
- Grip strength
- 50 foot walking time
- Joint swelling
- ESR
- Quality of Life Measures

Function (top 5)

- Self Care
- Physical activity - mobility
- Pain
- Role activities
- Mental health

b. Osteoarthritis: (top 13 ratings)

- Pain
- Patient global assessment
- Range of movement
- Physician global assessment
- Joint stiffness
- Qualitative aspects of sleep
- Walking time
- Activities of daily living
- Joint tenderness
- Analgesic consumption
- Joint swelling
- Signal joints
- Quality of Life Measures

Before any clinical studies are undertaken, investigators should decide what degree of response will be regarded as clinically useful.

With investigations of drugs used in rheumatic diseases, it is particularly important not to place excessive weight on objective responses as against well validated subjective responses - the latter might be a more sensitive indication of the patient's well-being. Measurements should be standardized as far as possible, and ideally be undertaken by the same investigator and at the same time of day on each occasion. All tests should be defined exactly by how measurements should be made and how questions should be asked. This is especially important in a multicentre trial where differences in approach between the various centres can all too easily occur. Questions put to patients should be standardized, with an alternative way of asking each question if at first it is not fully understood.

Withdrawal from the trial

Because of adverse reactions, lack of effect or lack of patient cooperation.

The reason for all deliberate withdrawals and dropouts should be clearly recorded. They should be scored as failure of/or intolerance to the trial drug and included in the statistical analysis unless they are clearly unrelated to therapy, e.g. intercurrent illness or injury, secondary exclusion or migration.

### Adverse reactions and side effects

Adverse reactions and side effects observed by the investigator and elicited from the patient in response to the question, "How is/are the medicine(s)/tablet(s) suiting you?" should be recorded. In addition, all medical events occurring during the course of the trial, even if not apparently related to the trial drug should be recorded.

### Measures to monitor compliance

Compliance can be checked during the trial by asking the patients, by counting the remaining tablets or by monitoring plasma drug levels or urine metabolites. The methods used should be stated in the protocol and it is commonly advisable to employ more than one.

### Exclusion of patients

General principles applicable to the exclusion of patients, e.g. pregnant women, are as for investigations of other classes of drugs but some special consideration might be applicable.

### Statistical consideration

Statistical advice should be taken early in the planning stage of a trial:

- a. To determine the number of patients who should take part in the study to achieve statistically significant discrimination, the number of patients can be pre-calculated using recognized formulae.
- b. To advise on the number of patients required to demonstrate any lack of clinically relevant differences between the two methods of treatment. In that case there should be agreement between the physician and the statistician as to the power of the statistical test.

The data should be analysed on an intention to treat basis, i.e. all patients randomized should be included in the statistical analysis.

Organizational aspects, i.e. obtaining informed consent, is very important and ideally patients should be given a copy of the informed consent form. The informed consent form should be written in a language understandable by the patient and should include a list of the adverse effects that the patient is likely to suffer.

### Guidelines for evaluating and developing antirheumatic drugs for rheumatoid arthritis

Antirheumatic drugs should improve symptoms; they may also have disease modifying effects.

#### 1. Symptomatic agents

These improve the symptoms and clinical features of inflammatory synovitis, and fall into three categories:

- 1.1 Non-steroidal Anti-Inflammatory Drugs (NSAIDs).
- 1.2 Steroids.
- 1.3 Others such as slow-acting antirheumatic drugs (SAARDs).

Slow-acting antirheumatic drugs incorporate immunosuppressive agents.

#### 2. Disease modifying agents

These modify the course of rheumatoid arthritis as demonstrated by either or both:

- (a) Prevention or decreased rate of progression of joint erosions.

- (b) Sustained improvement in function associated with decreased inflammatory synovitis.

Disease modification requires a prolonged effect.

This definition of disease modification is new and provisional.

All antirheumatic drugs should have a demonstrable symptomatic effect. It is hoped that new drugs will have a disease modifying effect but is anticipated their initial approval will result from the demonstration of a symptomatic effect. Classification as a symptomatic agent will be provisional. Both existing and new drugs may be reclassified as disease modifying if they meet the appropriate definition as outlined above.

Diffuse connective tissue diseases, systemic vasculitis and other rheumatic diseases require other therapeutic approaches and need evaluation; this has not been undertaken in the present document.

Development of guidelines for testing of drugs for use in osteoarthritis - so-called "chondroprotective" agents

1. Introduction. So-called "Chondroprotection" is a concept that some drugs may slow the rate of degeneration and enhance the rate of cartilage repair.

So-called "Chondrogression" suggests that some drugs, notably some NSAID's, may speed the rate of degeneration or inhibit cartilage repair. Both concepts derive from animal models and in vitro experiments, rather than validated human observations.

Currently the natural history of idiopathic osteoarthritis (OA) in humans is not clear, though the process is likely to begin long before clinical presentation.

Certain cartilage abnormalities are likely to be reversible, e.g. GAG replenishment and others irreversible (e.g. destruction of collagen micro architecture). These and other biological principles need to be taken into account when designing clinical trials and deciding on primary end-points.

2. With respect to primary end-points the following groups of potential patients exist:
- (a) Prevention of OA developing in "at risk" joints, e.g. post anterior cruciate ligament rupture;
  - (b) Inhibition of progression of established OA;
  - (c) "Repair" of damaged cartilage.

Group (b) is the most likely target group for physicians and industry.

Within the above groups, further end-points should be clearly defined:

- (i) Symptomatic/functional improvement  
Studies will require months, rather than weeks duration.
- (ii) Anatomic/biochemical aspects of the joint. Currently, no one measurement technique has sufficient reliability, validity and responsiveness.

Anatomical studies of disease progress (MRI, C.T., ultrasound, plain X-ray) require more than one technique or one technique with statistical validation with respect to reliability, validity and responsiveness.

Duration of such studies require years rather than months.

Currently there is no data to support the concept that any drug is 'chondroprotective' in man and we recommend that the term be abandoned.



FOURTH JOINT WHO/ILAR TASK FORCE  
MEETING ON RHEUMATIC DISEASES

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GLOSSARY OF TERMS

ACE	- Angiotension-1 converting enzyme
ARD	- Antirheumatic Drug
CRP	- C-reactive protein
EC	- European Community
ESR	- Erythrocyte Sedimentation Rate
FDA	- Food and Drug Administration, USA
Health Care Worker	- A person who delivers health care to patients but may not be medically qualified; nurse, village health worker, etc.
IA	- Intra-articular
IFPMA	- International Federation of Pharmaceutical Manufacturers Associations
ILAR	- International League Against Rheumatism
IM	- Intramuscular
IV	- Intravenous
Medical Practitioner	- A physician, medical doctor, or similarly qualified individual licensed to prescribe drugs in a country.
MRI	- Magnetic Resonance Imaging
NSAID	- Non-steroidal anti-inflammatory drug
OA	- Osteoarthritis
OTC	- Over the counter, non-prescription distribution of drugs
RA	- Rheumatoid Arthritis
REM	- Rapid Eye Movement
Rheumatologist	- A medically qualified physician with specialty training in rheumatic diseases and their treatment
SAARD	- Slow-acting antirheumatic drug
SLE	- Systemic Lupus Erythematosus
USA	- United States of America
WHO	- World Health Organization

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