UNIT NO. 3

THERAPEUTIC AGENTS IN JOINT PAINS

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ABSTRACT

Pain is the commonest symptom in rheumatology and still presents a major therapeutic challenge. In each joint condition, effective management depends on the cause of pain. Paracetamol is both an analgesic and antipyretic and in doses up to 3 gm daily rarely causes unwanted side-effects. It is now known that there are two such enzymes namely COX-1 and COX-2. Standard NSAIDs inhibit both isoforms while the COX-2 inhibitors selectively block formation of pro-inflammatory prostaglandins while sparing those that protect the gastro-intestinal tract. There are over 100 arthritis conditions but the big "four" are osteoarthritis, rheumatoid arthritis, gout and septic arthritis. Be familiar with the drugs you use and monitor carefully the potential side-effects in particular blood counts, liver and renal function. Shared care with a rheumatologist is the best way to manage patients with severe rheumatic diseases that require life-long therapy.

OBJECTIVES

This unit covers the classification, usefulness, side-effects, important interactions and prescribing tips of therapeutic agents in joint pain. At the end of this unit, the course participants should be able to:

- Understand the pharmacologic effects of analgesics and NSAIDs
- Understand the proven benefits, limitations and remaining concerns with use of COX-2 inhibitors
- Learn how to tailor specific treatment for specific conditions
- Describe the prescribing tips on therapeutic agents in joint pains.

1. ANALGESICS AND NSAIDS

Pain is the commonest symptom in rheumatology and still presents a major therapeutic challenge. Pain processing is complex and clinical exploitation of this complexity is only just beginning.

In each joint condition, effective management depends on the cause of pain. Inflammatory pain as in rheumatoid arthritis can be targeted via blockade of chemical mediators with agents ranging from non-steroidal anti-inflammatory drugs (NSAIDs) to inhibitors of tumour necrosis factor-alpha (TNF-alpha). When pain is mechanically induced as in osteoarthritis, management may rely on basic analgesics such as paracetamol.

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1.1 Paracetamol

Paracetamol is both an analgesic and antipyretic and in doses up to 3 gm daily rarely causes unwanted side-effects. Skin rashes are commonest, but blood disorders and acute pancreatitis have been reported. Paracetamol overdose can lead to liver failure and it is a common practice to use a smaller dose in patients with liver disease.

Paracetamol is a first choice in symptomatic treatment of OA and a common adjunctive analgesic in inflammatory conditions although it is less effective than NSAIDs.

1.2 Non-steroidal Anti-inflammatory Drugs (NSAIDs)

In 1971, Sir John Vane suggested that NSAIDs act by inhibiting the synthesis of prostaglandins through inhibiting the synthesis of prostaglandins through blockade of the cyclo-oxygenase (COX) enzyme on arachidonic acid. It is now known that there are two such enzymes namely COX-1 and COX-2. Standard NSAIDs inhibit both isoforms while the COX-2 inhibitors selectively block formation of pro-inflammatory prostaglandins while sparing those that protect the gastro-intestinal tract.

2. TWO BROAD CLASSES OF COX-INHIBITORS

COX-nonspecific inhibitors demonstrate no meaningful biologic or clinical differences in inhibition of COX-1 versus COX-2 activity. Such compounds include commonly used NSAIDs, such as ibuprofen, indomethacin, naproxen and diclofenac acid.

The second class is the COX-2 inhibitors. This group inhibits more COX-2 than COX-1 thus retaining the analgesic and anti-inflammatory activity but reducing the gastro-intestinal side-effects. They are a safer option than regular NSAIDs in patients who are at risk for gastrointestinal bleeding (eg. patients with a history of peptic ulcer disease, gastritis, alcoholism, concomitant steroid or anticoagulant use).

On the other hand COX-2 enzyme is expressed in the kidney and its inhibition may potentially exacerbate fluid retention, oedema formation, hypertension and renal failure. The effects of COX-2 inhibition in vascular disease also require further study. COX-2 enzyme is reportedly involved in vascular prostaglandin production.

COX-2 inhibitors, should not be combined with traditional NSAIDs and check whether your patient has a history of ischaemic heart disease, stroke, thrombosis or hypertension or whether they are sensitive to aspirin, sulpha drugs or other NSAIDs. At every visit blood pressure measurement and check for oedema should be done. Concurrent use of NSAIDs and warfarin has been associated with increase incidence of bleeding.

3. TAILORING SPECIFIC TREATMENT FOR SPECIFIC CONDITIONS

There are over 100 arthritis conditions but the big "four" are osteoarthritis, rheumatoid arthritis, gout and septic arthritis.

3.1 Osteoarthritis

This condition is by far the commonest. The prevalence will rise as the population ages. This topic will be dealt elsewhere.

3.2 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, polyarticular, symmetrical, inflammatory disease with a distinct predilection for the proximal joints of the hands and feet. Estimated prevalence in this part of the world is about 0.6%. It affects females three times more often than males.

Because of the chronic, systemic nature of the disease, patient's life span is significantly reduced with a 5-year survival similar to that of stage IV Hodgkin's disease or triple vessel coronary artery disease in those with severe RA. Significant soft-tissue damage and bone erosion occur within 2 years of disease onset. Therefore early, aggressive treatment is recommended often using a combination of DMARDs within weeks of diagnosis.

NSAIDs traditionally the first agent in RA treatment do not alter the course of the disease. Recent evidence suggest that disease-modifying anti-rheumatic drugs (DMARDs) might modify disease and are generally less toxic than NSAIDs. Furthermore, combination of such drugs are more efficacious than single-agent therapy. Therefore, combination DMARD therapy early in the course of RA has become the standard approach. Hydroxychloroquine and salazopyrine are the most effective agents in mild to moderate RA. They can be used in combination with NSAIDs.

Other DMARDs are methotrexate (MTX), leflunomide (ARAVA), and the biologic agents Infliximab (Remicade) and Etanercept (Enbrel). Close monitoring of blood counts and liver function are necessary.

Prednisolone – Steroids should not be used in the long-term management of RA. However they are useful initially as "bridge therapy" while waiting for the DMARDs to take effect (which may take 2-6 weeks). Once the DMARDs have taken effect, prednisolone can be slowly withdrawn. In some patients it may not be possible to withdraw steroids completely but never go beyond 10 mg/day. Monitor blood pressure, glucose level, lipids and bone mineral density if steroids are given for more than three months.

3.3 Gout

Gout is a clinical syndrome caused by a group of heterogenous disorder and is characterized by deposition of monosodium urate crystals leading to synovial inflammation. Attacks usually begin as a severe monoarticular synovitis in the lower extremities eg. the first metatarsophalangeal joint, the ankle and the soft tissue of the mid-foot. Eventually the disease can become polyarticular. Not all attacks of gout are associated with a raised uric acid. Hyperuricaemia can be caused by increased uric acid production, reduced uric acid clearance and acquired causes like diuretic usage.

3.3.1 Evaluation

The "gold standard" for diagnosis of gout is joint aspiration and demonstration of characteristic needle-shaped, negatively birefringent monosodium urate crystals under polarised light. When crystals are not demonstrated, a presumptive diagnosis can be made by the classical clinical presentation, positive family history and rapid resolution of symptoms with anti-inflammatory drugs. Patients should also undergo evaluation for hypertension and hyperlipidaemia, two potentially treatable conditions that often accompany gout. Most cases of asymptomatic hyperuricaemia do not need treatment unless the levels are very high.

3.3.2 Treatment of an acute attack

Colchicine 0.6 mgm 3-4 times/day.

NSAIDs – to the maximum tolerated dose.

However in patients who are intolerant of NSAIDs, oral steroids is an excellent alternative. Prednisolone 0.5 mg/kg/day tapered over 7 days is recommended.

3.3.3 Prevention of Recurrence

In patients who get repeated attacks eg. more than 2-3 attacks per year it is useful to give the following maintenance treatment.

Colchicine 0.6 mg/day plus an oral long acting NSAIDs. This will reduce recurrent attacks and prevent further damage to the joint.

3.3.4 Reduction of uric acid levels

(a) Xanthine oxidase inhibitors

Allopurinol is the only available xanthine oxidase inhibitor at the moment. The initial dosage is 300 mgm or more depending on the level of uric acid and the weight of the patient. For patients with tophaceous gout, long term treatment with allopurinol is necessary. Dosage adjustment is necessary in patients with impaired renal function. Certain medications like azathioprine (Imuran) are inactivated by xanthine oxidase inhibitor. When azathioprine is given concomitantly with allopurinol, the dose of the former should be reduced by 25% - 30% to avoid catastrophic hematological consequences.

Allopurinol often causes skin rash and occasionally Steven-Johnson syndrome, so great care should be taken when using the drug. It should not be used to treat asymptomatic hyperuricaemia.

(*b) Uricosuric Agent*

Probenecid (Benemid) 500 mg bd is an excellent uricosuric agent and can be considered in these with normal renal function and no history of nephrolithiasis.

(c) Others

Fenofibrate and Losartan are also known to reduce uric acid.

Besides drug treatment it is important to consider proper diet, treatment of hypertension and lipid abnormalities and modify life style.

3.4 Septic Arthritis

Septic arthritis remains a relatively uncommon problem but require proper diagnosis and immediate treatment. In any acute monoarthritis in adults, joint aspiration, Gram-stain and culture of synovial fluid remain vital diagnostic procedures. Staphylococcus aureus remains the commonest causal agent but gonococcus is an important differential diagnosis. Since prosthetic joint surgery is growing rapidly, between 0.5% and 2% of prostheses becomes infected over the ten years following the procedure. A number of viruses have also been implicated as causing inflammatory arthritis. These include the human parvovirus, hepatitis B and C and the retrovirus HIV 1 and 2. Symptoms respond to NSAIDs and are usually self-limiting.

Occasionally following a bacterial infection (especially of the GIT or urinary tract) an asymmetrical polyarthritis may occur. This can also follow a simple viral infection. Since no infective organisms can be demonstrated in joint fluids, such conditions are collectively called reactive arthritis. Back-ache is also a common complaint. The condition is usually self-limiting and NSAIDs are recommended. Occasionally one may have to use DMARDs.

4. PRESCRIBING TIPS ON THERAPEUTIC AGENTS IN JOINT PAINS

- Most rheumatic patients require long-term or life-long therapy and follow-up
- Be familiar with the drugs you use and monitor carefully the potential side-effects in particular blood counts, liver and renal function
- NSAIDs have 2 actions – a quick acting analgesic effect (within hours) and a slow-acting inflammatory effect (may take 2 weeks). Therefore do not use a *"as when necessary"* regime at the beginning until pain and swelling have settled
- Traditional NSAIDs are generally safe in young, healthy individuals. Consider using COX-2 inhibitors in elderly patients, those with history of peptic ulcer disease and dyspepsia
- Be careful using any NSAIDs in patients with renal dysfunction. If you must, reduce the dose and monitor renal function. Low dose steroids may be a safer alternative (in RA, chronic gout) in spite of its many well-known side-effects
- Shared care with a rheumatologist is the best way to manage patients with severe rheumatic diseases that require life-long therapy.

LEARNING POINTS

- Pain is the commonest symptom in rheumatology and still presents a major therapeutic challenge. In each joint condition, effective management depends on the cause of pain
- Paracetamol is a first choice in symptomatic treatment of OA and a common adjunctive analgesic in inflammatory conditions although it is less effective than NSAIDs
- It is now known that there are two such enzymes namely COX-1 and COX-2. Standard NSAIDs inhibit both isoforms while the COX-2 inhibitors selectively block formation of pro-inflammatory prostaglandins while sparing those that protect the gastro-intestinal tract
- There are over 100 arthritis conditions but the big "four" are osteoarthritis, rheumatoid arthritis, gout and septic arthritis
- Be familiar with the drugs you use and monitor carefully the potential side-effects in particular blood counts, liver and renal function
- Shared care with a rheumatologist is the best way to manage patients with severe rheumatic diseases that require life-long therapy.