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GOUT: A SYSTEMATIC REVIEW

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ABSTRACT

Gout is a type of rheumatic disease that occurs when there is an excessive accumulation of uric acid in the body, which is known as hyperuricemia. Gout causes many changes and effects the body in a very bad way by causing joint pain that comes and goes, it can also cause inflammation which is nothing but the by-product of accumulated monosodium urate crystals in the body which is also known as tophi it is found in the synovial fluid and lining. Hyperuricemia, as suggested by its name is a condition which is caused when there is build-up of uric acid in the body by either increased production of uric acid or reduced excretion of uric acid, either can cause of hyperuricemia. Treatment of gout involves managing hyperuricemia through various interventions such as dietary and lifestyle modifications, as well as the use of pharmacologic agents to lower urate levels. Additionally, acute gouty arthritis can be managed with medications such as colchicine, nonsteroidal anti-inflammatory drugs, and/or corticosteroids. It is important to note that pharmacists play a crucial role in patient education and improving the overall care of patients with gout. Newer pharmaceuticals in the medical arsenal are demonstrating their effectiveness and complementing established medications. Additional significant aspects in the management of gout involve educating patients, implementing dietary and lifestyle modifications, and discontinuing hyperuricemia drugs.

Keywords: colchicine; gout; inflammatory arthritis; monosodium urate; mechanism of action; Management of gout; Indomethacin; Naproxen.

INTRODUCTION

The crystallized monosodium urate (MSU) deposition from serum urate is the cause of gout, results in inflammatory arthritis with symptoms such as joint swelling, redness, heat, pain, and stiffness. Colchicine, which is derived from colchicum lants is a natural product, has been utilized to treat gouty arthritis for a long period of time [1], and colchicine when given in low dose works for long term prophylaxis and also manages acute gout flares.[2] [3] [4].

According to current treatment guidelines, colchicine has multiple functions, it has been observed that gout flares can be prevented also acute gouty arthritis can be treated. It is highly recommended that within24hrs of onset appropriate pharmacological treatment should be taken as soon as possible generally colchicine which is used as first line of defence against gout all these instructions are given by the ACR guidelines of on how to manage gout, some fist line of therapy for acute flair pain is also advised and some examples of the following are corticosteroid and NSAIDs.[5] Recently there has been an update which uses glucocorticoids, NSAIDs and colchicine for treatment acute gouty arthritis, it has been recommended by the European league against rheumatism.(EUAR) It has also been indicated that during first 6-12 months of the therapy by using urate lowering agents against acute gouty attack colchicine can be used for prophylaxis.

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Inflammation and gout

To comprehend the various effects of colchicine on gout, we need to first understand that debilitating condition accompanies by the symptoms are caused by what type of inflammatory cascade. Gout occurs when MSU microcrystals interact with the local tissue environment, triggering a disease process. In individuals with acute gouty arthritis, the affected synovium is inflamed and swollen due to the infiltration of neutrophils, mononuclear phagocytes, and lymphocytes, which is also responsible for injury to blood vessels. The range of leukocytes, cytokines, and chemokines that play a role in the innate immune system response are likely involved in the precise biochemical mechanisms linking MSU crystal precipitation to joint inflammation, but they are not yet fully understood.

MSU Crystal Formation

In acute gouty arthritis, there are many events that take place, but the most common one is precipitation of urate into MSU crystals. However, the process by which MSU crystals form directly at the site of joint inflammation is not well understood. MSU crystals form when the concentration of urate in plasma exceeds its solubility (~7 mg/dL).[5] In addition to plasma concentration, other factors affecting urate solubility in vitro include pH, temperature, ionic strength, and the binding of urate to plasma macromolecules,[6],[7],[8],[9],[10] However, environmental conditions and mechanisms that favour or limit crystal formation in vivo are likely different from those in vitro models. If a person is consuming a lot of red meat, drinking excessive alcohol, cell death from trauma or anti-cancer therapy MSU crystal formation within joints can take place. There are many possible MSU crystal nucleating agents that can be used some of the common ones used can be albumin,[11],[14] Crystallization can be stabilized by many different agents like immunoglobulin (Ig)G (Ig)M and circulating antibodies in the blood [11][12][13]

MSU Crystal Stimulation of Pro-Inflammatory Cells

Danger-associated molecular patterns (DAMPs), namely endogenous MSU crystals, are recognized by the innate immune system, particularly neutrophils and macrophages/monocytes, as well as mast cells and dendritic cells [15], [16], [17], [18], [19].

Dendritic cells and macrophages are activated by uric acid DAMP signalling to secrete pro-inflammatory cytokines, including interleukin (IL)-1β [20], [21]. A major research topic has been the mechanism and different pathways involved in instigating a series of inflammatory reactions by pro-inflammatory cells.

Colchicine

Colchicine has been approved by the FDA for preventing gout and managing acute gouty flares. Colchicine is a very versatile drug, it has been recommended by doctors for its ability to treat many different conditions like cirrhosis, pseudogout. Colchicine has many important properties one of the major ones being its ability to act as an anti-inflammatory drug. This initiative intends to discuss colchicine's mechanism of action, potential side effects, toxicity, dosage, pharmacodynamics.

Mechanism of action of colchicine in gouty arthritis

It has been seen that colchicine works wonders for inflammation which is a symptom caused by acute gouty arthritis. It even works for smaller concentration at micro levels, it also causes suppression of expression of gene

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that are involved in cell regulation by inhibiting the MSU crystals activation of NLRP3 inflammasome.[22][23][24][25] It is also seen that the release of IL-1β is blocked. It works differently on different levels for example when on nanomolar level it can be seen that it is very useful for adhesion protein expression which is on endothelial cells, also regulating the release and maturation of cytokinesis, and there is expression of L selectin caused by IL-1.[26][27]28] It also aids in the conversion into cytokines from neutrophil chemotaxis by process of reduction. There is a build of colchicine that takes place inside neutrophil to concentration of 40-200 nmol/L, for microtube polymerization that is way above its range of 24nmol/L.[29][30] It can be seen that the effects that take place on these pathways are in some correlation with inhibition of microtubule polymerization by this it can be assumed that in colchicine's mechanism of action in treatment of gout they are the primary target . [31]A single dose of 0.6-mg colchicine leads to a plasma concentration of approximately 3 nmol/L.

Leukocytes produce lactic acid which has been observed to been reduced by colchicine, thereby decreasing uric acid deposition and phagocytosis, response of the inflammatory system can be reduced. It is a known fact that it is an old drug, to be used in treatment for acute gouty arthritis it has just got approved by the FDA.[37] colchicine is really helpful for gouty attacks however it should not be used during the later stages of the attack or in other words should be used when it is well established. There was a randomized trial to see the efficacy that the low does produces compared to high does for which the low dose colchicine (1.8 mg over 1 hour) produced almost same result as high dose colchicine (4.8 over 6 hours) in plasma concentration, [38].

Indomethacin

There are several conditions for which indomethacin can be used for, it is typically a non-steroidal anti-inflammatory drug which can be used for different diseases and health conditions like swelling, tenderness, and different forms of arthritis such as rheumatoid arthritis It also provides relief for shoulder pain resulting from bursitis and tendinitis. The immediate-release capsules and suspension of indomethacin are useful in treating acute gouty arthritis. The drug functions by inhibiting prostaglandins production in the body, which is known for playing a very important role in causing fever and inflammation in the body.

To provide healthcare professionals from different disciplines with a comprehensive understanding of indomethacin, it is important to highlight how the drug works, and some other important factors such as how much concentration of the dose is required, pharmacodynamics, pharmacokinetics, monitoring, interaction that have some sort of relevance, and how it can be used off-label.

Mechanism of action of Indomethacin

Indomethacin, a type of non-steroidal anti-inflammatory drug (NSAID), functions by hindering the production of prostaglandins that are synthesized by cyclooxygenase (COX) enzymes, which are essential in inflammation, fever, and pain. Prostaglandins is used for many functions and some of its important functions are maintaining platelet activity and renal function. The inhibition of COX is in correlation with the adverse effects of NSAIDs. similarly, there is also relation between COX and thromboxane A2 which has number of important roles in the body like acting as a mediator of platelet aggregation also an important factor is that its inhibition has been seen to account for anti-platelet effects of NSAIDs, COX-2 has been found to be a factor in the production of prostaglandins which in turn causes inflammation, pain and fever. Indomethacin, as a non-selective COX

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inhibitor, may have more GI-associated side effects than COX-2 selective NSAIDs.[39][40] It is a known fact that indomethacin has a great anti-viral activity and has been used against hepatitis B virus and coronavirus.[41][40] But even though it is great and effective against them there is still no clinical proof that its will have the same effect against COVID-19.[42]

Prostaglandin E2 has been seen to of a lot of use as well if used in moderation and helps in relaxing smooth muscle also it aids in the closure of ductus arteriosus. It is very rare but in some young infants who have a respiratory distress syndrome, this condition causes the inability of ductus arteriosus to close and this can very much likely cause patent ductus arteriosus (PAD) which is caused because of the exceeding the normal concentration of prostaglandin E2. It is highly insisted that it should be treated as soon as possible as the longer it is left untreated the chances that it can cause differential cyanosis increases. Indomethacin can aid in the closure of PDA by inhibiting PGE2 synthesis.[43][44].

Naproxen

Naproxen was initially approved for prescription use in 1976 but was later approved as an over the counter (OTC) medication by the FDA in 1994. Naproxen is a wonder drug and for good reasons as it can be used against number of diseases and physical conditions like osteoarthritis, bursitis, acute gout. Now everything has its drawbacks it might be minor or major like this naproxen has its own drawbacks while it is great for use against many diseases like acute gouty arthritis, inflammation, and dysmenorrhea it still lacks the ability to prevent joint and tissue damage, and it cannot stop rheumatoid arthritis from progressing. But there are ways to stop conditions like rheumatoid arthritis from progressing, for such cases the primary and preferred drugs are disease modifying anti-rheumatic drugs though naproxen is still used just not as a primary source to treat such conditions [45][46]

Naproxen is also used off-label for treating acute migraines and migraine prophylaxis. Some consider it a first-line abortive remedy for acute migraines. Moreover, it can be used for chronic migraine prevention alongside other medications such as beta-blockers, anti-depressants, and anticonvulsants.[47]

Mechanism of action of Naproxen

The anti-inflammatory and analgesic effects caused by the consumption of naproxen are caused because it competitively binds with both COX-1 and COX-2 isozymes, it does so by blocking arachidonate binding. The formation of prostaglandin G(PGG) from arachidonic acid takes place with the help of 2 enzymes COX-1 and COX-2, prostaglandins formation takes place like this which is just the first step in its synthesis and rapid physiological responses that are mediated through thromboxanes. The expression of COX-1 takes place in most of the tissues and helps in maintaining healthy renal function and there are circulating hormones to whose response hemostasis takes place, and hemostasis in response to circulating hormones. On the other hand, COX-2 is not as common and gets expressed in only selected tissues which consists of reproductive organ, kidney bones and the brain

Naproxen's anti-inflammatory mechanism is due to its inhibition of COX-1 and COX-2, with a greater effect on COX-2. Although it is seen that COX-1 is very common, there are some sites at which it also gets expressed some of these inflammatory sites are rheumatoid arthritis infected persons joints. So, as it is obvious that

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targeting of both COX-1 and COX-2 takes place by naproxen it is more selective for the former. Furthermore, Naproxen indirectly produces analgesic effects by inhibiting further prostaglandin production, particularly prostaglandins E and F, which sensitize pain receptors.[48]

Naproxen undergoes extensive liver metabolism, and around 95% of the drug is excreted in the urine. Naproxen's half-life has been calculated and has been estimated to be around 12 to 17 hours

CONCLUSION

There were various steps taken in developing pharmacological drugs for the treatment of gout. Nowadays there are numerous drugs available for the treatment of acute gouty arthritis. In this review paper, I discussed some of the drugs that are used on a wider scale than the others like colchicine which is usually taken as the first line of defence against acute gouty arthritis. Similarly, naproxen and indomethacin have their own uses. Although we know colchicine can be trusted to treat flares, the exact mechanism or to put it simply how it is exactly efficiently working to counter is not yet known. The information that we have right now tells us that it works by increasing the efficacy of anti-inflammatory mediators while simultaneously downregulating pro-inflammatory pathways. These multiple effects of colchicine in the future will surely expand its usage to other therapeutic areas. While prescribing these drugs the concentration of doses should be adjusted by the doctor to the lowest effective dose and for the shortest duration possible. Further, the pharmacists should make sure that the dosage prescribed is correct and also inform the patients about the drug and what effects it may cause on the body. Patients should always be informed about the risks that come with the medication that they are consuming.

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