Practice research in the field of gout - clinical pharmacology of antihyperuricemic drugs

Reinders, Mattheus Karsien

Chapter 1

Scope and objectives

Introduction

Gouty arthritis is among the earliest diseases that have been recognised as a clinical entity. First identified by the Egyptians in 2640 BC, podagra (acute gout occurring in the first metatarsophalangeal joint) was later recognised by Hippocrates in the fifth century BC, who referred to it as 'the unwalkable disease'. Hippocrates also noted the link between the disease and an intemperate lifestyle, referring to podagra as an 'arthritis of the rich', as opposed to rheumatism, an 'arthritis of the poor' [1].

In history, gout seems a common disease, and many historic figures were suffering from gout [2-9]. Factors that might increase gout incidence back then, were lead contamination of water and a "bourgondic" lifestyle. In 1679, Van Leeuwenhoek observed microscopic gouty crystals. These crystals result from urate deposition in tissues in presence of hyperuricemia. They induce episodic arthritis, which initially are infrequent, usually affecting the foot, and respond well to anti-inflammatory medications such as colchicine and non-steroidal anti-inflammatory drugs. However, these measures do not stop urate deposition from progressing. More frequent and widespread attacks may develop, with increasing resistance to anti-inflammatory therapy. Permanent joint damage may result from gouty erosions, and tophi formation may be complicated by ulcerations and sepsis. Thus, optimal management requires timely introduction of antihyperuricemic therapy to provide a gradient for resorption of the crystals [10].

In the 1950s-1970s, several antihyperuricemic drugs became available for treatment of gout, such as allopurinol, benzbromarone, and probenecid. Allopurinol acts by inhibiting xanthine oxidase, thereby preventing formation of urate (uric acid). Benzbromarone and probenecid act by enhancing the renal excretion of urate. However, a lack of information exists on the risk-benefit ratios of these drugs for the treatment of gout [11]. In a meta-analysis published in 2006, only one randomised controlled trial of good quality assessing antihyperuricemic drugs was found [11].

In 2003, benzbromarone was withdrawn from the global market because of reports of severe hepatotoxicity [12]. In 2004, it returned in The Netherlands (and Spain), but its use was restricted to patients allergic to allopurinol. Recently, reports state that allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrosis [13].

No consensus exists to what extent sUr should be lowered. For instance, the recent European recommendations use a target sUr concentration of 0.36 mmol/l (6.1 mg/dl), the recent British guideline uses 0.30 mmol/l, and the Dutch practitioners standard uses 0.38 mmol/l [14-16]. It is sometimes believed that values below the threshold of monosodium urate at body temperature (37 °C), 0.41 mmol/l are good enough. However, gout symptoms usually occur in the extremities where body temperature is lower than in the centre, and therefore solubility of monosodium urate is lower than 0.41 mmol/l [17]. In addition, solubility of monosodium urate in synovial fluid is influenced by other factors, like pH, concentration of cations, level of articular dehydration, and the presence of such nucleating agents as non-aggregated proteoglycans, insoluble collagens, and chondroitin sulphate [18].

From prospective observational and retrospective data, a strict control of sUr is necessary to successfully diminish tophi and prevent recurrent gout attacks [19-23].
Numerous publications identify that gout management is often sub-optimal, despite detailed understanding of the pathogenesis and pathophysiology of the disorder, the ability to establish the diagnosis with certainty, and the expected effectiveness of lifestyle and pharmacological interventions. Barriers to successful gout management include diagnostic inaccuracy, a paucity of guidelines, sub-optimal patient education and patient adherence, co-morbidities and drug-drug interferences that complicate treatment of gout, and limited urate-lowering alternatives [24].

Objective of the thesis

The objective of this thesis is to study the pharmacological and clinical aspects of antihyperuricemic dugs in the treatment of gout in clinical practice, with the focus on efficacy and tolerability.

Outline of the thesis

This thesis comprises of four parts: (1) management of gout, (2) outcome research with antihyperuricemic drugs, (3) therapeutic drug monitoring of allopurinol, and (4) rasburicase for treatment of gout.

References

1. Nuki G, Simkin PA. A concise history of gout and hyperuricemia and their treatment. Arthritis Res Ther 2006;8:S1-5.
2. Dequeker J. Gout: the patrician malady. BMJ 1999;318:64A.
3. Ordi J, Alonso PL, de Zulueta J, et al. The severe gout of Holy Roman Emperor Charles V. N Engl J Med 2006;355:516-20.
4. Boonen A, van der Linden S. Case number 33: about being a famous European and suffering from gout... Ann Rheum Dis 2005;64:528.
5. Espinel CH. Michelangelo's gout in a fresco by Raphael. Lancet 1999;354:2149-51.
6. Weissmann G. Galileo's gout. Pharos Alpha Omega Alpha Honor Med Soc 2004;67:4-7.
7. Pinals RS. Theodore Roosevelt's inflammatory rheumatism. J Clin Rheumatol 2008;14:41-4.
8. Espinoza R, González C. [The disease of admiral Christopher Columbus] Rev Med Chil. 1997;125:732-7 (Article in Spanish).
9. Appelboom T, Bennett JC. Gout of the rich and famous. J Rheumatol 1986;13:618-22.
10. Wong ML. Optimal management of chronic gout: attempting to render the (t)issues crystal-clear. N Z Med J 2005;118:U1533.
11. Sutaria S, Katbamna R, Underwood M. Effectiveness of interventions for the treatment of acute and prevention of recurrent gout--a systematic review. Rheumatology (Oxford) 2006;45:1422-31.
12. Anonymous. Benzbromarone - withdrawn due to reports of liver damage. WHO Pharmaceuticals Newsletter 2003:1.

13. Halevy S, Ghislain PD, Mockenhaupt M, et al; EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol 2008;58:25-32.
14. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1312-24.
15. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the Management of Gout. Rheumatology 2007; doi:10.1093/rheumatology/kem056b.
16. Dutch College of General Practitioners' "Gout" Standard, 2nd ed. 2004; Http://nhg.artsennet.nl/upload/104/standaarden/M72/start.htm (September 19th, 2007).
17. Loeb JN. The influence of temperature on the solubility of monosodium urate. Arthritis Rheum 1972;15:189-92.
18. Choi KH, Mount DB, Reginato AM. Pathogenesis of gout. Ann Intern Med 143:499-516.
19. Li-Yu J, Clayburne G, Sieck M, et al. Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol 2001;28:577-80.
20. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 2004;51:321-5.
21. Yamanaka H, Togashi R, Hakoda M, et al. Optimal range of serum urate concentrations to minimize risk of gouty attacks during anti-hyperuricemic treatment. Adv Exp Med Biol 1998;431:13-8.
22. McCarthy GM, Barthelemy CR, Veum JA, et al. Influence of antihyperuricemic therapy on the clinical and radiographic progression of gout. Arthritis Rheum 1991;34:1489-94.
23. Pérez-Ruiz F, Calabozo M, Pijoan JI, et al. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum 2002;47:356-60.
24. Becker MA, Chohan S. We can make gout more successful now. Curr Opin Rheumatol 2008;20:167-72.