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

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Chapter 6

Summary and future perspectives

Summary

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 likely 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. Furthermore, a lack of information exists on the risk-benefit ratios of antihyperuricemic drugs for gout treatment.

This thesis studies the clinical pharmacology of antihyperuricemic dugs in the treatment of gout in clinical practice, with focus on efficacy and tolerability. Studies and reviews of this thesis focus on: management of gout, outcome research with antihyperuricemic drugs, therapeutic drug monitoring of allopurinol, and rasburicase for treatment of gout.

Management of gout

In **chapter 2.1**, we reviewed the literature on management of gout and presented a therapeutic strategy. Limited information on drugs indicated for the treatment of gout is available, making it difficult for physicians to make informed treatment decisions. The current therapeutic strategy is often based on clinical experience. Lifestyle advice is of limited value in the prevention of gout, particularly with regard to restricting alcohol, losing weight in cases of obesity, ensuring adequate diuresis and adhering to a low-purine diet, as most patients are reluctant to make such changes. Therefore, the condition is often treated with pharmacological therapies.

Presently, oral colchicine and non-steroidal anti-inflammatory drugs (NSAIDs) are first-choice agents for systemic treatment of acute gout. In the absence of contra-indications, NSAIDs are a convenient and well-accepted option for treatment of acute gout. In case of tophaceous or recurrent gout, the use of urate-lowering drugs is recommended. Allopurinol is currently the first choice drug despite its AE profile at the population level. Many of the currently available treatment options for gout have unwanted side effects highlighting the importance of emerging therapeutics for the treatment of the disease.

Benzbromarone (**chapter 2.2**) is an old, but very potent urate-lowering drug, and possesses some distinct, recently discovered pharmacological features, which are important for effective and safe use in treatment of gout. Although benzbromarone is on the market for several decades, its place in treatment of gout compared to allopurinol is unclear, because of insufficient trials of good quality. The toxicity of benzbromarone is generally limited, but serious benzbromarone-induced hepatic failure is reported in rare cases. The underlying mechanism has not yet been fully explained, but formation of reactive metabolites by CYP2C9 resulting in mitochondrial toxicity, and CYP2C9 allelic variants might play a role. Important drug-drug interactions may occur with CYP2C9-substrate drugs, but clinical data are lacking up until now.

Outcome research with antihyperuricemic drugs

In **chapter 3**, several studies concerning the efficacy and tolerability of antihyperuricemic drugs in the treatment of gout in clinical rheumatologic practice are presented. In 2003, benzbromarone was withdrawn from the global market. In the Netherlands, suggested alternative treatments were allopurinol (in standard dosage) or probenecid. We studied the market withdrawal of benzbromarone in gout patients in **chapter 3.1**, and investigated the efficacy of two alternative treatment strategies: allopurinol (standard dosage) and allopurinol-probenecid combination therapy. A prospective, open study was carried out in 51 patients. Patients were given 200-300 mg allopurinol (stage 1); when allopurinol failed to attain the target serum urate concentration, sUr ≤0.30 mmol/l (5.0 mg/dl), probenecid 1,000 mg/day was added (stage 2). We found that previous treatment with benzbromarone monotherapy (mean dosage 138 mg/day) resulted in 92% of patients reaching target levels sUr ≤0.30 mmol/l with a mean sUr decrease of 61% compared to baseline. In stage 1, 32 patients completed treatment with allopurinol monotherapy (mean dosage 256 mg/day), which resulted in 25% of patients attaining sUr target levels. Decrease in sUr levels was 36%, which was significantly less compared to treatment with benzbromarone. In stage 2, 14 patients received allopurinol-probenecid combination therapy, which resulted in 86% of patients attaining target sUr levels (after failure on allopurinol monotherapy), which was comparable to previous treatment with benzbromarone. Decrease in sUr levels was 53%, which was a non-significant difference compared to previous treatment with benzbromarone. From the results, it was concluded that benzbromarone is a very effective sUr-lowering drug. Allopurinol in standard dosage was shown to be a less potent alternative for most selected patients to attain target sUr levels. In patients failing on allopurinol monotherapy, the addition of probenecid proves to be an effective treatment strategy for attaining sUr target levels. The results of this study stress the need for effective, evidence-based treatment strategies for lowering of serum urate in gout patients.

In The Netherlands, the use of benzbromarone is restricted to gout patients allergic to allopurinol, or otherwise not treatable with this drug. The Dutch general practitioners' guideline also includes patients who cannot be treated sufficiently with allopurinol. In **chapter 3.2**, we investigated the efficacy and tolerability of allopurinol (standard dosage) as first-choice antihyperuricemic treatment for gout, and compared the efficacy and tolerability of benzbromarone and probenecid as second-choice treatment. A multi-centre, open-label, randomised controlled trial was carried out in 96 gout patients with a calculated creatinine clearance >50 ml/min who were prescribed 300 mg allopurinol daily for 2 months (stage 1). In 82 eligible patients, 24% attained target sUr ≤0.30 mmol/l, and sUr concentrations decreased 36% from baseline; 11% stopped allopurinol because of adverse drug reactions. Then, 62 patients failing on allopurinol were randomised to benzbromarone 200 mg/day or probenecid 2,000 mg/day (stage 2). After 2 months, 22 out of 24 patients (92%) were treated successfully with benzbromarone, with a sUr decrease of 64% on average. Treatment success with probenecid was 20 out of 31 patients (65%), with a sUr decrease of 50%. This study showed a

poor efficacy and tolerability profile of allopurinol 300 mg/day to attain a biochemical predefined target level of sUr ≤0.30 mmol/l after 2-months treatment. Whether higher doses of allopurinol would increase treatment success, remains subject of further research (chapter 3.4). In patients failing on allopurinol 300 mg/day, benzbromarone 200 mg/day is significantly more effective and better tolerated than probenecid 2,000 mg/day.

Serum urate is a well-accepted surrogate parameter for short-term evaluation of gout treatment. Furthermore, information on clinical outcomes, such as prevention of recurrent gout attacks and diminishment of tophi, is essential. A lack of long-term, good-quality, prospective data exists addressing the efficacy of serum urate (sUr) lowering treatment to prevent these clinical symptoms. We conducted an observational follow-up study (**chapter 3.3**) to assess the rate of recurrent gouty arthritis in 50 patients with a history of recurrent gouty attacks, normal renal function, using antihyperuricemic treatment, and who completed a randomised controlled trial. After 10.6 months on average, incidence of gout attacks was largely reduced compared to baseline rates: 74% of patients were free of gouty attacks (100% reduction), and 18% of patients had 50-99% reduction of gouty attacks. Serum urate concentrations were 0.28 [± 0.08] mmol/l. We found a high reduction in incidence of gout attacks, that was better than obtained in most previous studies. This might be explained by the good control of serum urate in this study. No correlation was found between reduction of gout attacks and sUr or study drug used, due to lack of power. We concluded that antihyperuricemic therapy is highly effective in reducing and preventing gout attacks in gout patients with normal renal function.

In **chapter 3.4**, we investigated the efficacy and tolerability of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day to attain a target sUr ≤0.30 mmol/l. A multi-centre, open-label, randomised controlled trial was carried out in 65 patients recently diagnosed with gout, who were randomised to allopurinol 300 mg/day or benzbromarone 100 mg/day (stage 1). When the target sUr was not reached, the dosage was doubled. After stage 1 treatment success was 8 out of 31 (26%) with allopurinol 300 mg/day, and 13 out of 25 (52%) with benzbromarone 100 mg/day. Overall treatment success with allopurinol 300-600 mg/day was 21 out of 27 (78%), and with benzbromarone 100-200 mg/day was 18 out of 23 (78%), a non-significant difference. In this study, dosage increase of allopurinol and benzbromarone did not affect tolerability. This study showed that efficacy of allopurinol (and to a lesser extent benzbromarone) in gout patients can be markedly increased with increasing dosage. The overall efficacy of allopurinol and benzbromarone was not significantly different.

Therapeutic drug monitoring of allopurinol

Chapter 4 concerns the therapeutic drug monitoring of allopurinol treatment. From previous studies it is known that antihyperuricemic efficacy of allopurinol is related to the serum concentration of oxipurinol, the active metabolite of allopurinol. Reference values of oxipurinol 5-15 mg/l (trough) are suggested, but poorly investigated. Given the poor efficacy results of allopurinol in literature and clinical practice, optimisation of allopurinol therapy is warranted.

Therapeutic drug monitoring of allopurinol might be particularly useful in case of patients with renal impairment, oxipurinol-lowering drug-drug interactions, or suspected poor adherence.
In **chapter 4.1**, a reversed-phase high-performance liquid chromatography method with UV-detection (HPLC-UV) to obtain a method for the quantification of allopurinol and oxipurinol in human serum, was validated technically and clinically. The method showed acceptable performance on all major aspects of the validation (linearity, intra- and inter-day precision, accuracy, specificity, and lower/upper limits of quantification). For clinical validation, the serum allopurinol and oxipurinol concentrations in 66 gout patients were determined using this HPLC-UV method. Measured serum allopurinol and oxipurinol concentrations in clinical practice showed large variability with a range of <0.5-4.3 mg/l for allopurinol and <1.0-39.2 mg/l for oxipurinol, respectively. From these results, we concluded that the proposed method could be employed for the assay of allopurinol and oxipurinol in gout patients.

Uricase for gout treatment

Recently, a new class of powerful urate-lowering drugs has become available with rasburicase, recombinant uricase. Rasburicase is developed for the treatment and prevention of tumour-lysis syndrome. In **chapter 5**, the potential role of rasburicase in treatment of severe, treatment-resistant gout was reviewed, and explored in two cases.

Future perspectives

From the chapters 2.1, 2.2, and 3.1, we conclude that a need for more evidence and education on treatment of gout exists, although the pathogenesis of the disease is well understood and antihyperuricemic therapies are available for decades. Indeed, (only) very recently two important guidelines have been developed: the EULAR recommendations on gout (2006) and the British guideline (2007). The - in some countries temporarily - withdrawal of benzbromarone made clear that this was not in the benefit of gout patients in general, because of scarcity of drugs for antihyperuricemic treatment. The benefit-risk evaluations of alternative drugs might not have been addressed properly, and better efforts might have been done for vigilance and understanding of the hepatotoxicity. Since allopurinol is the only drug currently available worldwide, it is very important to know how to use this drug safely and effectively. Chapter 3.2, 3.4 and 4, show that at least in patients with normal renal function, allopurinol often is inadequately dosed and that target serum urate concentrations can be reached with good tolerability by increase of allopurinol dosage and by optimising serum oxipurinol trough concentrations. In the end, good control of serum urate is associated with good control of gout symptoms (chapter 3.3).
Subject of further research is to what extent these findings can be generalised to patients with renal dysfunction, a large group in gout. This is important, because uricosuric drugs are likely to be less effective in renal dysfunction, and a need for optimisation of allopurinol dosage regimens according to renal function exists.

Currently, new antihyperuricemic drugs have been developed for gout treatment: febuxostat, a xanthine oxidase inhibitor, and pegloticase, a pegylated form of uricase. New drugs for treatment of gout are welcomed. However, the benefit-risk profiles of these drugs are not undisputed, since febuxostat is associated with liver enzyme elevations, and pegloticase with antibody formation. These new drugs might help management of gout, but more issues require attention to bridge the gap between clinical practice and potential treatment possibilities, such as optimisation of current treatment regimens, evidence of benefit of long-term treatment of gout on clinical outcomes, and patient's adherence.