Bio Medical Reviews 1: 47-52 (1992)

Bulgarian - American Center, Varna, Bulgaria
Editor: G.N. Chaldakov

THE FUNGAL ETIOLOGY OF GOUT AND HYPERURICEMIA: THE ANTIFUNGAL MODE OF ACTION OF COLCHICINE

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ABSTRACT

• *The concept of a fungalImycotoxin etiology of gout/ hyperuricemia in humans was first reported by Costantini (1989) (1). Gout and/or hyperuricemia have been induced in animals by the fungal species Ustilago maydis, Chaetomium trilaterale, Saccharomyces cerversiae, and by the mycotoxins, aflatox'm, ochratoxin, oosporein, oxalic acid. Gout and/or hyperuricemia have been induced in humans by the yeast Candida utilis and by the fungal metabolites cyclosporin, ergotamine and penicillin. Gout is documented to be etiologically linked to beer, a Saccharomyces fermented beverage. Beers contain significant amounts of ochratoxin and large amounts (7 to 9 mg/dl of uric acid, a metabolite produced by the brewers's yeast Saccharomyces cen'ersiae. Consistent with the fungal etiology of gout and hyperuricemia, the mode of action of colchicine in the treatment of gout is antifimgal. Colchicine shares antitubulin activity with griseofulvin, a potent antifimgal antibiotic. Griseofiilvin is as equally effective in the treatment of gout as colchicine. Similarly, another antitubulin drug, vinblastine is also antifimgal and effective in the treatment of gout. All of the other drugs used to treat gout and/or hyperuricemia possess antifimgal activity (Costantini 1989).*

THE FUNGAL ETIOLOGY OF GOUT AMD HYPERURICEMIA

• **Ustilago Maydis/Moldy Corn-Induced Gout.** Jarmai (1925) (2) reported a goose which developed gout after eating moldy corn. Hutyra et al (1926) (3) noted that gout in birds was caused by the smut fungus Ustilago maydis, a common cause of moldy corn. U. maydis, as well as a number of other fungi in the food chain, produces the mycotoxin oosporein.

Oosporein Induced Gout in Chickens And Turkeys. Pegram et al (1981, 1982) (4,5) fed oosporein to chickens and turkeys. This induced severe articular and visceral gout. Neither hyperuricemia nor renal failure occured to account for gout. This induction of both visceral and articular gout in the same animal appears to end the ongoing dispute as to whether or not these are two separate disease entities.

Fungus Induced Gout in Chickens (Chaetomium trilaterale). Manning and Wyatt (1984) (6) fed chickens corn contaminated with the oosporeinproducing fungus Chaetomium trilaterale. All infected birds developed acute tophaceous gout without either renal failure or hyperuricemia.

Ochratoxin Induced Gout and Hyperuricemia. Ochratoxin-induced gout in chicks was reported by Peckham et al (1971) (7). Ochratoxin-induced hyperuricemia in chickens was shown by Kubena et al (1983) (8). Serum uric acid rose to 15.6 mg%. Ochratoxin is often present in the food chain and in beer (Nip et al 1975) (9). This findling of ochratoxin in beer corelates with the work of Gibson et al who found that beer was the most popular beverage consumed in a group of 61 gouty men. Nearly all of these gouty men were heavy beer drinkers with 41% drinking more than 2.5 liters of beer daily.

Aflatoxin-Induced Gouty Tophi and Gouty Nephropathy in Monkeys. Aflatoxin is common in the food chain. Bourgeois et al (1971) (10) fed aflatoxinto the macaque and found numerous clusters of urate crystals, surrounded by inflammatory cells including giant cells, in the kidneys in 5 of 20 dosed macaques. In addition, the renal lesions were near-identical to those described by Sommers and Churg (1982) (11) in kidney biopsies of patients with chronic hyperuricemia and gout.

Oxalic Acid-Induced Gout. Oxalic acid is a mycotoxin produced by many different fungal species. It was

reported to induce gout in chickens by von Kossa (1899) (12). It is important to note that uric acid degrades to oxalic acid, a finding described by Wells (1914) (13). This explains why both oxalate and urate are both usually present in kidney stones which occur in gouty patients.

Yeast Autolysate-Induced Hyperuricemia in Rats. Long-term feeding of rats with yeast autolysate has caused hyperuricemia associated with a rise in the level of anti-DNA antibodies (Nikolenko et al 1989) (14). These findings appeared to correlate with the finding of significantly elevated titres of anti-DNA in 70 of patients with primary gout. The elevated anti-DNA titres correlated with the severity of gouty arthritis and the severity of morphological renal manifestations of gout. The anti-DNA findings also correlated with blood B-lymphocyte counts and with other immunological indices.

Yeast (Saccharomyces Fermented Beer and Wine)-Induced Gout In Humlans. Beer and or wine are the classical inducers of attacks of acute gout in humans. Ultraviolet microscopy has demonstrated uric acid, purines, lysine and S-adenosylmethioline in the vacuoles of S. cerevisiae (Svihla et al 1963) (15). Beer and wine are fermentations of Saccharomyces cereversiae. Actually, drinking beer and wine is quite the same as drinking a fungal culture; all of the media, all if the remaining live fungus, all of the fungal antigenic cell wall and cellular contents, and all of its metabolites including not only the alcohol, but generous amounts of mycotoxins and uric acid.

While all contemporary studies have attempted to implicate the alcohol in fermented beverages as the cause of hyperuricemia, the older literature contains references to the yeast cell content of beer. Ingestion of beer whose alcohol content had been completely removed by distillation was still associated with large amounts of purine bodies being found in the urine (Lindsay 1913) (16).

Preformed uric acid is present in large amounts in beer. The actual amounts of uric acid found in beer are summarized in Table I.

Moreover, alcohol itself is immunotoxic, which increases the incidence of infections in general. The

TABLE I. URIC ACID CONTENT OF VARIOUS BEERS

Brand of Beer	Uric Acid
Miller Beer	7.34 mg/dl
Olympia Beer	7.05 mg/dl
Budweiser Beer	8.09 mg/dl
Taiwan Beer	9.35 mg/dl

combination of immunotoxic alcohol and mycotoxins in beer and wine probably represents synergism of a fungal/mycotoxin etiology of gout and hyperuricemia. Large ammounts of ochratoxin, which causes gout and hyperuricemia in animals, has been found in beer by Krough et al (1974), Chu et al (1975), and Nipet al (1975) (17,18,19). Gibson et al. found in a group of 61 gouty men, that nearly all were found to be beer drinkers with 41% drinking more than 2.5 liters of beer daily.

Candida Utilis Induced Hyperuricemia In Humans Edozien et al (1970) (20) documented that feeding C. utilis to human subjects caused severe hyperuricemia. Their results are summarized in Table II.

Rousch (1961) and Svihla (1959) (21,22) described the presence of uric acid and uric acid crystals in the

TABLE II. HYPERURICEMIC EFFECTS OF URIC ACID CONTAINING YEAST

	Baseline Before Yeast Feeding	45g Yeast per day	90g Yeast per day	135g Yeast per day
Serum Uric Acid (mg%)	4.5	7.2	9.0	9.6

cytoplasm of C. utilis. The existence of preformed uric acid and urate crystals in the cytoplasm of C. utilis provides proof of a fungal source of uric acid and preformed urate crystals, a finding quite similar to the finding of oxalic acid and oxalate crystals which originate from Aspergillus niger in aspergillomas found in humans. It was also determined that 5 grams of the yeast was found to contain 450 mg of uric acid. That it was indeed uric acid was chemically confirmed by the purified uricase method of Kalckar. A fungal etiology of urate crystals in gouty tophi is quite consistent with etiology of gout.

Cyclosporin-Induced Gout In Humans. Cyclosporin is a fungal metabolite produced by Tolypociadium inflatum Gams. Cyclosporin-induced hyperuricemia and gout are being increasing reported by a number of organ transplant centers (Lin et 1989, West et al 1987,Gores et al 1988) (23,24,25). Gout has occured in as many as 24% of cyclosporin-treated patients. Most interestingly, none of the patients in four different series of transplantations in which the immunosuppressant azathioprine was used experienced a single episode of gout. This difference suggests that the induction of gout was not due to a mechanism involving suppression of the immune system.

Cyclosporin and azathioprine are both cytotoxic agents, particularly against cells of the immune system. All cytotoxic agents possess antifungal activity. Cyclosporin has been documented to possess selective antifungal activity against Cryptococcus (Mody et al 1989) (26). The remote possibility that the antifungal effect was in any way related to the immunosuppressant effects of Cyclosporin was essentially ruled out by their observation that the improved survival was noted in both immunologically intact and congenitally T-cell deficient mice. Cyclosporin dramatically increases the risk of infection in general and of fungi other than Cryptococcus. This appears to be similar to the phenomena seen with therapeutic use of penicillin causing an overgrowth of other microbes including yeast infections.

Ergotamine-Induced Gout In Humans. Ergotamine tartrate has been shown to cause acute attacks of gout in humans. Ergotamine is a fungal metabolite produced by Claviceps purpurea (Talbott 1964) (27).

Penicillin-Induced Gout In Humans. Penicillin is a fungal metabolite produced by Penicillium notatum. It is known to induce acute attacks of gout in humans (Talbott 1964).

PREVIOUSLY POSTULATED MOD EOF ACTION OF COLCHICINE

• **If Etiology Is Unknown, Explaining Therapy Is Pure Speculation.** There are very few absolute truisms in medicine. One which cannot be debatable is that when the cause of a disease is unknown, one simply cannot explain why.a particular drug is effective in treating that disease. Any and all explanations are entirely postulative.

Explaining Antigout Therapy Has Been Entirely Postulative. Since the underlying etiology of gout and hyperuricemia has heretofore been unknown, all prior explanations of therapy have been purely postulative and have been based entirely upon the effects of drugs oh the two obvious manifestation of gout, inflammation and hyperuricemia. These postulates have led to the commonly held perception that hyperuricemia results in crystal deposition which is the cause of the inflammation. This postulation is fatally flawed in that there is actually no consistent elevation of plasma uric acid levels and attacks of gout; urate crystals are omnipresent in gouty lesions; and, episodes of inflammation occurs only quite sporadically-even years apart. Furthermore, the most effctive drug in treating an acute attack of gout is colchicine which has no effect upon uric acid nor is the drug antiinflammatory. In addition, there is the problem that the dnigs which lower plasma uric acid levels do not relieve an acute attack of gout.

Previously Postulated Mode of Action of Colchicine. The actual mechanism of action of colchicine in the treatment of gout has remained unknown. This state of events is most certainly not due to a paucity of studies either in clinical medicine nor in the basic biological sciences. Colchicine has captured the attention of a broad array of scientists around the world and over a quite long period of time. Its dramatic and easily visualized effect on the cellular spindle has been the subject of considerable investigation. Yet, despite all of this attention, the mechanism of its dramatic action in treating an acute attack of gout has continued to remain one the great mysteries of medical science.

The presently held theory of the mechanism of action of colchicine in gout is one of cytotoxic immunosuppression resulting in an antiinflammatory effect. This concept is based upon in vitro studies of the effect of toxic doses of colchicine upon white blood cells and these types of toxicological studies have resulted in the following scenario:

> Colchicine arrests cell mitosis in the metaphase, due to failure of spindle formation, and may prevent cells from entering mitosis. Colchicine has the same effects on the leukocytes incapable of responding to the toxicity of urate crystals. It is this intereference with the immune system responsiveness of the acute gouty granulomatous-type inflammatory reaction which gives the patient relief of his inflammation.

The scenario is supported by data such as colchicine inhibits leukocyte adhesiveness (Malawista 1965) (28) amoeboid motility (Malawista 1965) (29), mobilization (Fruhman 1960) (30), chemotaxis (Phelps 1970) (31), degranulation of lysosomes (Rajan 1966) (32), and leukocyte metabolism during phagocytosis (Goldfinger 1965, Wechsler et al 1965) (33, 34). The most potent inhibitory effects of colchicine are on chemotaxis (Phelps 1970) (35) and random motility of leukocytes under the influence of urate (Phelps 1969) (36). However, in order to produce any of these findings, it is necessary to give, per unit mass of experimental material, up to approximately 100 times the therapeutic dose which is effective in gouty patients (Talbott 1965).

Several clinical studies have documented that the leukocytes are not actually affected by colchicine administered to patients in therapeutic levels. Colchicine in clinically effective doses produced no detectable ultrastructural changes in the leukocytes in synovial biopsies of patients with acute gouty arthritis (Agudelo and Schumacher 1973) (37). In patients treated with 0.6 to 1.8 mg per day of colchicine to prevent recurrences of familial Mediterranean fever, neutrophils were capable of normal phagocytosis, produced normal amounts of pyrogen, and migrated normally, both randomly and in response to chemotactic stimuli (Dinarello et al 1976) (38). Furthermore, colchicine failed to influence the behavioural responses to the irritating effects of urate crystals in urate arthritis induced by injecting urates into the ankle joint of rats (Coderre and Wall 1988) (39).

Obviously, the postulate that colchicine is antiinflammatory by restricting the function of neutrophils has been essentially disproved in both animals and in humans.

AHTIGOUT AMD ANTIFUNGAL ACTIVITY OF COLCHICINE

• **Antigout Effectiveness of Colchicine.** Colchicine is a plant alkaloid whose benefit in the treatment of gout is recorded in the most ancient medical records. Early descriptions of its use leave little doubt of its effectiveness: " In the first trial of the medicine, it (colchicine) proves in most instances a powerful palliative or

short cure; removing the paroxysm as by a charm, and not infrequently without any very sensible operation upon the stomach, or upon any of the excreting organs".

Scudmore (1817) (40)

Colchicine has always been, and still is, the most specific treatment for acute gouty attacks (Ahern et al 1987) (Famaey 1988) (41) (42). Even the administration of anti-urate drugs often requires the addition of colchicine to control continuing acute attacks of gout.

Antifungal Activity of Colchicine. Colchicine is a plant-derived alkaloid. Such alkaloids are anti-predator and antifungal in their actions as plant protectors. (Mothes et al 1988) (43).

The antifungal activity of Colchicine against Aspergillus niger was documented by Shankhla and Sharma (1969) (44). Other reported data demonstrating the antifungal activity of colchicine was reviewed by Egisti and Dustin (1955) (45). This data is summarized in Table III.

Species	Results
Allomyces javanicus	changes were induced
Aspergillus spp.	mutants were produced
Butrylis cinerea	hyphae became hypertrophied
Caprinus radians	condida influenced
Diaparthe perniciosa	prevented condida formation
Mucor sp.	no changes noted
Penicillium notatum	polyploids
Psilocyte semilanceolata	condida changed
Saccharomyces cerversiae	cytological changes, cells enlarged, dumbbell-shaped nuclei, inhibition of growth

TABLE III. ACTION OF COLCHICINE ON FUNGI

Recently, in a murine Candida study comparing the results of intravenous phorbol myristate acetate and intrapertional colchicine, both drugs completely eliminated the epidermal neutrophilic infiltrates characteristic of these infections (Sohnle and Hahn 1989) (46). The resultant degree of Candida invasion into the dermis was very significant in the phorbol myristate acetate treated animals but quite minimal in the colchicine treated animals. The results are quite indicative of the in vivo antifungal protective effect of colchicine.

The fact that colchicine is an antitubulin drug which shares this mode of action with the antifungal antibiotic griseofulvin has been entirely ignored in the clinical applications of colchicine.

We have here a situation where the major mode of action of these two drugs, sharing no other apparent action, has been entirely ignored in understanding the clinical effectiveness of one of the drugs, colchicine. The extent of this error of perception becomes quite apparent in the light of the observation that griseofulvin, a specific antifungal antibiotic possessing no other significant pharmacological property, is equally as effective as colchicine in relieving an acute attack of gout.

ANTIGOUT AMD AHTIFUHGAL ACTIVITY OF GRISEOFULVIH

• **Antigout Effectiveness of Griseofulvin.** There are two reports in the medical literature of dramatic responses of acute gout to the specific antifungal agent griseofulvin. Both reports appeared in 1962 and there have been no additional followup studies reported since that time.

The rational for these trials was that gouty patients given griseofulvin for superficial fungal infections observed that their painful joints had also markedly improved.

In the first study, the use of moderate to high doses of griseofulvin to treat acute gouty arthritis resulted in complete remissions in 14, partial remission in 2, out of 23 patients within 24 to 48 hours (Slonim et al 1962) (47) .There were 23 patients with acute gouty arthritis in the series. Included were histologic proof of tophi in 15 patients; dramatic clinical improvement in 22 patients during colchicine trial administered by standard technic for a previous acute attack in 12; two or more serum uric acid levels greater than 6,5 mg, per cent in 22 cases; and x-ray evidence of bone destruction in 17 of the group. Side effects were negligible but 6 out of the 7 patients who did not improve suffered vomiting episodes during the period of drug dosing and were felt to not have retained therapeutic amount of the drug. 1.0 to 4.0 g. of griseofulvin was given orally at the onset of the study to the gouty patients, with further dosage at 6 hours spacings. Eighteen of these patients recived 4 to lOg total dosage during the first day and 0 to 6 g on the second. Higher doses were prescribed for 5 patients to demonstrate, if possible, an effect on serum and urine uric acid concentrations; none was seen.

In the second report, 20 patients with acute gout were treated and favorable improvement was noted in 15 (Wallace and Nissen 1962) (48). Once again,, the optimal response occured within 24 to 48 hours. Patients were given 6-10 g of griseofulvin in divided doses.

Antifungal Activity of Griseofulvin. Griseofulvin is a specific antifungal antibiotic. It was first isolated from Penicillium griseofuvium dierckx in 1939 (Oxford et al) (49), but it was not investigated further at that time because it lacked antibacterial activity. In 1946 Brian et al (50) found a metabolite in Penicilium janczewskii which caused shrinking and stunting of fungal hyphae. They named this "curling factor" which was subsequently found to be griseofulvin. During the next decade, it was widely used to treat a variety of fungal diseases of plants and ringworm of cattle. Its potential for the treatment of human infections was not realized until Gentles (1958) (51), searching for potential therapeutic agent to control fungal infections in Scottish miners, demonstrated that oral griseofulvin was effective in experimental Microsporum canis infection of guinea pigs. It was soon shown that the drug was also effective in human ringworm infections

(Williams et al 1958, Blank et al 1959) (52,53). Griseofulvin is now generally accepted as the drug of choice for treatment in the majority of these fungal diseases.

AHTIGOUT AMD ANTIFUNGAL ACTIVITY OF VINBLASTIHE

• **Antigout Effectiveness of Vinblastine.** Another member of the antimicrotubule group of agents effective in treating gout is vinblastine. It has been demonstrated to be as effective as colchicine in the treatment of acute gout (Krakoff 1965) (54).

Antifungal Activity of Vinblastine. In 1983, the similarity of actions of vinblastine, griseofulvin and colchicine was demonstrated in a unicellular alga. Electron microscopy demonstrated conspicuous mohpological abnormalities resulting from inhibition of microtubule dependent protoplasmic streaming (Mizukami and Wada 1983) (55). The authors noted that very similar changes had been previously reported in Fusarium acuminatum treated with another antimicrotubule agent, methyl benzimidazole-2-ylcarbamate.

It should be noted that the latter compound is an azole and that the azoles are evolving as a most promising group of antifungal agents with several members of the group in current use (ketoconazole, fluconazole, etc.) and a number of others are near-ready for marketing.

CONCLUSION

• The unified concept of a fungal etiology and an antifungal mode of action of antigout drugs provides a clinically meaningful therapeutic drug and dietary approach not only for the physician, but, most importantly, for the patient afflicted with gout, particularly those who are been drinkers and are consuming other yeast-fermented beverages and foods such as wine, bread and cheese.

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