

Class action of oral coumarins in the treatment of a patient with chronic spontaneous urticaria and delayed-pressure urticaria

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Summary

Chronic spontaneous urticaria is a common condition, with a lifetime prevalence of 0.5–1.0%. It has a significant effect on quality of life, comparable to having triple-vessel coronary artery disease. Warfarin and nicoumalone are synthetic derivatives of the plant toxin coumarin. We report the first case of successful response to both warfarin and nicoumalone in the same patient, thereby demonstrating a class action of synthetic coumarins in the disease. Complete response with both coumarins occurred once an INR above 2.0 was achieved, and was maintained during a 12-month follow-up. The mechanism of action of coumarins on urticaria is not known, but may be related to decrease in thrombin production or to interference of activation of other inflammatory proteins produced during the coagulation process. Side-effects of anticoagulation can be catastrophic, and coumarin treatment currently remains reserved for restricted severe recalcitrant cases only.

Chronic urticaria (CU) is defined by daily transient weals with or without angio-oedema, with a duration of > 6 weeks. Urticaria is the result of dermal oedema induced by mast-cell degranulation, which causes the release of inflammatory mediators including histamine and various cytokines. In at least 30% of patients, the degranulation of mast cells is autoimmune in nature, caused by circulating functional IgG autoantibodies to the IgE receptor on mast-cell membranes, or less commonly to IgE itself, and may be detected by the autologous serum skin test or the 'gold standard' basophil histamine release assay.¹ In the remainder of patients with CU, the pathogenesis remains unknown. Recent reports have hypothesized that the pathogenesis

of urticaria may also be related to activation of the coagulation pathway.

We report the first case of successful response to both warfarin and nicoumalone in the same patient, demonstrating class action of synthetic coumarins in the disease.

Report

A 22-year-old woman presented with a 5-year history of chronic spontaneous urticaria and delayed-pressure urticaria (DPU), which had been diagnosed on the basis of her medical history and clinical findings. She often had to attend the emergency department, and was unable to attend her workplace on numerous occasions. Treatment with combinations of H1 and H2 histamine antagonists had been unsuccessful.

On physical examination, typical spontaneous urticarial weals were seen on the trunk and limbs. On subsequent consultations, the patient had bilateral, symmetrical cutaneous swellings on the soles of both

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feet and on the waist at the sites of pressure from clothing from the previous day. She also presented on other subsequent occasions with typical asymmetrical angioedema of the eyelids and lips.

A skin biopsy was not taken. Laboratory investigations gave normal results for full blood count, renal and thyroid tests, erythrocyte sedimentation rate and C-reactive protein. Autologous serum skin testing and basophil histamine release assay gave negative results.

Treatment was started after the first presentation with ciclosporin, oral tacrolimus and tranexamic acid, but all three failed. After careful consideration of other treatment options and full discussion of the potentially serious side-effects, anticoagulation therapy with warfarin was instituted. Complete remission occurred once an international normalized ratio (INR) of < 2.0 was achieved. Unfortunately, the patient developed symptoms of fever and urinary frequency, which she attributed to the warfarin. She discontinued treatment, and her urticaria subsequently relapsed.

Given the previous treatment success with warfarin, an alternative coumarin anticoagulant, nicoumalone (acenocoumarol; Sinthrome; Alliance Pharmaceuticals, Wiltshire, UK), was started. It was equally efficacious once an INR of > 2.0 was achieved, with complete response maintained at the 12-month follow-up visit. Improvement of the DPU was confirmed by negative challenge testing while the patient was taking a coumarin. Her symptoms would only recur on the occasions that her INR reduced to subtherapeutic levels.

The coagulatory and inflammatory pathways are closely interlinked, in particular with relation to production of thrombin, a key proinflammatory mediator. In the extrinsic pathway of the coagulation cascade, tissue factor binds to Factor VIIa, activating Factor IX, and Factor X. Activated Factor Xa converts prothrombin to thrombin, which results in the formation of fibrin from fibrinogen. There is increasing indirect evidence that activation of the extrinsic coagulation pathway may be important in the pathogenesis of urticaria. Investigators have confirmed tissue-factor expression within dermal eosinophils from skin biopsies of patients with urticaria, and found increased levels of circulating Factor VIIa, thrombin–antithrombin complex, fragment F1+2 and D-dimer (surrogate indicators of coagulation-pathway activation and thrombin production). Furthermore, once an episode of urticaria has settled, the increased levels of fragment F1+2 and D-dimer return to normal.² However, it is still unclear whether these changes are central to the pathogenesis of urticaria, or

simply are secondary, as a marker of inflammation that is already present.

Thrombin is a serine protease. It binds to protease-activated receptor (PAR), which is expressed by numerous inflammatory cells, and activates transcription factors regulating expression of tissue factors, adhesion proteins and cytokines, and directly activates mast cells and C5.³ Coumarins inhibit vitamin K reductase, thereby preventing carboxylation by γ -glutamyl carboxylase of various target proteins, including the coagulation factors II, VII, IX and X, which are essential for the production of thrombin.⁴ Disruption of thrombin production may explain the therapeutic effect of anticoagulation in urticaria. Aside from factors of the clotting cascade, coumarins also inhibit carboxylation of other vitamin K-dependent proteins, and it is also feasible that the mechanism of coumarin action is independent of the coagulation cascade itself.

Treatment of CU with warfarin was first described in 1979. Since then, there have been a further 11 reports of successful use of warfarin in CU, including a limited placebo-controlled, double-blind crossover trial of three patients.^{5–8} A single case of nicoumalone treatment in nonsteroidal anti-inflammatory drug-induced urticaria has also been reported.⁹ Further indirect evidence of activation of the coagulation pathway in urticaria has also been provided by anecdotal reports of the successful use of heparin. The mechanism of action of heparin is to activate antithrombin III, which subsequently inactivates thrombin and other factors. Asero *et al.*¹⁰ reported that five of eight patients who had failed to respond to antihistamine and prednisolone had marked symptom improvement with nadroparin and tranexamic acid treatment. A further case has been reported of complete response at 15 months in a patient treated with heparin, similarly to our case, with the urticaria only recurring whenever the heparin was discontinued.¹¹

Chronic spontaneous urticaria is a common condition, with a significant negative effect on quality of life, comparable to having triple-vessel coronary artery disease.

To our knowledge, this is the first patient to have shown a class effect of oral coumarins in the treatment of chronic spontaneous urticaria. Side-effects of anticoagulation can be catastrophic, and coumarin treatment currently remains reserved for restricted recalcitrant cases by physicians experienced in managing urticaria. The precise pathogenesis of CU is still unknown in those who do not have chronic autoimmune urticaria, and the mode of coumarin action in urticaria requires further investigation.

Learning points

- At least 30% of patients with CU have an autoimmune pathogenesis with circulating functional IgG autoantibodies to the IgE receptor on mast-cell membranes or rarely to IgE itself.
- In the remaining cases of chronic spontaneous urticaria, recent reports have hypothesized that the pathogenesis may also be related to activation of the coagulation pathway and subsequent inflammation.
- In the published literature, 11 cases of successful warfarin anticoagulation in the treatment of chronic spontaneous urticaria have been described to date.
- We report the first case of successful response to both warfarin and nicoumalone in the same patient, indicating a class action of synthetic coumarins in the disease.
- The precise mechanism of action of coumarins in urticaria is not known, but may be related to a decrease in thrombin production or interference of activation of other inflammatory proteins produced during the coagulation process. Further research in this field is required.
- Side-effects of anticoagulation can be catastrophic, and coumarin treatment remains reserved for restricted recalcitrant cases by physicians experienced in managing urticaria.

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