

# Remission of rosacea induced by reduction of gut transit time

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## Summary

Rosacea is a chronic disorder characterized by hypersensitivity of the facial vasculature, presenting with intense flushing eventually leading to chronic erythema and telangiectasia. Although the precise aetiology of rosacea is not known, numerous associations with inflammatory gastrointestinal tract disorders have been reported. Furthermore, substance P-immunoreactive neurones occur in considerably greater numbers in tissue surrounding affected blood vessels suggesting involvement of neurogenic inflammation and moreover plasma kallikrein–kinin activation is consistently found in patients. In this report, a patient without digestive tract disease is described, who experienced complete remission of rosacea symptoms following ingestion of a material intended to sweep through the digestive tract and reduce transit time below 30 h. It is possible that intestinal bacteria are capable of plasma kallikrein–kinin activation and that flushing symptoms and the development of other characteristic features of rosacea result from frequent episodes of neurogenic inflammation caused by bradykinin-induced hypersensitization of facial afferent neurones. The possible relevance of this hypothesis to other conditions featuring afferent hypersensitivity, such as fibromyalgia, is considered.

## Report

Numerous associations have been reported between digestive tract disorders and rosacea. Such diseases include ulcerative colitis,<sup>1</sup> Crohn's disease,<sup>2</sup> gastritis,<sup>3</sup> coeliac disease,<sup>4</sup> hypochlorhydria,<sup>5</sup> abnormalities in jejunal mucosa<sup>4</sup> and *Helicobacter pylori* infection.<sup>6</sup>

In managing patients with rosacea, the clinical efficacy of several chemically diverse families of antibiotics has never been convincingly explained. One possible explanation might lie in their capacity to reduce or modify the intestinal flora or other physiological aspects of the gastrointestinal tract. To investigate possible associations between rosacea and the gut further, this report describes the effects of modifying gastrointestinal tract transit time in a patient with rosacea.

A 24-year-old male who had suffered rosacea for 6 years was studied. Various oral antibiotic treatments

had been tried with varying success, but symptoms had relapsed on all occasions. The patient did not have a history of digestive tract disease and had previously tested negative for *H. pylori* infection. However, in an earlier examination the patient had demonstrated significantly increased intestinal permeability, although this investigation used polyethylene glycol-400 which has disputed reliability. As a child, the patient had suffered from asthma, severe migraine and suspected, but unconfirmed, attention-deficit hyperactivity disorder.

On examination, the patient presented with moderate facial erythema, consistent with rosacea. The patient also suffered Raynaud's syndrome and reported infrequent migraines and occasional episodes of cluster headaches. The patient displayed no symptoms of digestive tract disease, except possibly mild abdominal bloating. However, the patient did report occasional episodes of reduced stool frequency, sometimes accompanied by a worsening of rosacea symptoms. The patient was not taking any medication at the time of the investigation.

Thirty grams of coarse wheat bran was mixed with warm water and a small amount of sugar to improve the taste. This mixture was consumed 30 min to 1 h

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after each of the three daily meals. Fluid consumption was also increased. Whole gut transit time (WGTT) was measured by the passage of ingested charcoal capsules. The wheat bran was intended to greatly reduce the transit time of food through the intestines, the rationale being that accelerated passage of food would inhibit excessive fermentation by bacteria and ultimately reduce or modify the bacterial population within the intestines. Prior to wheat bran administration, WGTT was > 70 h.

After 7 days of treatment, WGTT was measured at 28 h. Stool frequency and size was significantly increased. Rosacea symptoms were markedly improved with reduced erythema and reduced sensitivity of the facial skin. After 14 days of treatment, there were no apparent symptoms of rosacea. The facial skin appeared normal and without detectable erythema. All vascular hypersensitivity was abolished and the patient no longer demonstrated a tendency to flush. The patient's Raynaud's symptoms were also eliminated and although not measured directly the patient's abdominal bloating was visibly reduced.

The treatment was continued for a further 5 weeks and remission was maintained. The patient also reported remission from migraine and cluster headaches and reported a general sense of well being. However, during the sixth week the patient reported upper abdominal burning sensations. These symptoms worsened and the patient's rosacea returned with severity. The patient's cheeks and nose were profoundly erythematous. Ocular symptoms were also present with conjunctival hyperaemia and blepharitis. The patient also reported episodes of migraine and bronchoconstriction.

The wheat bran was immediately discontinued and symptoms attenuated within 4 days. Although not in remission, rosacea symptoms remained improved from baseline. After a further week the wheat bran was re-administered. Within 2 days the burning sensations returned and rosacea symptoms rapidly worsened again. Wheat bran was discontinued and the patient was tested for coeliac disease, which proved negative. The patient continued to experience worsening of symptoms following consumption of wheat for the following 6 months. After 12 months and considerable avoidance of wheat products the patient was able to resume moderate consumption of wheat without detectable worsening of rosacea symptoms.

The remission of symptoms produced by ingesting wheat bran in this manner, suggests that the efficacy of antibiotics in treating rosacea may be due to their activity against intestinal bacteria. However, the acute worsening of symptoms following prolonged

consumption of wheat bran and the simultaneous occurrence of burning sensations also indicate that wheat bran itself was capable of provoking rosacea symptoms. This suggests that rosacea symptoms may be mediated by substances produced in response to inflammation in the digestive tract.

Bradykinin may be responsible since the plasma kallikrein-kinin system (PKKS) is significantly activated in patients with intestinal inflammation.<sup>7</sup> PKKS activation is consistently found in rosacea patients vs. controls<sup>8</sup> and increases in plasma bradykinin concentrations correlate closely with rosacea flushing episodes induced by alcohol consumption.<sup>9</sup> Resident bacteria in the intestines have been widely implicated in the pathogenesis of inflammatory bowel disease (IBD) and oral metronidazole has been found to be particularly efficacious in improving symptoms in both rosacea and IBD.<sup>10</sup> Furthermore, intestinal intramural injections of bacterial cell wall fragments in Lewis rats are capable of PKKS activation.<sup>11</sup>

However, the vascular symptoms in rosacea patients appear to involve neurogenic inflammation. Substance P-immunoreactive neurones are increased considerably around blood vessels in the papillary dermis in lesional skin in rosacea patients vs. normal skin from similar locations.<sup>12</sup> Rosacea symptoms often acutely worsen following consumption of spicy foods, which is consistent with neurogenic inflammation induced by capsaicin. Rosacea is also associated very significantly with migraine,<sup>13</sup> which suggests that rosacea is part of a more general underlying disorder and further supports the involvement of neurogenic inflammation, which is widely implicated in the pathogenesis of migraine.

Therefore, it is hypothesized that the vascular hypersensitivity in rosacea is a consequence of bradykinin-induced hypersensitization of facial afferent neurones and that flushing symptoms and the development of chronic erythema result from the frequent occurrence of neurogenic inflammation.

It is possible that this hypothesis may have relevance to the pathogenesis of other diseases that feature afferent hypersensitivity and associate with bowel disorders, such as fibromyalgia and related affective spectrum disorders. Fibromyalgia patients exhibit a high incidence of small intestinal bacterial overgrowth (SIBO) and both bowel and neurological symptoms are significantly improved following eradication of SIBO using minimally absorbed antibiotics.<sup>14</sup> It is also possible that this hypothesis may have relevance in accounting for some of the symptoms of sensory hypersensitization in regressive-onset autism, in which patients demonstrate significant alterations to the composition, location and populations of intestinal microflora<sup>15</sup> and exhibit

significant short-term improvement following administration of a minimally absorbed antibiotic.<sup>16</sup>

Data from this single patient indicate that larger studies should be conducted to assess the relevance of intestinal bacteria in the pathogenesis of rosacea.

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