Role of faecal gas analysis for the diagnosis of IBD

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Abstract

The diagnosis of IBD (inflammatory bowel disease) is based on the clinical evaluation of symptoms and signs leading to a series of investigations. The investigations used are often unpleasant for patients; they are invasive, costly and potentially dangerous. Blood tests for plasma viscosity and CRP (C-reactive protein) are abnormal in the majority of patients with both Crohn’s disease and ulcerative colitis, but they lack specificity, as both are raised in countless infectious and inflammatory diseases. When the intestine is inflamed, white cells pass into the lumen and enter the faeces. Calprotectin and lactoferrin are neutrophil proteins; they can both be measured in the faeces of patients with active IBD and show good sensitivity and specificity for inflammatory diseases of the intestine. However, they cannot be used to distinguish between infectious diseases and IBD; moreover, both of these faecal markers are raised in the presence of faecal blood.

If asked, patients often report that the odour of flatus, or the gas emitted from faeces during defecation, is pungent during flare up of their IBD. Some more experienced patients have suggested that the change in odour precedes other symptoms of a relapse of IBD.

Clostridium difficile

It has long been observed that faecal samples from patients with CDAD (Clostridium difficile-associated diarrhoea) are also pungent. Indeed, some experienced nurses claim to be able to diagnose CDAD from the odour of faeces. CDAD is a major nosocomial infection; there are approximately 50 000 cases per annum in England and Wales; and the infection adds €3 billion to the cost of European healthcare each year. However, the biggest problem is the significant morbidity and mortality associated with CDAD. Treating CDAD was hampered by diagnostic delays; several days in many centres. As a result, EIA (enzyme immunoassay) tests have been developed to identify the faecal toxins produced by C. difficile; these tests are rapid, but their specificity and sensitivity has been called into question by the Health Protection Agency.

Our research group have studied the VOCs (volatile organic compounds) emitted from faeces. We have developed a standardized procedure for collecting faeces, extracting VOCs and then analysing the compounds using gas chromatography–MS [1].

Although the aim was to study the VOCs in samples from patients with IBD, the work began with normal controls and patients with CDAD [2]. We described over 300 VOCs that were emitted from faeces of normal donors taking an ad lib. diet; many of the VOCs were found in the samples of the majority of subjects, which suggests that the interaction between common foods and shared species of bacteria led to shared metabolic products. We also observed stability in the VOCs in several small longitudinal studies.

Our early studies of CDAD found that the VOC ‘profiles’ from patients were markedly different from those of healthy subjects and patients with other kinds of diarrhoea. The work was developed, and a mathematical model built based on the presence/absence of specific VOCs showed that they can be used to distinguish between CDAD, ulcerative colitis and Campylobacter infection [2].

Cholera

Cholera is a terrifying illness. The ‘stool’ passed is extremely voluminous and watery, and said to resemble ‘rice-water’; however, even in clinics that are used to treating cholera,
there can be uncertainty, as sometimes dysentery or rotavirus can look like cholera. Clinical staff have observed that the cholera stool has a characteristic smell which, surprisingly, is pleasant; so we investigated the VOCs associated with cholera and compared them with those of healthy controls from the same city. There were very few VOCs emitted from cholera samples; one of which is used in the perfume industry [3].

NEC (necrotizing enterocolitis)
NEC is a devastating illness of premature babies; its aetiology is unknown and its diagnosis often delayed as early clinical features are non-specific. Twins are predisposed to NEC. We collected daily samples from several twin pairs from one neonatal intensive care unit with the aim of finding some discordant for NEC; several were found. The VOCs emitted from the faeces obtained from twin pairs were remarkably similar, until the prodrome of NEC. In the days preceding the diagnosis of NEC, the VOC pattern of the sick baby exhibited fewer VOCs than the healthy sibling and there was a loss of ester compounds [4].

Inflammatory bowel disease
Armed with these data, we undertook a cross-sectional study of the VOCs emitted from samples of patients with ulcerative colitis, Crohn’s disease and diarrhoea-predominant IBS (irritable bowel syndrome), as well as healthy controls; the IBD samples included patients in relapse and remission. VOCs were extracted and named using our standard protocol. The VOC patterns in each disease group were compared using univariate analysis followed by discriminant function analysis. The models were assessed using two independent techniques. The models were able to differentiate between active Crohn’s disease and ulcerative colitis from controls, active Crohn’s disease and ulcerative colitis from inactive disease, IBS and IBD, and IBS and controls. For each, the certainty was of the order of 80–90%.

Future developments
Analysis of these data is ongoing, but the indications are that the VOC patterns in IBD differ during relapse and remission; this suggests that the microbial environment and/or its metabolism changes with disease activity, or that the inflammatory process itself influences the generation of VOCs. The story is complex; there is a shift in acids and aldehydes that may be explained, in part, by a pH change during disease flares. However, the differences between Crohn’s disease and ulcerative colitis imply that the results are not simply a reflection of a change in transit time. Perhaps more importantly, VOC-based models could distinguish between C. difficile infection, Campylobacter infection and active ulcerative colitis.

We have also explored the potential for a sensor-based device to differentiate between various forms of diarrhoea. Initial work was conducted using samples of CDAD and hospital-acquired diarrhoea without C. difficile. A study of over 200 samples has been presented: the sensor-based device could be used to differentiate between these groups with over 90% accuracy. These data are encouraging, but they may be better than they look as, in that series, the CDAD was diagnosed using the EIA. A prospective study of 2000 samples of hospital acquired diarrhoea is ongoing; this time the microbiological diagnosis for CDAD is based on the cytotoxicity assay. Work to investigate the potential of this device to diagnose IBD has just begun.

We have shown that the pattern of VOCs emitted from faeces varies in the presence of infectious and non-infectious gastrointestinal diseases. The potential for a point-of-care device to diagnose IBD is under investigation; such a device would transform the management of patients with both acute and chronic diarrhoea.

References

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