IRRITABLE BOWEL SYNDROME: A DRUG DEVELOPMENT MINEFIELD

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Background

Irritable bowel syndrome (IBS) is a disorder characterised by abdominal pain and a disordered bowel habit often associated with a feeling of abdominal distension. It is frequently accompanied by a variety of other symptoms such as backache, lethargy, nausea and even bladder and gynaecological complaints (1-3). Symptoms can occur intermittently or continuously and, in terms of severity, the condition can be trivial or virtually incapacitating. One of the most striking features of IBS is its high prevalence (4), with up to 10%-15% of the population being affected in all the countries that have been studied so far – it is also more common in females. It accounts for a large number of general practitioner consultations and as much as 40% of the workload of consultants specialising in gastrointestinal diseases. Despite these figures, it is thought that many sufferers do not consult their doctor and it has been shown that general practitioners only refer approximately 20% of their patients with IBS for a specialist opinion (5).

The cause of IBS is entirely unknown. Indeed, it is not even clear whether it is a single entity or represents a variety of disorders presenting in a very similar manner. It was originally thought that symptoms largely resulted from disordered motility of the colon, although more recently opinion has swung towards favouring an abnormality of perception either at the peripheral or central level (6). Of course, it is likely that both abnormalities, disordered motility and sensitivity, may occur simultaneously, possibly in varying degrees in different individuals. Whatever the pathophysiology turns out to be, it is generally agreed that the whole length of the gastrointestinal system is affected rather than any specific area (e.g. the colon). Why some individuals develop IBS and not others is unknown, but a reasonable hypothesis is that an individual may be genetically predisposed and is then triggered by

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one or more of a variety of noxious events, ranging from environmental through to psychological. However, it is no longer acceptable to regard IBS as a purely psychological condition.

It has been traditional in the field of IBS research to divide patients up according to their predominant bowel habit. Thus, patients whose bowel habit is usually loose are labelled diarrhoea predominant IBS, with those at the other end of the spectrum being classified as belonging to the constipated predominant subtype. Some subjects fluctuate between these extremes and are labelled as alternators. Whether this classification has any pathophysiological utility is debatable, but it is certainly clinically useful when considering which drugs may be helpful or avoiding those that may exacerbate a particular bowel habit abnormality.

In the absence of a "test" for IBS, the diagnosis is based on the clinical presentation – mainly abdominal pain and a disordered bowel habit. It is important that other possible conditions are excluded, but the emphasis should be on a positive diagnosis rather than there being nothing wrong, thus, it must be IBS. There is no evidence of a relationship between cancer of the colon and IBS, but it is sensible to exclude the former in anybody over the age of 40-45 by either colonoscopy or barium enema. In an attempt to introduce some diagnostic consensus, the Rome Working Party was established some years ago. From this emerged the Rome I (7) criteria and, subsequently, the Rome II (8) criteria, which have been invaluable for ensuring homogeneity of patient populations for research purposes. However, their utility for prevalence studies is less clear, as they probably underestimate the size of the problem. For instance, the Rome II criteria are more restrictive than Rome I, and both are more restrictive than the older Manning criteria (9).

Management

Initial management should always include a thorough explanation of the condition, coupled with an exploration of any lifestyle changes that might be considered worthwhile, such as stress avoidance and getting a good night's sleep. In addition, many patients, particularly women, omit breakfast, which can have a detrimental effect on bowel habit as a result of failure to induce a morning gastrocolonic reflex. It is probably fair to say that there are currently no really effective drugs available for the treatment of IBS and, with the exception of the brief appearance of alosetron, no new drugs have come onto the market for at least two decades. Currently, the most frequently prescribed medications are the antispasmodics, which can either have antimuscarinic activity or act by inhibiting smooth muscle contractions. They were introduced on the basis that the pain of IBS resulted from spasm, but even though this hypothesis has been challenged, antispasmodics, nevertheless, do seem to have some beneficial effects (10). Laxatives and antidiarrhoeals are also helpful, depending on the bowel habit. Polyethylene glycol, sodium picosulphate and bisacodyl are probably the best choices for constipation, and loperamide is most commonly used for diarrhoea. The concept that these medications, particularly the laxatives, can "damage" the bowel is probably untrue and patients need to be vigorously reassured on this point as they are often reluctant to take them for this reason.

Patients always assume that diet plays a crucial role in their condition, particularly as many find that eating often makes them worse. The problem is that eating, or even the thought of food, leads to stimulation of gastrointestinal activity (11), irrespective of what is being eaten, and this can often result in the patient concluding, erroneously, that they have a food intolerance. One of the most common recommendations made to patients is to eat more fibre. This advice is based on an unsubstantiated hypothesis dating back to the 1970's, which suggested that IBS was a "fibre deficient" disorder (12). In fact, subsequent clinical trials have largely failed to demonstrate any benefit of bran and recently our group has shown that bran is actually detrimental to hospital based patients with IBS (13) – a good example of the need for evidence based medicine. Interestingly, commercially available forms of fibre, such as ispaghula derivatives, are sometimes helpful in patients with IBS, but even these can disagree with some people (13). There is some evidence to suggest that exclusion diets may be helpful in IBS (14) and, undoubtedly, dramatic improvements can occur with this approach. Reports on the response rates vary and, ideally, this form of treatment is best supervised by a dietician experienced and interested in treating IBS in this way.

If patients do not respond to education, spasmolytics, dietary modification or lifestyle changes, then a number of other measures are worthy of consideration. The most important is a trial of antidepressants, particularly the tricyclics, for which there is some evidence of efficacy (15). There is little information on the use of serotonin reuptake inhibitors in IBS but they are still worth trying, espe-
cially in constipated patients where tricyclics can worsen this symptom. These drugs seem to have activity in IBS outside their antidepressant properties, as they characteristically seem to become effective more quickly and often require lower doses than is observed in depression. Furthermore, they frequently help patients who are not obviously depressed. Unfortunately, when antidepressants are effective they often have to be taken long term, with the patient promptly relapsing when they are stopped. This can be a problem, as they are not without their side effects, and many patients are reluctant to take a drug which they perceive as being “mind dulling” and really only suitable for people with “psychiatric” disorders. Other approaches that have also been shown to help are hypnosis (16) and psychotherapy (17) but, unfortunately, these are time consuming, costly and only available in specialist centres with enthusiasts providing the treatment.

Thus, as far as treatment of IBS is concerned, we have the picture of an extremely common condition, which is inclined to be a life long affliction for which current medications, possibly with the exception of antidepressants, are largely marginal in effectiveness. This results in patients with anything more than trivial disease becoming dissatisfied with the treatment being offered and their medical attendants becoming frustrated by their inability to be helpful in any way. This situation explains why patients stop consulting their doctors and turn to other sources of help, such as alternative forms of medicine, for which, sometimes, extravagant claims are made.

Economics

Trying to evaluate the economics of IBS is a particularly difficult exercise (18). Direct costs in terms of drug expenditure are not excessive because the currently available medications are cheap and do not make a large contribution to national drug expenditure, even when taken on a regular basis. Chronic severe cases of IBS are notorious for undergoing multiple expensive investigations and even surgery, thus accumulating considerable individual costs to the health service. However, it has to be remembered that these patients represent only a minor proportion of the already small percentage (20%) of IBS patients referred to hospitals. Therefore, in terms of direct costs to health service budgets, IBS is not a major burden, although this could be instantly transformed if a new and inevitably much more expensive medication were introduced, as most patients would, at least, want to try it. Just because health service costs are currently not especially high, it does not mean that these patients are not costly in other ways, and it is now being recognised that they take considerable amounts of time off work and, even when at work, do not feel they are functioning efficiently. A particularly striking statistic is that up to 25% of tertiary care patients that are eligible to work are permanently off sick because of their problem (19). The other way that these patients are costly is to themselves. Any new “cure” for IBS, such as aloe vera, is nearly always expensive and avidly consumed, and the number of complicated and costly diets being offered is absolutely bewildering. The other “cost” of IBS is the impact that this disorder has on the quality of life. The measurement of the quality of life is a relatively new science but its application to IBS has already clearly revealed the extent of suffering in this disorder (20) with scores comparable to those seen in patients with chronic renal or cardiac disease. In the tertiary care setting it is not an exaggeration to say that some patients’ lives have been totally destroyed by the disorder. Thus, the economics of IBS are far from straightforward – the condition may be cheap to the health service, but to society and the individual patient it is much more costly.

Drug development

The considerable market potential for a new, effective medication for IBS has not escaped the pharmaceutical industry, and even if a drug were effective in only a small subgroup of the disorder it would be profitable by virtue of the sheer size of the IBS population. The ideal drug would have to be safe, help all subgroups of the disorder and should not have any prescribing restrictions. If a potential drug was only active in a subgroup of patients, it would preferably not make any of the other subgroups worse – a busy general practitioner is not going to want to be concerned about who can and who cannot have the drug. A rapid onset of action would be an advantage so that the drug could be used in either an as necessary or continuous dosing regime.

The major challenge facing the pharmaceutical industry is how to design a drug for a condition in which the cause is unknown and even the pathophysiology is poorly understood. It is not even known whether abdominal pain and discomfort have the same origins. The other problem is that different patients rate different aspects of their con-
condition as the most intrusive (21). For instance, one patient may consider the pain to be the worst feature, whereas another may put distension or their bowel problem as most troublesome. Added to all this is the fact that IBS patients frequently complain of a number of “non-specific symptoms” such as headaches, nausea, dry mouth and lethargy. It is, therefore, important that a new drug does not make any of these features worse, which is a formidable task, as they are the very symptoms that are reported even with placebos in clinical trials. Another more recent obstacle to drug development is the current attitude of the regulatory authorities, which seem to be demanding absolute drug safety on the grounds that IBS is not a lethal disorder. Not only is this an unrealistic demand on any new drug, but totally ignores all the quality of life issues that surround the condition and their consequences.

The current approach to drug development has been to take what is known about the pathophysiology of IBS and try designing drugs that combine selectivity with the minimum of unwanted effects associated with that class of drug. For instance, antimuscarinics are well known to cause bradycardia, blurred vision and a dry mouth. A gut selective antimuscarinic would be expected to only minimally affect the heart or eyes and, ideally, would not affect the salivary gland, although this latter goal might be impossible to achieve, as the salivary gland could be regarded as part of the gastrointestinal system. Antimuscarinics are widely used in IBS, despite the fact that excessive contractility is not currently a fashionable hypothesis. However, it seems reasonable to assume that even if contractions are not excessive in IBS they may be perceived as being more painful as a result of gut hypersensitivity and, therefore, there might be some merit in reducing their magnitude. The gut contains large amounts of serotonin, which is considered to be an important neurotransmitter possibly involved in a wide variety of physiological processes, including visceral sensitivity (22-24). A number of receptors for serotonin have already been described, with attention being especially focused on the 5HT₃, 5HT₄ and, to a lesser extent, on the 5HT₁ receptors, as far as IBS is concerned. A good example of how confusing the whole area can be for the outsider is the fact that, at present, both 5HT₁ receptors and antagonists are under investigation for potential use in IBS. Some neuropeptides can have profound activity on the gut, where they can, for instance, contract or relax smooth muscle. Analogues or antagonists of these peptides are a logical approach to treating IBS. An antagonist of cholecystokinin is already undergoing clinical trial (25) and neuropeptide (26) is also receiving considerable attention. Another approach to therapy is to attempt to develop a “gut specific analgesic”, and one strategy would be to modulate the endogenous pain control system that uses endorphins (27). A number of endorphin receptors exist and, so far, the κ receptor has been the focus of most attention (28). A variety of other targets, such as the vanilloid (29) and cannabinoid (30) receptors, may also emerge as potentially fruitful areas of exploration. Lastly, it is well known that IBS is more common in females, that symptomatology varies during the menstrual cycle and that women seem to be more susceptible to gut sensitising events – for instance, gastroenteritis or experimentally induced diarrhoea (31). There is also preliminary evidence indicating that women may respond better than men to some potential IBS medications (32). All this suggests that modification of the sex hormonal environment may have therapeutic potential. This area is very much in its infancy but it has been claimed that modulation of pituitary gonadotrophins (33) may benefit some patients with chronic abdominal pain.

Conclusions

Predictions for the future of IBS and the related functional gastrointestinal disorders have to be rather guarded until we understand much more about the underlying pathophysiology. As well as continuing with basic research, we must be prepared to accept that current pathophysiological concepts may be incorrect and it is also important to look for clues from clinical observation. For instance, why do antidepressants or hypnosis work so well in some individuals? Is, after all, the problem all in the mind, even if that means in terms of disordered perception rather than psychologically – if so, the drugs of tomorrow may have to target the brain rather the gut.

References