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Lubiprostone

A Viewpoint by Lawrence R. Schiller

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Constipation is often viewed as a minor problem by physicians and is considered either as an acute problem to be managed with simple laxatives or as a chronic problem best treated with fibre supplementation. By contrast, recent work has focused on the importance of chronic constipation in the affected patients and their dissatisfaction with traditional remedies.[1] This has highlighted the need for new treatments.

Insights into the enteric nervous system and epithelial function have led to the development of new classes of agents for the management of chronic constipation. The first of these new agents was tegaserod, a drug designed as a peripheral serotonin 5-HT_4 receptor agonist that enhances peristalsis by modulating neurotransmitter release by enteric neurons. The most recent is lubiprostone, a selective activator of type 2 chloride channels (ClC-2).

ClC-2 channels are widely distributed in tissues throughout the body.[2] They form a family of transmembrane proteins that share a common structural motif and allow vectorial chloride movement across the cell membrane. This can have important effects on transmembrane electrical potential and cell volume. About one dozen different chloride channels in all sorts of organisms have been defined by electrical characteristics, selective inhibitors and sequencing.

ClC-2 channels are expressed in many epithelia, including those in the gut, and are thought to play a major role in regulating cell volume. Physiologically, they are activated by hypotonicity, low extracellular pH and hyperpolarisation. It is unclear how much chloride secretion is mediated by these channels in the gut under physiological circumstances, since another type of chloride channel, the cystic fibrosis transmembrane regulator, is co-localised in the apical membrane of the enterocyte and is thought to be the major route of chloride secretion in many conditions.

Lubiprostone is a direct activator of the ClC-2 channels in the intestine. It works from the luminal side by interacting with the ClC-2 channel itself; no distinct receptor is required. It is poorly absorbed from the gut; blood levels are less than the detection limit of the assay and are irrelevant to its action. When administered orally, its effects are limited to the gut. After activation of the ClC-2 channels of enterocytes, chloride is able to enter the lumen and draw sodium and water into the lumen, supposedly increasing luminal fluid volume, stimulating gut activity and relieving constipation. Other mechanisms of action might also be responsible for its beneficial effects in patients with constipation; this should be a fruitful area of research.

Whatever the precise mechanism of action, it is clear from well designed studies that lubiprostone is an effective agent for the treatment of constipation in many individuals with chronic constipation. Moreover, it appears to be a safe agent with little toxicity. Despite its action involving the electrolytes, patients did not develop significant fluid or electrolyte imbalances. One problem that was noted more often with the drug during clinical trials was nausea. Although about one-third of patients developed nausea, this adverse effect was a cause for stopping treatment in only ≈9% of patients. How much of a problem this will prove to be in practice remains to be seen; dose reduction may be an effective countermeasure. Physicians are also advised to check a pregnancy test in women of childbearing age before starting therapy; the drug is not advised for pregnant women because of increased foetal loss seen in animal studies.

The role of this new agent in the management of chronic constipation will be explored by clinicians in the years to come. Key unresolved questions include which patients are most likely to respond, when to institute treatment and how to use it in combination with other agents. The answers to these questions will determine the ultimate impact of this agent on what can be a troublesome problem for many individuals. ▲

References

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