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Increased colonic bile acid exposure: a relevant factor for symptoms and treatment in irritable bowel syndrome (IBS)

Bajor A *et al.* Gut 2015; 64: 84-92.

Prescribing information can be found at the end of this presentation

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08-2017 JB7346 | UK Communication Tool

Background

- Irritable bowel syndrome (IBS) is one of the most common GI functional disorders
- Affects up to 20% of the Western population
- Pathophysiology of IBS not completely understood
- Response to bile acids on colonic motor and secretory functions seems to be exaggerated in patients with IBS
- In different IBS subgroups, modulating the colonic bile acid exposure has been an effective treatment strategy

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Study aims

- If excessive amounts of bile acids reach the colon, watery stools and an erratic bowel pattern are seen
- Bile acid malabsorption (BAM), diagnosed with SeHCAT, is common in patients with chronic diarrhoea
- Other tests used to diagnose BAM are:
- Serum concentration of 7α-hydroxy-4-cholesten-3-one (C4), which reflects the rate of the hepatic bile acid synthesis
- Fibroblast growth factor (FGF) 19, which suppresses bile acid synthesis
- There may be a role for BAM in a subset of patients with IBS

Aiming to assess whether increased amounts of bile acids entering the colon have a role in pathogenesis and pathophysiology of IBS
As a proof of concept, a secondary aim was to assess the effect of colestipol on IBS symptoms in patients with low SeHCAT retention values

Methods

- Patients with phenotypically well characterised IBS enrolled
- SeHCAT retention and plasma concentration of C4 (corrected for plasma total cholesterol; C4c) and FGF19 measured and results compared with those of healthy controls
- Patients with SeHCAT retention values <20% on day 7 were offered an open label treatment with a gradually increasing dose of the bile acid binder colestipol during an 8-week period

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On enrolment

- Gastrointestinal Symptom Rating Scale–IBS (GSRS-IBS) completed
- Body-mass index measured

First SeHCAT day

- Blood samples taken after an overnight fast for analyses of C4 and FGF19

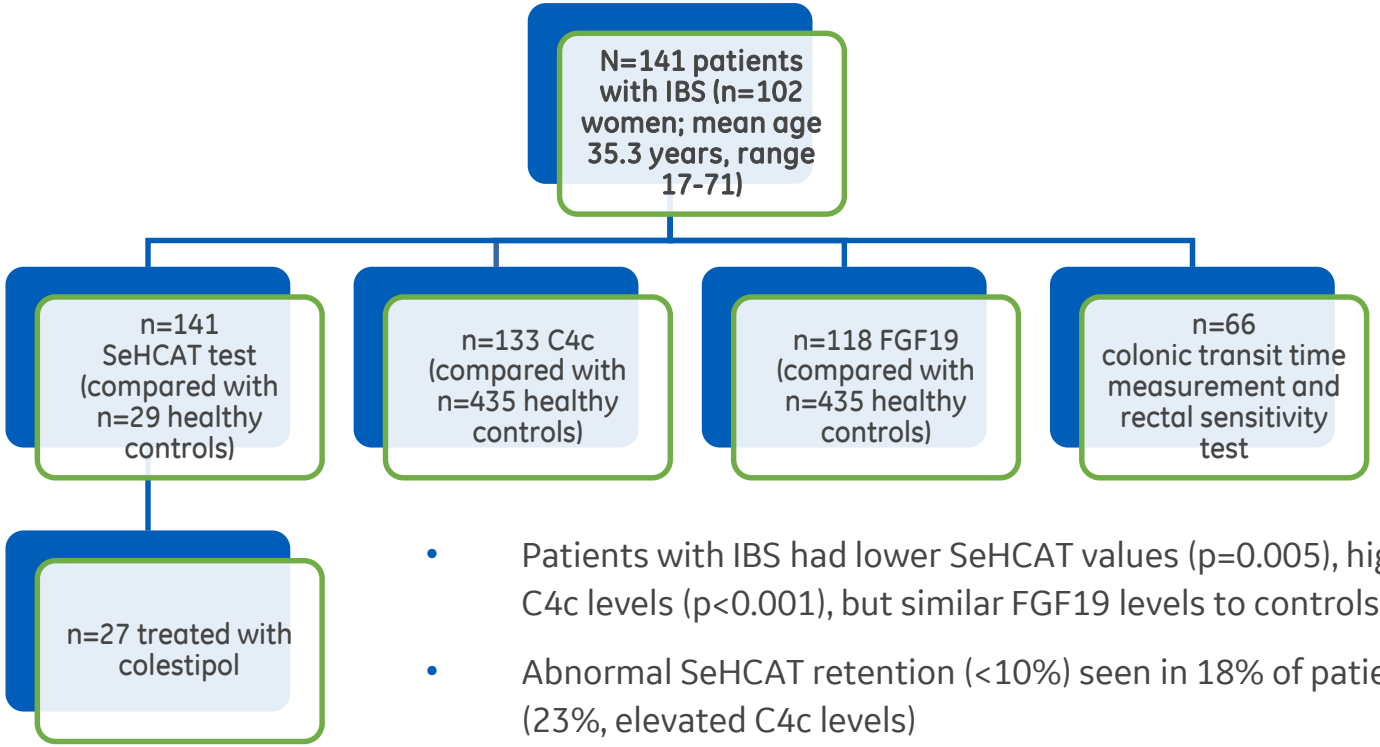
During week of SeHCAT tests

- All bowel movements recorded on a diary card
- Stool form graded based on the Bristol Stool Form Scale
- Colonic transit time and rectal sensitivity with a rectal barostat assessed in a proportion of patients

During treatment with colestipol

- Daily bowel habits recorded on a diary card
- IBS Severity Scoring System (IBS-SSS) questionnaire completed every other week

Results



- Patients with IBS had lower SeHCAT values (p=0.005), higher C4c levels (p<0.001), but similar FGF19 levels to controls
- Abnormal SeHCAT retention (<10%) seen in 18% of patients (23%, elevated C4c levels)
- Patients with IBS with SeHCAT retention <10% had more frequent stools, accelerated colonic transit time, rectal hyposensitivity, a higher body-mass index, higher C4c and lower FGF19 levels
- Colestipol treatment improved IBS symptoms
- 15/27 fulfilled criteria for treatment response (adequate relief ≥50% of weeks 5–8)

Conclusions

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- Abnormal SeHCAT retention and/or high C4 levels, indicating increased bile acid exposure to the colon, occurs in a substantial proportion of patients with predominantly non-constipated IBS
- The SeHCAT test, as a measure of the bile-acid turnover rate, correlates with hepatic bile acid synthesis and relates to bowel habit and colonic transit time, as well as with body-mass index and markers of general metabolism
- The positive symptomatic response to open-label treatment with colestipol (a bile acid binding agent) in patients with IBS with low SeHCAT values supports a role of bile acids in IBS symptomatology

Implications for clinical practice

This study highlights a role for bile acids in symptom generation in a subset of patient with IBS, which has important future treatment implications in this large patient group

PRESCRIBING INFORMATION SeHCAT 370kBq Capsules ([^{75}Se]tauroselcholic acid)
Please refer to full national Summary of Product Characteristics (SPC) before prescribing.
Indications and approvals may vary in different countries. Further information available on request.

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PRESENTATION Hard gelatin capsule containing [^{75}Se]tauroselcholic acid [370kBq at the activity reference date].

INDICATIONS This medicinal product is for diagnostic use only. Used for the investigation of bile acid malabsorption and measurement of bile acid pool loss. It may be used in the assessment of ileal function, in the investigation of inflammatory bowel disease and chronic diarrhoea and in the study of entero-hepatic circulation.

DOSAGE AND METHOD OF ADMINISTRATION Normal adult and elderly dose is one capsule administered orally. No paediatric dosage form or clinical experience of the use of this product in children. The same dose used adults should be used in children. A careful assessment of the risk/benefit ratio should be undertaken before use of the product in children due to increased effective dose equivalent. Careful consideration of the activity to be administered to patients with hepatic impairment is required since increased radiation exposure is possible. Drinks of 15 ml of water are recommended before, during and after swallowing capsule to ensure passage to the stomach. Patient should be in standing or sitting position.

CONTRAINDICATIONS Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS If hypersensitivity or anaphylactic reactions occur, administration must be discontinued immediately and if required, intravenous treatment initiated. The necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available. Caution advised in administration of SeHCAT to patients with severe hepatic dysfunction or biliary tract obstruction. Radiation dose to liver will be significantly increased in these patients. Exposure to ionising radiation must be justifiable on the basis of likely benefit.

The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result. For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should be as low as reasonably achievable to obtain the required diagnostic information. Careful consideration of the benefit risk ratio in patients with hepatic impairment is required since increased radiation exposure is possible. No data are available for the paediatric population however careful consideration of the indication is required since the effective dose per MBq is higher than in adults. This medicinal product contains 3.01 mmol (71.04 mg) sodium in each capsule which should be taken into account in patients on a low sodium diet.

INTERACTIONS No interaction studies have been performed and no interactions reported to date.

PREGNANCY AND LACTATION When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about the potential pregnancy, alternative techniques not using ionising radiation (if there are any) should be offered to the patient. No data are available on the use in human pregnancy. Animal reproduction studies have not been carried out. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only essential investigations should therefore be carried out when the likely benefit exceeds the risk to the mother and foetus. Before administration to a breastfeeding mother, consideration should be given as to whether the investigation could be reasonably delayed until after the mother has ceased breastfeeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. If administration is considered necessary, breastfeeding should be interrupted and breast milk discarded for three to four hours after administration, after which breastfeeding can be resumed.

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UNDESIRABLE EFFECTS Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 0.26 mSv when the maximal recommended activity of 370 kBq is administered these adverse reactions are expected to occur with a low probability.
Immune system disorders: Hypersensitivity (unknown frequency).
DOSIMETRY Effective dose for a healthy adult administered one 370kBq capsule of SeHCAT is typically 0.26mSv. In most clinical investigations for which this substance is used (e.g. Crohn's disease) the effects of impaired ileal absorption and shorter gastrointestinal transit time tend to reduce the dose commitment compared with the normal case. However, in patients with severe cholestatic jaundice, the liver dose has been estimated to be about 100 times the normal value.
MARKETING AUTHORISATION HOLDER GE Healthcare Limited, Amersham Place, Little Chalfont, HP7 9NA, UK.
CLASSIFICATION FOR SUPPLY Subject to medical prescription (POM).
UK MARKETING AUTHORISATION NUMBER PL 0221/0105.
PRICE £195.
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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to GE Healthcare.

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