SeHCAT (tauroselcholic [^{75}selenium] acid) for the investigation of bile acid diarrhoea in adults: a systematic review and cost-effectiveness analysis

Marie Westwood,[1]* Isaac Corro Ramos,[2] Nigel Armstrong,[1] Edyta Ryczek,[1] Hannah Penton,[3] Marscha Holleman,[3] Caro Noake[1] and Maiwenn Al[3]

[1]Kleijnen Systematic Reviews Ltd, York, UK
[2]Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, the Netherlands
[3]Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, the Netherlands

*Corresponding author marie@systematic-reviews.com

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Scientific summary

SeHCAT for adult bile acid diarrhoea

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Scientific summary

Background

Bile acid diarrhoea (BAD) is a form of chronic diarrhoea in which the recycling of bile acids in the body is not functioning properly. Bile acids are produced by the liver and stored in the gallbladder until they are released into the small bowel to aid digestion. Usually, bile acids are reabsorbed into the liver in the final section of the small bowel. If they are not reabsorbed or the body produces more bile acid than can be reabsorbed, excess amounts of bile travel from the small bowel to the colon, stimulate salt and water secretion and bowel movements, and result in diarrhoea. The most common form of BAD is caused by overproduction of bile acid in people with no physical damage to the bile acid recycling system; however, BAD can also appear as a secondary condition following damage to the small bowel or another part of the bile acid recycling system.

Tauroselcholic [^{75}selenium] acid (SeHCAT™) (GE Healthcare, Chicago, IL, USA) is a radiopharmaceutical capsule that is indicated for use in the investigation of bile acid malabsorption (BAM) and the measurement of bile acid pool loss. A SeHCAT test involves two outpatient appointments in the nuclear medicine department of a hospital. During the first appointment, the patient swallows a SeHCAT capsule and then waits for up to 3 hours before a baseline scan is taken. A follow-up scan is taken on day 7 after the first appointment. The result of the test is given as the proportion of SeHCAT remaining in the body after 7 days. To calculate the result, the amount of radioactivity detected in the follow-up scan is divided by the amount of radioactivity detected in the baseline scan. Diagnosis of BAD is usually made when $\leq$ 15% of the SeHCAT remains in the body.

Current British Society of Gastroenterology guidelines list BAD among the 'common disorders' to be investigated as part of secondary clinical assessment and state that a positive diagnosis of BAD should be made by either using SeHCAT testing or measuring the serum bile acid precursor 7-alpha-hydroxy-4-cholesten-3-one, depending on local availability. In contrast, the National Institute for Health and Care Excellence (NICE) diagnostics guidance (DG) 7, published in 2012, states that there is insufficient evidence to determine whether or not SeHCAT is a cost-effective option for diagnosing BAM among people with diarrhoea-predominant irritable bowel syndrome (IBS-D) or functional diarrhoea (FD) or people with Crohn's disease who have not undergone ileal resection, and recommends its use in research only. The availability and use of SeHCAT testing vary across the UK; in some secondary care settings, bile acid sequestrant (BAS) treatment of BAD is started without a diagnostic test being performed (trial of treatment).

This assessment was an update to the assessment that informed NICE DG7 and has been undertaken to ensure that the guidance is based on current evidence.

Objectives

This assessment aimed to evaluate the clinical effectiveness and cost-effectiveness of SeHCAT for investigating BAD and the measurement of bile acid pool loss among adults referred to secondary care for the investigation of chronic diarrhoea with an unknown cause, or adults with suspected or diagnosed IBS-D (i.e. people with suspected primary BAD) and adults with chronic diarrhoea and a diagnosis of Crohn's disease who have not undergone ileal resection (i.e. people with suspected secondary BAD).

Methods

Assessment of clinical effectiveness

Sixteen databases, including MEDLINE and EMBASE, research registers and conference proceedings were searched for relevant studies from inception to November 2020. Search results were deduplicated against the existing project library, from our previous assessment for DG7, and new records were independently screened for relevance by two reviewers. Full-text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. The methodological quality of included predictive accuracy studies (studies assessing the accuracy of the SeHCAT test for predicting response to treatment with BAS) was assessed using quality assessment of diagnostic accuracy studies-2 (QUADAS-2) tool. The methodological quality of the observational studies that reported treatment outcome only for those participants with a positive SeHCAT result was assessed using a topic-specific adaptation of a published checklist (as used in our previous assessment).

Meta-analysis was considered inappropriate, owing to the small number of test accuracy studies with varying diagnostic thresholds and between-study heterogeneity with respect to population (prior investigations), treatment regimen, definition of response, follow-up period and SeHCAT administration; therefore, we employed a narrative synthesis. The clinical effectiveness results section of this report is structured by clinical application (diagnosis of primary BAD and diagnosis of secondary BAD in people with Crohn's disease who have not undergone ileal resection).

Assessment of cost-effectiveness

In the health economic analyses, the cost-effectiveness of SeHCAT for the assessment of BAD was estimated in the two different populations described previously (adults with suspected primary BAD and adults with suspected BAD who have Crohn's disease without ileal resection). For both populations, the cost-effectiveness of SeHCAT (at a test cut-off point of 15%), compared with both trial of treatment with BAS and no SeHCAT, was assessed. The cost-effectiveness analysis combined a short-term diagnostic decision-analytic model (with an assumed duration of 6 months) and a long-term (lifetime) Markov model.

In the SeHCAT branch of the short-term decision-analytic model, patients who tested positive were assumed to receive treatment with BASs. Patients who did not respond followed the no-SeHCAT branch. In the BAS trial-of-treatment strategy, all patients are treated with a BAS, and those not responding followed the no-SeHCAT path. In the no-SeHCAT strategy, patients could receive a colonoscopy, or not. If they tested positive for inflammatory bowel disease (IBD) following the colonoscopy, they could receive treatment for IBD. If they tested negative for IBD or did not receive a colonoscopy, patients were assumed to be treated for IBS-D. In the Crohn's disease model, no colonoscopy was included, and patients were assumed to immediately receive the relevant treatments for their diarrhoea.

The long-term Markov model consisted of three health states: diarrhoea, no diarrhoea and death. Patients who had a treatment response in the short-term model started in the 'no diarrhoea' health state and were assumed to continue to receive the relevant treatment from the short-term model. Patients who did not respond to treatment in the short-term model started in the 'diarrhoea' health state. No link between diarrhoea and increased mortality was identified; therefore, transitions to death were determined by background mortality. Transitions between the 'diarrhoea' and 'no-diarrhoea' health states were informed by clinical expert opinion, as clinical data regarding the long-term effectiveness of BAS, IBD and IBS-D treatments, and diarrhoea treatment among patients with Crohn's disease, were not identified. The cycle length was 6 months, and the model estimated the lifetime costs and quality-adjusted life-years (QALYs) of patients in each population.

When possible, input for the model was based on our SeHCAT systematic review, other published literature and UK databases. When such evidence was not available, expert opinion was used. The impact of uncertainty about the various input parameters on the outcomes was explored through probabilistic sensitivity analyses and scenario analyses. Incremental cost-effectiveness ratios (ICERs)

were estimated as additional cost per additional QALY. Analyses were conducted from an NHS and Personal Social Services perspective. Costs were sourced from year 2020 when possible; otherwise, costs were inflated. Total costs and QALYs were discounted at a 3.5% annual rate.

Results

Assessment of clinical effectiveness

The evidence base relating to the use of SeHCAT testing among adults referred to secondary care for the investigation of chronic diarrhoea with an unknown cause, or with suspected or diagnosed IBS-D (population 1), and adults with chronic diarrhoea and a diagnosis of Crohn's disease who have not undergone ileal resection (population 2) has not changed substantively since our previous assessment. This current assessment includes a total of 25 publications relating to 24 studies, compared with the 24 publications relating to 21 studies included in our previous assessment; six of the previously included studies did not meet the inclusion criteria for this assessment and nine new studies were included. All of the new studies were of the lowest level of evidence eligible for inclusion; these were observational studies that reported some outcome data for patients treated with BASs, in which only those patients with a positive SeHCAT test were offered treatment with a BAS.

Three studies, all of which were included in our previous assessment for DG7, provided limited data on the accuracy of the SeHCAT test for predicting response to treatment with BAS in population 1. One study reported sufficient data to allow the calculation of the performance of SeHCAT for predicting treatment response at the 7-day retention threshold of $\leq$ 15%, commonly used in UK clinical practice. The estimated sensitivity of SeHCAT in predicting a positive response to treatment with colestyramine, using the $\leq$ 15% threshold, was 100% [95% confidence interval (CI) 54.1% to 100%] and the corresponding specificity estimate was 91.2% (95% CI 76.3% to 98.1%). These results would appear to indicate that the use of SeHCAT, with a 15% threshold, could identify patients with IBS-D who may benefit from treatment with a BAS. However, it should be noted that CIs around the sensitivity estimate were wide and, although all 31 patients with a negative SeHCAT test result were classified as true negatives, this assessment was based on long-term follow-up and none of these patients received a trial of treatment with colestyramine. The remaining two studies provided data for SeHCAT thresholds of 5% and 8%.

Eight studies reported information about the rate of positive response to a trial of treatment with BAS among patients with a positive SeHCAT test, based on the 15% threshold, for population 1. The median proportion of patients with a positive SeHCAT test who received a trial of treatment with BAS was 86% (range 70–100%) and the median response rate was 68% (range 38–86%). The equivalent data from the predictive accuracy study by Merrick *et al.* 1985 indicated a treatment response rate of 67% among patients with 7-day SeHCAT retention values of $\leq$ 15%; in this study, 9 out of 12 (75%) patients with SeHCAT retention values of $\leq$ 15% received a trial of treatment with colestyramine. The remaining 13 studies reported information about the rate of positive response to a trial of treatment with BAS, using various SeHCAT test thresholds, predominantly 10% and/or 5%.

The single study that reported information about response to treatment with BAS for population 2 provided only limited information about response rates among patients with a positive SeHCAT test result (7-day retention value of $<$ 10%) who were treated with colestyramine or colestipol. Only 9 out of 24 patients with a positive SeHCAT test result received a trial of treatment with BAS and the numbers receiving each drug were not reported; eight out of nine (89%) patients treated with BAS responded positively.

Eight studies reported the proportion of treated patients who were intolerant of BAS, or discontinued treatment for unspecified reasons; rates of intolerance/discontinuation were generally high (median 15%, range 4–27%). There was insufficient information to determine whether or not levels of intolerance varied between colestyramine, colestipol and colesevelam.

Assessment of cost-effectiveness

For both populations, the SeHCAT 15% (i.e. a SeHCAT retention value of ≤ 15%) strategy dominated the other two strategies or resulted in ICERs below the common thresholds of £20,000 or £30,000 per QALY gained. Dominance or cost-effectiveness was led, in general, by treatment response, as the SeHCAT 15% strategy was the strategy with the highest response rate in the majority of the scenarios explored, including the base-case analysis for both populations. In scenarios in which the other two strategies were estimated to provide higher response rates than SeHCAT, the scenarios were probably based on unrealistic assumptions regarding response with no SeHCAT or BAS trial of treatment. Even in those scenarios in which overall response in the BAS trial-of-treatment strategy was higher than in the SeHCAT 15% strategy, the ICERs for the comparison of BAS trial of treatment and SeHCAT 15% were well above the £20,000 or £30,000 per QALY gained thresholds. SeHCAT 15% was also the strategy in which more colonoscopies were avoided.

Conclusions

Despite the apparent significance of BAM among adults with IBS-D or FD, and the expansion of provision of SeHCAT testing in the UK, there remains a surprising lack of evidence linking the use of SeHCAT testing to patient-relevant outcomes. The available evidence is largely limited to studies that describe the proportion of patients with a positive SeHCAT test result who responded positively to treatment with BAS. The optimal SeHCAT decision threshold, to define presence of BAM and select patients for treatment with BAS, is uncertain. The extent to which patients with 'borderline' or 'equivocal' 7-day SeHCAT retention values (e.g. between 10% and 15%) could benefit from treatment with BAS remains unclear, and the extent to which patients with 7-day retention values > 15% may benefit from treatment with BAS is unknown. It has been suggested that SeHCAT testing and the assignment of a diagnosis of BAM may improve adherence to treatment with BAS. However, despite some evidence indicating that these treatments are generally poorly tolerated, there is a lack of information about the relative rates of adherence for different BASs and about the acceptability, to patients, of SeHCAT testing. Finally, there is a paucity of evidence about the efficacy and safety of BASs for the treatment of patients who have been diagnosed with BAM.

Although the results of the economic evaluation conducted for both populations indicated that the SeHCAT 15% strategy dominated the other two strategies or resulted in ICERs below the common thresholds of £20,000 or £30,000 per QALY gained, there is great uncertainty surrounding these analyses. Therefore, the implications for service provision of SeHCAT testing are still uncertain; the main reason for this uncertainty is the lack of good-quality evidence. It is important to emphasise that data on SeHCAT accuracy and response to BAS are not sufficient to conduct a full economic evaluation. Further research should also include data collection on patients with a negative SeHCAT test result and patients not responding to BAS. Because cost-effectiveness studies usually adopt a lifetime time horizon, data on long-term effects are also required. Given the gaps in the health-related quality-of-life evidence, a priority in future research should be to provide diarrhoea-specific utilities for patients with Crohn's disease in general, as well as patients taking BAS, preferably using the EuroQol-5 Dimensions. Because cost estimates were highly uncertain, priority should also be given to the research of the costs of treatment of BAD, IBS-D, IBD and diarrhoea among Crohn's disease patients.

Study registration

This study is registered as PROSPERO CRD42020223877.

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