Commissioning Brief - Supporting Information

Dequalinium chloride for bacterial vaginosis

Closing date: 28 September 2017

This supporting document provides further information to support applicants for this call. It is intended to summarize what prompted the call and the existing evidence base, including relevant work from the HTA and wider NIHR research portfolio. It was researched and written on the basis of information from a search of relevant sources and databases, and in consultation with a number of experts in the field. Searches and information provided were up to date as of June 2017.

Source of topic
This topic was submitted by a Maternal, Neonatal and Child Health panel member following a conference hosted by the Royal College of Obstetricians and Gynaecologists where this uncertainty was raised.

Patient group
- This research will target women with bacterial vaginosis (BV).
- BV is caused by an imbalance of the normal vaginal flora with a reduction in the predominant Lactobacillus species and a large increase in anaerobic bacteria. It is not clear why this happens but it is not just one simple infection caused by one type of bacteria, it is a change in the balance of bacteria.
- BV doesn’t usually cause any vaginal soreness or itching, but often causes unusual vaginal discharge with a characteristic ‘fishy’ smell.
- BV isn’t serious for the vast majority of women, although it may be a concern if symptoms of BV develop in pregnancy and the woman has a history of pregnancy-related complications.
- It is not exactly known how common BV is, because it is often so mild that women may not go to the doctor. It may be that as many as about 1 in 3 women have BV at some time in their lives.
- Current estimated prevalence in the UK ranges from 12% in a study of pregnant women and 30% in women undergoing termination of pregnancy\(^1\).
- BV is not a sexually transmitted infection (STI) but women with BV are more susceptible to STIs, including HIV and pelvic inflammatory disease.
- It is possible that BV will gradually clear without treatment but antibiotics are usually prescribed for symptomatic BV to clear the condition.
- BV has a very high recurrence rate – this occurs in more than two-thirds of patients within three months of treatment\(^2\). This is not thought to be due to antibiotic resistance, but due to the failure of normal vaginal flora to become re-established\(^1\).
NICE and other guidance

The only NICE guidance relating to BV appears in Antenatal care for uncomplicated pregnancies (CG62, last updated 2016) which states that:

- Pregnant women should not be offered routine screening for bacterial vaginosis because the evidence suggests that the identification and treatment of asymptomatic bacterial vaginosis does not lower the risk of preterm birth and other adverse reproductive outcomes.

The British Association for Sexual Health and HIV (BASHH)\(^3\) published UK National Guidelines for the management of BV in 2012. The guidelines recommend treatment of symptomatic BV (and asymptomatic BV if offered) as follows:

- Metronidazole 400mg to 500mg taken orally twice daily for five to seven days or
- Metronidazole 2g single dose taken orally or
- Metronidazole gel (0.75%) administered vaginally once daily for five days or
- Clindamycin cream (2%) administered vaginally once daily for seven days or
- Tinidazole 2g single dose taken orally or
- Clindamycin 300mg taken orally twice daily for seven days

*Note: The guideline was published before the licensing of dequalinium vaginal tablets.*

Recently, NHS Wales\(^4\) and NHS Scotland\(^2\) have approved the use of Dequalinium chloride (Fluomizin®) as a treatment for BV with the restriction that it is used “in patients for whom the initial treatment is not effective or well tolerated”.

The study upon which this recommendation has been made is included in the completed research section of this brief. The Scottish Medicines Consortium notes that the company who manufacture dequalinium chloride applied to have the drug approved only as a second-line treatment but the study on which this is based did not differentiate between women who had failed on antibiotic therapy or treatment naïve patients.

The National Institute for Health and Care Excellence (NICE) has not published any guidance on the use of dequalinium, and it is not in the current NICE work plan\(^1\).

Current practice and proposed intervention

Current practice

BV is usually suspected by women when there are changes in discharge colour, consistency and smell. GP’s or practice nurses often diagnose BV by it’s typical symptoms but there are diagnostic tests available if necessary which can involve testing the pH of the discharge or sending a swab sample to the lab.

Treatment for bacterial vaginosis is simple and involves taking antibiotic tablets. There are several different antibiotics that can be used (see BASHH guidance above). These are taken either as a single dose or a longer course (up to one week). Creams or gels may also be prescribed which are used for up to seven days.

In women experiencing recurrent infections, antibiotic gels may need to be used over a number of months.

Proposed intervention

Recently, both NHS Wales and NHS Scotland have approved the use of dequalinium chloride as a second-line treatment for BV in cases where first-antibiotic treatment has failed. This brief proposes research to determine whether dequalinium chloride is effective as first-line treatment which may, depending on the findings, negate the need for antibiotic use in this condition. There is currently only one recently published study (within the past five years) identified during searches and this is the study upon which the above recommendations have been made.
Dequalinium chloride (brand name Fluomizin®) is an anti-infective and antiseptic agent belonging to the class of quaternary ammonium compounds. It is a surface-active substance and the primary mechanism of action is an increase in bacterial cell permeability and the subsequent loss of enzyme activity, finally resulting in cell death. Dequalinium chloride exhibits a rapid bactericidal activity and in the form of vaginal tablets exerts its action locally within the vagina. It is administered in the form of 10mg vaginal tablets for a treatment course of six days (https://www.medicines.org.uk/emc/medicine/31532).

Proposed advantages of dequalinium chloride include: it has a broad antimicrobial spectrum, it is less vulnerable to resistance, a high concentration of the substance at the infection site can be achieved, while systemic exposure is negligible.

Dequalinium chloride was licensed for use in the UK in June 2015 and is currently the only antiseptic licensed for treatment of BV in the UK.

Summary of completed research

Evidence Synthesis

Dequalinium for bacterial vaginosis (2017) This review, published in the BMJ’s Drug and Therapeutics Bulletin, notes that UK guidelines on the management of BV predate the licensing of dequalinium vaginal tablets and only include recommendations on the use of antibacterials to treat BV. Furthermore, national antimicrobial prescribing guidelines make no reference to use of dequalinium for the management of BV.

This review article highlights that there is only one published RCT to date comparing dequalinium with vaginal clindamycin cream (see Weissenbacher 2012, below) and that there are currently no studies comparing dequalinium with oral antibiotics.

This article highlights the following limitations of the Weissenbacher trial:
- Short follow-up period of 25 days after the end of treatment.
- No data on recurrence.
- The trial design used did not allow for collection of evidence as to whether DC is more effective in women who have failed previous therapy or who have recurrent disease.
- The trial did not include patient-centred outcomes.
- It was only single-blinded.
- It was a non-inferiority study with a wide margin of 15% that was not justified.

The review concludes that:
“Dequalinium is more expensive than oral or topical metronidazole, but less expensive than topical clindamycin. Based on the results of the only published trial, the most appropriate place in therapy for dequalinium vaginal tablets is as an alternative to clindamycin cream. The slightly shorter duration of treatment and tablet formulation may be preferred by some women. Although there is limited information on the development of resistance to dequalinium, it provides a possible alternative to reduce the use of topical antibacterial agents”.

Mendling (2016) Use of locally delivered dequalinium chloride in the treatment of vaginal infections: a review. This is a descriptive review with no pooling of results. Dates of searches not provided.

In terms of treatment of BV, the paper identified a total of 8 published studies testing dequalinium chloride (n=577 women). However, only two were controlled trials and only one (described under Primary Research) compared dequalinium chloride with antibiotic therapy. Other studies have compared with providone iodine or other therapies which are not prescribed in the UK.

The review concludes that the current formulation DQC 10 mg vaginal tablets (Fluomizin®) as 6-day therapy with its broad antimicrobial spectrum and excellent tolerability offers a safe and effective option for empiric therapy of different vaginal infections in daily practice.

Primary Research

This paper has been incorporated into the above review but it was the only trial found comparing dequalinium chloride with antibiotics for the treatment of BV:
Weissenbacher (2012) A comparison of dequalinium chloride vaginal tablets (Fluomizin®) and clindamycin vaginal cream in the treatment of bacterial vaginosis: a single-blind, randomized clinical trial of efficacy and safety. This was a multinational, multicenter, single-blind, randomized trial in 15 centers, including 321 women. Women were randomized to either vaginal dequalinium chloride (DQC) tablets or vaginal clindamycin (CLM) cream. Follow-up visits were 1 week and 1 month after treatment. RESULTS: Cure rates with DQC (C1: 81.5%, C2: 79.5%) were as high as with CLM (C1: 78.4%, C2: 77.6%). Thus, the treatment with DQC had equal efficacy as CLM cream. A trend to less common post-treatment vulvovaginal candidosis (VVC) in the DQC-treated women was observed (DQC: 2.5%, CLM: 7.7%; p = 0.06). Both treatments were well tolerated with no serious adverse events occurring. CONCLUSION: Vaginal DQC has been shown to be equally effective as CLM cream, to be well tolerated with no systemic safety concerns, and is therefore a valid alternative therapy for women with BV. This trial was sponsored by Medinova AG.

Research in progress

Evidence Synthesis
None identified during searches.

Primary Research
NCT02242695 Comparative Efficacy Study of 10 mg Dequalinium Chloride (Fluomizin) in the Treatment of Vulvovaginal Candidiasis. A clinical study to compare the clinical efficacy of vaginal tablets containing 10mg dequalinium chloride (Fluomizin) with the clinical efficacy of 100mg clotrimazole in patients suffering from vulvovaginal candidiasis, to assess safety of the two medications during the treatment, and to evaluate women's satisfaction with the two treatments. N=150, estimated completion April 2016. Thailand. Sponsored by Medinova AG.

Note: This is testing deqalinium chloride for the treatment of a different condition.

NIHR Evaluation Trials and Studies (NETS) research
HTA project 15/110/02: A randomised controlled trial to assess the clinical and cost effectiveness of topical lactic acid gel for treating second and subsequent episodes of bacterial vaginosis. Status: Active until Nov 2020.

References
2. Scottish Medicines Consortium dequalinium chloride 10mg vaginal tablets (Fluomizin®) SMC No. (1194/16), 07/11/2016.