Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Fusidic Acid for Ophthalmic Infections: A Review of Clinical and Cost Effectiveness and Safety

DATE: 22 February 2013

CONTEXT AND POLICY ISSUES

The antibiotic fusidic acid is available in a 1% suspension form (Fucithalmic) approved for the treatment of superficial infections of the eye caused by susceptible bacteria (*S. aureus*, *S. pneumonia* and *H. influenza*), in adults and children ≥2 years of age.[1] It is one of several ophthalmic antibiotics that may be prescribed to treat eye infections such as conjunctivitis or blephararitis. This product is formulated using a carbomer gel which provides sustained release of fusidic acid and prolongs the antibiotic's contact with the eye.[1] Thus, fusidic acid is usually administered as one drop every 12 hours, a less frequent dosing schedule than many other ophthalmic preparations.

The objective of this report is to evaluate the clinical effectiveness, safety and economic literature on fusidic acid to help inform a funding decision.

RESEARCH QUESTIONS

1. What is the evidence for the clinical effectiveness of fusidic acid, compared with other antibiotics, for ophthalmic infections?

2. What is the evidence for the safety of fusidic acid, compared with other antibiotics, for ophthalmic infections?

3. What is the evidence for the cost-effectiveness of fusidic acid, compared with other antibiotics, for ophthalmic infections?

KEY FINDINGS

Short term (seven day) treatment with topical fusidic acid resolved clinical signs and symptoms of conjunctivitis or chronic blepharitis in 76% to 91% of patients. Fusidic acid cure rates were not statistically significantly different than topical tobramycin, norfloxacin or ciprofloxacin based on three lower quality randomized controlled trials. Ocular discomfort and irritation were the

most frequent adverse events associated with topical antibiotics. No data were available on the cost-effectiveness of fusidic acid for the treatment of ocular infections.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Embase via OVID, The Cochrane Library (2012, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2002 and Jan 25, 2013.

Selection Criteria and Methods

One reviewer screened citations to identify studies that met the inclusion criteria. Potentially relevant articles were retrieved based on the review of titles and abstracts. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1.

Table 1: Selection Criteria

Population	Adults and children (≥ 2 years of age) with superficial infections of the eye and its adnexa (conjunctivitis and blepharitis infections)
Intervention	Fusidic acid (Fucithalmic)
Comparator	Any of: norfloxacin, ciprofloxacin, erythromycin, sulfacetamide, tobramycin, gentamycin
Outcomes	Q1: effectiveness for treatment of ophthalmic infections Q2: harms/adverse events Q3: cost-effectiveness versus any comparators
Study Designs	Q1 & 2: Health technology assessment, systematic review, meta-analysis, randomized controlled trial, observational study Q3: Economic evaluation

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, were described in a systematic review included in this report, or were published prior to January 2002.

Critical Appraisal of Individual Studies

The quality of systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[2] A numeric score was not provided, instead individual study strengths and limitations were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 107 citations. Upon screening titles and abstracts, 102 citations were excluded and five potentially relevant articles were retrieved for full-text review. An additional four potentially relevant reports were retrieved from grey literature. Of the nine potentially relevant reports seven were excluded. Two systematic reviews met the inclusion criteria.[3,4] The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

One additional reference of potential interest is provided in Appendix 2.

Summary of Study Characteristics

The characteristics of the systematic reviews are summarized in Appendix 3. The systematic reviews evaluated pharmacologic and non-pharmacologic interventions for chronic blepharitis (Lindsley et al.[3]) and bacterial conjunctivitis (Epling[4]). From these reports, only the studies that included the intervention and comparators specified in Table 1 were summarized.

From Epling's systematic review,[4] two RCTs compared topical fusidic acid to comparators relevant to this report: topical norfloxacin (Wall 1998) and tobramycin (Jackson 2002). Both of these studies were single blind trials. Wall et al. enrolled 400 patients over 1 year of age with suspected bacterial conjunctivitis. The patients received either fusidic acid 1% viscous drops twice daily or norfloxacin 0.3% drops four times daily for seven days. Among those enrolled, 34% were culture positive.[4] In the study by Jackson et al., 487 patients were treated for seven days with either fusidic acid 1% viscous drops, one drop twice daily, or tobramycin 0.3%, one to two drops, four to six times daily. The patients enrolled ranged from two to 85 years of age. Of the 66% who were culture positive, 30% had pathogenic bacteria on quantitative microbiology.[4]

In the review by Lindsley et al.,[3] one randomized controlled trial (RCT) (Adenis 1996) was relevant to the research question in this report. This study enrolled 77 patients with acute conjunctivitis or acute or chronic blepharitis. Patients were randomized to open label ciprofloxacin 0.3% ophthalmic solution (two drops every two hours for the first 48 hours, then every four hours from day two to six) or fusidic acid 1% viscous drops (one drop twice a day), and were followed for seven days. Any patients who had negative bacterial cultures on day 0, or who did not complete follow-up, were excluded (n=38). The participants had a mean age of 53 years (range 6 to 93), and 52% were female. The study was conducted in France.

Summary of Critical Appraisal

The critical appraisal of the systematic reviews is summarized in Appendix 4.

The systematic review by Epling[4] was rated as lower quality as it used less robust methods or failed to report the methods in sufficient detail. The author searched multiple databases for relevant articles, with no language restrictions however, the selection of articles was not done in duplicate by two independent reviewers. No information was provided on methods for data extraction, or quality assessment of individual studies. The overall quality of evidence for each intervention was rated using GRADE. From this systematic review, the two RCTs relevant to this report were limited by their lack of double blinding (both were single blind studies). In addition, Jackson et al. reported some outcomes for only a subset of patients in whom

pathogenic bacteria were present (i.e. no intention to treat analysis). Further details on the validity assessment of the individual studies were not reported by Epling.[4]

The review by Lindsley et al.[3] used robust methods to identify, select, appraise and summarize studies. From this systematic review,[3] the one RCT relevant to this report (Adenis 1996) was rated by the systematic review authors as having an unclear risk of selection bias (method to randomize patients and conceal allocation were not reported), high risk of performance and detection bias (due to the open label design), high risk of attrition bias (failure to follow intention to treat analysis), and a low risk of reporting bias. The review authors also noted that despite randomization, there were imbalances between groups at baseline.[3] The systematic review authors reported outcomes for the subgroup of patients with blepharitis, thus there is no information in the review on the outcomes in patients with conjunctivitis.

Summary of Findings

Efficacy

Among patients with conjunctivitis, no statistically significant difference was detected between fusidic acid and tobramycin or norfloxacin on the proportion of patients achieving a clinical cure after seven days of treatment (Table 2).[4] The microbial cure rate was also not statistically significantly different between fusidic acid and tobramycin.[4]

In the systematic review by Lindsley et al.,[3] the RCT comparing topical fusidic acid to ciprofloxacin found no statistically significant difference between groups on the proportion of participants with blepharitis who were cured or improved after seven days (relative risk (RR) 1.00 [95% confidence interval (CI) 0.58 to 1.71], n=15).

Table 2. Summary of RCT results[3,4]

Author, year, population	Interventions	Microbial cure	Clinical cure	Adverse events
Jackson 2002 conjunctivitis	Fusidic acid	81%	Age 2-9 yrs: 77% Age >9 yrs: 76%	AE: 4% (tearing, burning, irritation, stinging, allergic reaction, conjunctival injection) WDAE: n=2
	Tobramycin	88%, P=0.34	Age 2-9: 83%, P=NS Age >9: 73%, P=NS	AE: 2% (irritation, pain, red eye, photosensitivity, discharge), P=NR WDAE: n=2
Wall 1998 conjunctivitis	Fusidic acid	NR	91%	Bad taste: 6% Stinging: 37%
	Norfloxacin	NR	93%, P=0.49	Bad taste: 20%, P=0.001 Stinging: 50%, P=0.007
Adenis 1996 blepharitis	Fusidic acid	NR	80%	AE: n=2
	Ciprofloxacin	NR	80%, P=NS	AE: n=2

AE=adverse event, NR=not reported; NS=not statistically significant; WDAE=withdrawals due to adverse events; yrs=years

In both systematic reviews, the overall evidence comparing one topical antibiotic to another was rated as low quality, and there was no clear evidence that one antibiotic was more effective than others at achieving a clinical or microbial cure.[3,4]

Safety

Ocular discomfort and irritation were the most frequently reported adverse events.[3,4]

The incidence of adverse events was similar among patients with conjunctivitis treated with fusidic acid or tobramycin (Table 2).[4] Patients treated with norfloxacin reported a statistically significantly higher incidence of bad taste and stinging, compared to those who received fusidic acid.[4]

In the RCT comparing topical fusidic acid to ciprofloxacin, there were four adverse events reported; two in each treatment group.[3] No further details were provided on the nature of these adverse events.

Cost-effectiveness

No studies evaluating the cost-effectiveness of fusidic acid compared with other antibiotic treatments were identified.

Limitations

This report is limited by the paucity of recent high quality clinical trials evaluating the clinical effectiveness and safety of topical fusidic acid. The fusidic acid studies identified in our literature search or in published systematic reviews were published in 2002 or earlier. The three RCTs summarized in this report had methodological limitations including the lack of double blinding, and failure to follow intention to treat analysis.

One of the systematic reviews used less robust methods and was rated as lower quality.[4] No economic studies were identified in the literature search.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence on the clinical effectiveness and safety of fusidic acid for eye infections was limited to three lower quality randomized controlled trials.

Short term (seven day) treatment with topical fusidic acid resolved clinical signs and symptoms of conjunctivitis or chronic blepharitis in 76% to 91% of patients compared to 73% to 93% of those who received other topical antibiotics. The cure rate between antibiotics was not statistically significantly different for fusidic acid versus tobramycin, norfloxacin or ciprofloxacin.

Ocular discomfort and irritation were the most frequently reported adverse events. The incidence of adverse events was similar for fusidic acid versus ciprofloxacin or tobramycin, and higher for norfloxacin versus fusidic acid.

No conclusions can be drawn on the cost-effectiveness of fusidic acid due to the absence of economic evaluations.

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REFERENCES

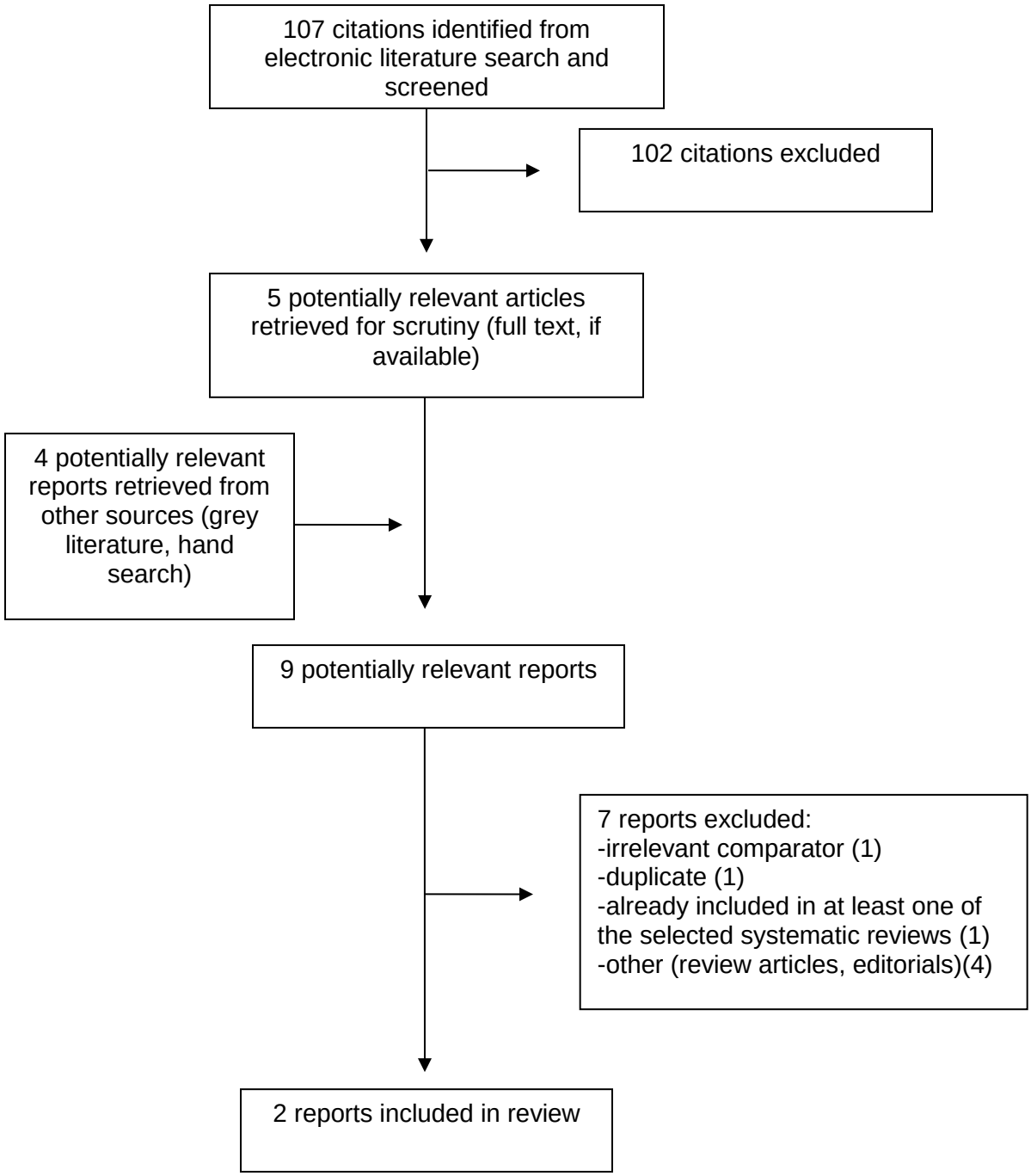
1. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association. Fucithalmic; 2013 [cited 2013 Feb 6]. Available from: https://www.e-therapeutics.ca Subscription required.

2. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2013 Jan 10];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

3. Lindsley K, Matsumura S, Hatef E, Akpek EK. Interventions for chronic blepharitis. Cochrane Database Syst Rev. 2012;5:CD005556.

4. Epling J. Bacterial conjunctivitis. Clin Evid (Online). 2012;02:704. PubMed: PM22348418

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional References of Interest

Systematic review of placebo controlled studies

1. Sheikh A, Hurwitz B, van Schayck CP, McLean S, Nurmatov U. Antibiotics versus placebo for acute bacterial conjunctivitis. Cochrane Database Syst Rev. 2012;9:CD001211. PubMed: M22972049

   BACKGROUND: Acute bacterial conjunctivitis is an infection of the conjunctiva. Both the palpebral and the bulbar ocular conjunctival surfaces are usually affected and typically become red and inflamed. Antibiotic therapy is widely used for the treatment of acute bacterial conjunctivitis. This Cochrane Review was first published in The Cochrane Library in 1999; updated in 2006 and again in 2012. OBJECTIVES: To assess the benefits and harms of antibiotic therapy in the management of acute bacterial conjunctivitis. SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 7), MEDLINE (January 1950 to July 2012), EMBASE (January 1980 to July 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 18 July 2012. SELECTION CRITERIA: We included double-masked randomised controlled trials (RCTs) in which any form of antibiotic treatment had been compared with placebo/vehicle in the management of acute bacterial conjunctivitis. This included topical, systemic and combination (for example, antibiotics and steroids) antibiotic treatments. DATA COLLECTION AND ANALYSIS: Two authors (UN and SM) independently checked and reviewed the titles and abstracts of identified studies. We assessed the full text of all potentially relevant studies. We graded the included RCTs for methodological quality using Cochrane methodology. We performed data extraction in a standardised manner. We performed random-effects meta-analyses using RevMan. MAIN RESULTS: We identified 11 eligible RCTs which randomised a total of 3673 participants. One further trial, which was published in abstract form in 1990 but has yet to be reported fully, is currently 'awaiting assessment'. Six of the 11 included studies have been included for the first time in this latest (2012) update. The trials were heterogeneous in terms of their inclusion and exclusion criteria, the nature of the intervention, and the outcome measures assessed. We judged two of the trials to be of high quality and graded the remainder as poor quality.Meta-analyses of data on clinical and microbiological remission rates revealed that topical antibiotics were of benefit in improving 'early' (days two to five) clinical (risk ratio (RR) 1.36, 95% confidence interval (CI) 1.15 to 1.61) and microbiological (RR 1.55, 95% CI 1.37 to 1.76) remission rates. At the 'late' time point (days six to 10), antibiotics were found to still confer modest benefits in clinical remission (RR 1.21, 95% CI 1.10 to 1.33) and microbiological cure rates (RR 1.37, 95% CI 1.24 to 1.52). By days six to 10, 41% (95% CI 38 to 43) of cases had resolved in those receiving placebo. We found no data on the cost-effectiveness of antibiotics. No serious outcomes were reported in either the active or placebo arms of these trials, suggesting that important sight-threatening complications are an infrequent occurrence. AUTHORS' CONCLUSIONS: Although acute bacterial conjunctivitis is frequently self limiting, the findings from this updated systematic review suggest that the use of antibiotic eye drops is associated with modestly improved rates of clinical and microbiological remission in comparison to the use of placebo. Use of antibiotic eye drops should therefore be considered in order to speed the resolution of symptoms and infection.

APPENDIX 3: Summary of Systematic Reviews

Author, year / Characteristic	Lindsley 2012[3]	Epling 2012[4]
Population	Patients >15 years old with chronic blepharitis	Adults and children with suspected or confirmed bacterial conjunctivitis, or with gonococcal conjunctivitis
Intervention	Topical antibiotics or corticosteroids, systemic antibiotics or corticosteroids, other pharmacologic treatments or eyelid hygiene therapies	Topical antibiotics, systemic antibiotics, ocular decongestants, saline, warm compresses
Comparator	Interventions mentioned above alone or in combination, placebo, or no treatment	Another active agent, placebo or no treatment
Outcomes	Subjective improvement in symptoms judged by patients or other examiners, microbial outcomes (e.g., eradication of bacteria), adverse events, quality of life, economic costs	Time to cure or improvement, change in clinical signs or symptoms, microbial outcomes
Study design	Randomized controlled trials (RCT) or quasi-randomized controlled trials (CCT)	Systematic review of RCTs, or RCTs that were at least single blinded Observational data were included for harms outcomes
Exclusions		RCTs with 20 or fewer participants or less than 80% follow up; open label studies unless blinding was impossible
Validity assessment	Risk of bias evaluated for each study (selection, performance, detection, attrition and reporting bias)	Key limitations of included studies were summarized narratively; GRADE was used to rate the quality of the evidence for each intervention and the outcomes of interest
Synthesis methods	Conducted a meta-analysis of studies when studies were clinically similar	Appears to be narrative summary; no description of data synthesis provided in the methods
Literature search	Conducted search of multiple databases up to February 2012 No language limitations No grey literature search Hand search of reference list of included studies Screened 1,800 articles for inclusion	Conducted search of multiple databases up to July 2011 No language restrictions Reviewed adverse event alerts from FDA and UK MHRA Number of articles screened for inclusion was not stated
Included studies	34 (26 RCTs, 8 CCT)	44 systematic reviews, RCTs or observational studies
Comments	1 RCT compared fusidic acid viscous drops to ciprofloxacin ophthalmic solution (Adenis 1996)	Fusidic acid viscous drops were compared to topical norfloxacin (1 study), tobramycin (1), chloramphenicol (5), rifamycin (1), or lomefloxacin (1)

CCT=controlled clinical trial; RCT=randomized controlled trial; MHRA=Medicines and Healthcare products Regulatory Agency

APPENDIX 4: Validity Assessment of Systematic Reviews

AMSTAR[2] checklist item	Lindsley 2012[3]	Epling 2012[4]
1. Was an 'a priori' design provided?	Yes	Unclear
2. Was there duplicate study selection and data extraction?	Yes	No (Abstracts screened by librarian; full text articles selected by one contributor)
3. Was a comprehensive literature search performed?	Yes	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	No
5. Was a list of studies (included and excluded) provided?	Yes	Included – Yes Excluded – No
6. Were the characteristics of the included studies provided?	Yes	Yes (RCTs only)
7. Was the scientific quality of the included studies assessed and documented?	Yes	Unclear
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Unclear
9. Were the methods used to combine the findings of studies appropriate?	Yes	Yes
10. Was the likelihood of publication bias assessed?	Yes	No
11. Was the conflict of interest stated?	Yes	Yes

RCT=randomized controlled trial