Gentamicin as an alternative to ceftriaxone in the treatment of gonorrhoea: the G-TOG non-inferiority RCT

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Scientific summary

The G-TOG RCT

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Scientific summary

Background

Gonorrhoea is a common sexually transmitted infection (STI) that causes genital pain and discomfort; in women it can lead to pelvic inflammatory disease and infertility, and in men it can lead to epididymo-orchitis. The current treatment is ceftriaxone plus azithromycin, but there is increasing evidence of cephalosporin resistance, which is reducing this regimen's effectiveness against gonorrhoea. A small but increasing number of patients have already been found to have highly resistant strains of gonorrhoea, which have been associated with treatment failure. The Gentamicin in the Treatment Of Gonorrhoea (G-TOG) trial aimed to determine whether or not gentamicin is non-inferior to ceftriaxone in the treatment of gonorrhoea.

Objectives

Primary objective

The primary objective was to determine whether or not gentamicin is an acceptable alternative to ceftriaxone for the treatment of gonorrhoea. This was addressed by determining whether or not the microbiological clearance of *Neisseria gonorrhoeae* in participants allocated to gentamicin was non-inferior to the clearance for participants allocated to ceftriaxone.

Secondary objectives

The secondary objectives were to determine:

- whether or not a single intramuscular (i.m.) dose of gentamicin is safe and well tolerated
- whether or not a single i.m. dose of gentamicin is cost-effective, from the perspective of the NHS, when used to treat gonorrhoea
- the relationship between clinical effectiveness and the laboratory measurement of antibiotic effectiveness [the minimum inhibitory concentration (MIC) required to inhibit growth of *N. gonorrhoeae*].

Methods

Trial design

Blinded, multicentre, non-inferiority, randomised trial comparing the clinical effectiveness, cost-effectiveness and safety of gentamicin with those of ceftriaxone for the treatment of gonorrhoea.

Recruitment

Participants were recruited from outpatient sexual health clinics in England. Some clinics with a large proportion of men who have sex with men attending were specifically selected to maximise the number of participants with pharyngeal and rectal infections.

Eligibility

Adults aged 16–70 years were eligible for recruitment if they had received a positive diagnosis of uncomplicated, untreated (i.e. they not received any antibiotic in the previous 28 days that could have treated gonorrhoea, either partially or completely) genital, pharyngeal and/or rectal gonorrhoea in the previous 4 weeks. The diagnosis was based on a positive Gram-stained smear on microscopy or a positive nucleic acid amplification test (NAAT).

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The exclusion criteria were having known concurrent bacterial STI (apart from chlamydia); having known bacterial vaginosis and/or *Trichomonas vaginalis* infection; having known contraindications or an allergy to gentamicin, ceftriaxone, azithromycin or lidocaine; having a current clinical diagnosis of complicated gonorrhoea infection, for example pelvic inflammatory disease or epididymo-orchitis; weighing < 40 kg; and receiving or having received ceftriaxone, gentamicin or azithromycin within the preceding 28 days. Pregnant and/or breastfeeding women were also excluded. Participants were eligible to participate in the trial only once.

Interventions

Both treatments were administered from routine clinic stock as a single i.m. injection.

For the ceftriaxone group, 500 mg of ceftriaxone in powder formulation was dissolved in 1% lidocaine and administered as a single 2-ml i.m. injection.

For the gentamicin group, 240 mg (3 × 80 mg in 2-ml vials) of gentamicin was administered as a single 6-ml i.m. injection.

In addition, all participants received a single oral dose of 1 g of azithromycin, which is currently given in the UK as standard treatment alongside ceftriaxone.

Outcomes

Primary outcome

The primary outcome was clearance of *N. gonorrhoeae*, confirmed by a negative Aptima Combo 2® (Hologic Inc., Marlborough, MA, USA) NAAT, 2 weeks post treatment (as recommended by the British Association for Sexual Health and HIV) at all infected sites.

Secondary outcomes

The secondary outcomes were:

- clinical resolution of symptoms
- frequency of nausea/vomiting, hearing loss, dizziness and rash
- frequency of any other adverse events (AEs) reported by participants
- tolerability of injection as assessed by the participant on a visual analogue scale (VAS)
- comparative cost-effectiveness.

The relationship between clearance of *N. gonorrhoeae* and in vitro measurement of antibiotic MIC to inhibit *N. gonorrhoeae* growth was also assessed.

Effectiveness, tolerability and safety were assessed at a follow-up visit 2 weeks post treatment.

Sample size

Based on 96% clearance for the ceftriaxone regimen, a total sample size of 646 participants (323 in each group) was required for analysis to detect non-inferiority with a lower 95% confidence interval (CI) for the absolute risk difference of 5%, 90% power and a one-sided significance level of 0.025. To allow for a loss to follow-up of 10%, the trial aimed to recruit a total of 720 participants.

Randomisation and blinding

Randomisation was in a 1 : 1 ratio, stratified by recruiting centre. A computer-generated pseudorandom code, using permuted blocks of randomly varying size, was created by the Nottingham Clinical Trials Unit in accordance with their standard operating procedure and held on a secure server. Participants, investigators and research staff assessing the participants were blinded to treatment allocation. The sequence of

treatment allocations remained concealed until the database was locked at the end of the trial, when it was revealed to data analysts.

Statistical methods

Demographic and clinical measures were compared between the randomised arms at baseline using appropriate descriptive statistics for continuous and categorical variables.

The primary approach to between-group comparative analyses was by intention to treat without imputation of missing outcome data. Sensitivity analyses were conducted to investigate the impact of missing primary outcome data using simple and multiple imputation. The primary outcome comparing gentamicin with ceftriaxone was the difference in the proportion of participants clear of infection at 2 weeks' follow-up, along with the 95% CI. Gentamicin was regarded as non-inferior if the lower 95% CI for the risk difference in confirmed clearance was ≥ -5 percentage points (i.e. nearer zero). This was evaluated using a generalised estimating equation for binary outcomes, adjusted by recruiting centre as a random effect, with robust standard errors.

The secondary outcomes were similarly analysed using appropriate regression models dependent on data type, adjusted for clinic site and baseline value of the outcome variable, if collected. To explore treatment efficacy by site of infection, for each of the three infection sites, we separately estimated clearance by treatment arm along with 95% CIs.

The relationship between clinical effectiveness and MIC was examined visually.

Safety and tolerability analyses were descriptive. Frequency counts and percentages of the prespecified main categories of AEs were presented by treatment arm.

Health economics

The economic analysis compared the costs associated with the current standard treatment, ceftriaxone, with those of the proposed alternative treatment, gentamicin, in the treatment of gonorrhoea. Given that the primary objective of the trial was to determine non-inferiority of gentamicin compared with ceftriaxone, the economic analysis focused on establishing whether or not the use of gentamicin rather than ceftriaxone was cost neutral in the treatment of gonorrhoea. This involved the collection and analysis of data on costs and NHS resource use to determine whether or not there were any differences between the two treatments. These data were collected via trial processes and a patient questionnaire at the 2-week follow-up.

Results

The trial randomised 720 participants: 358 to receive gentamicin and 362 to receive ceftriaxone. Eighty-one per cent of participants were male, 69% were white and 13% had an human immunodeficiency virus infection. Fourteen participants did not receive their allocated medication, of whom 10 were in the gentamicin group and four were in the ceftriaxone group. Primary outcome data were available for 306 participants (85%) randomised to receive ceftriaxone and 292 participants (82%) randomised to receive gentamicin. In total, 299 (98%) of the participants allocated to ceftriaxone had clearance at 2 weeks, compared with 276 (91%) of the participants allocated to gentamicin, an adjusted risk difference of –6.4% (95% CI –10.4% to –2.4%). Clearance at genital sites was 98% and 94%, at pharyngeal sites was 96% and 80% and at rectal sites was 98% and 90% in ceftriaxone- and gentamicin-allocated participants, respectively. Nausea was experienced by 12% and 14% of participants, vomiting by 1% and 4%, reduction in hearing by 2% and 1%, dizziness/unsteadiness by 7% and 7% and skin rash by 2% and 4% in the ceftriaxone and gentamicin groups, respectively. The majority of participants reported injection site pain (98% and 99% in the ceftriaxone and gentamicin treatment groups, respectively), with the mean pain score, measured by a VAS, greater in the

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gentamicin group (21 vs. 36). The median time to resolution of injection pain was 1 hour for ceftriaxone and 1.5 hours for gentamicin. Fifteen per cent of participants allocated to ceftriaxone and 13% allocated to gentamicin reported at least one AE. The majority of AEs were mild (45/54 in the ceftriaxone group and 35/43 in the gentamicin group). One serious AE (grade 4 dizziness) was reported and it was not considered to be related to the trial treatment.

The economic analysis found that, from a health-care perspective, treatment with gentamicin was not cost neutral compared with standard care. Average patient treatment costs were found to be higher for the gentamicin trial arm (£13.90, 95% CI £2.47 to £37.34) than for the ceftriaxone arm (£6.72, 95% CI £1.36 to £17.84). However, within the economic evaluation, it was not possible to consider the potential issues associated with antimicrobial resistance (AMR) in gonorrhoea.

Conclusions

Implications for health care

The G-TOG trial was unable to demonstrate the non-inferiority of gentamicin compared with ceftriaxone in microbiological clearance of gonorrhoea at 2 weeks' follow-up. Therefore, it is likely that clinicians will want to continue to use ceftriaxone (plus azithromycin) as their preferred first-line therapy. Secondary analyses suggested that gentamicin was potentially non-inferior to ceftriaxone with respect to clearance of genital gonorrhoea (94% vs. 98%), so it is possible that gentamicin could be used for patients who are allergic or intolerant to ceftriaxone or who have a gonorrhoea infection that is resistant to ceftriaxone. However, further work would be needed to confirm non-inferiority. The lower cure rates for rectal (90%) and pharyngeal infection (80%) make gentamicin a less attractive treatment option, but antibiotics are generally less effective at these sites and gentamicin may still be useful as a second- or third-line therapy. A repeat test for gonorrhoea to ensure microbiological cure would be advisable following gentamicin therapy.

Azithromycin is currently used as part of dual therapy for gonorrhoea to 'protect' ceftriaxone by theoretically reducing the risk of resistance developing and by providing microbiological cover in case cephalosporin resistance develops. The observation in the G-TOG trial that a 1-g dose of azithromycin, even in combination with gentamicin, has a significant failure rate raises concerns about the effectiveness of 1 g of azithromycin in the treatment of gonorrhoea and, therefore, whether or not its use as a component of dual therapy will reduce the risk of future AMR developing.

A single dose of 240 mg of gentamicin was found to cause few AEs and had a safety profile comparable to that of ceftriaxone, which provides reassurance regarding its use in clinical practice.

The economic analysis showed that, currently, gentamicin is likely to be more costly than ceftriaxone in the treatment of gonorrhoea. However, it was not possible to take into account the costs associated with AMR for gonorrhoea.

Recommendations for research

Further exploration is needed into why gentamicin treatment is not effective in some patients and whether or not its efficacy can be predicted. Whole-genome sequencing may allow the identification of specific genetic markers of *N. gonorrhoeae* resistance and provide insights into the mechanisms and predictors of resistance.

The development of a preventative or therapeutic gonococcal vaccine is a priority because of increasing resistance and limited future antibiotic options. Greater understanding of the immune response to infection is required to facilitate this.

A 1-g dose of azithromycin combined with gentamicin was associated with a relatively high failure rate, with the lowest clearance rates seen in pharyngeal infection. This suggests that azithromycin may not be the optimal antibiotic to use as part of dual therapy designed to slow the spread of resistance. Further studies are required to evaluate alternative 'second agents'.

Further research is needed to examine the costs associated with AMR in gonorrhoea. In addition, there is a need for the development of appropriate methods for economic evaluations of interventions to address AMR in gonorrhoea and other disease areas.

Trial registration

This trial is registered as ISRCTN51783227.

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