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Treatment of Sexually Transmitted Infections with Single-Dose Therapy

A Double-Edged Sword

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Abstract

Since the advent of the antimicrobial era, single-dose therapy has been a valuable tool in the management of genital infection. Most of the common sexually transmitted infections (STIs) such as gonorrhoea, syphilis, trichomoniasis and chancroid can be treated in this way, as can genital infections which are not sexually transmitted such as bacterial vaginosis and genital tract candidiasis. Until recently, treatment for *Chlamydia trachomatis* infection required a multi-dose regimen, but single-dose azithromycin has now been shown to be an effective and acceptable alternative to this. Unfortunately, eradicative therapy has proven to be elusive for the viral STIs such as genital herpes simplex infection, human papilloma virus infection and human immunodeficiency virus (HIV) infection.

The main advantage of single-dose therapy lies in its convenience and in its ability to ensure virtually 100% compliance. This addresses the problems of reduced clinical efficacy and the difficulties in assessing the response to therapy which complicates poor treatment compliance.

However, some single-dose regimens for STIs do have drawbacks, particularly in certain situations. This may be with respect to efficacy, for example in syphilis with single-dose benzathine penicillin therapy, particularly for pregnant women and individuals infected with HI. Alternatively, it may involve toxicity, for example with single-dose metronidazole therapy for trichomoniasis or bacterial vaginosis where a higher rate of gastrointestinal adverse effects may be expected than if a lower multi-dose regimen is used. In addition, single-dose therapy, for example with nevirapine, given to the mother in labour and to the baby after delivery significantly reduces the risk of mother to child HIV transmission, but resistance mutations are frequently detected in the viral genome after the brief exposure to the drug, which could jeopardise its future use.

Single-dose therapy clearly has both advantages and disadvantages. We have reviewed a range of these in a variety of situations, focussing on their applications, effectiveness, compliance and toxicity, highlighting how single-dose therapy may be a double-edged sword.

Single-dose, directly observed therapy has been the ideal treatment for sexually transmitted infections (STIs) for many years. *Neisseria gonorrhoeae* has been treated this way since the start of the antibiotic era, initially with penicillin but with the emergence of resistant strains now with a fluoroquinolone or cephalosporin. *Treponema pallidum* remains exquisitely sensitive to penicillin, and uncomplicated early syphilis can be treated with a single dose of intramuscular benzathine benzylpenicillin. *Haemophilus ducreyi* (the infectious agent that causes chancroid) and *Trichomonas vaginalis* infection are also treatable with single-dose antimicrobial therapy, as are the genital tract conditions bacterial vaginosis and vulvovaginal candidiasis. Until recently, genital *Chlamydia trachomatis* infection was the only common bacterial STI not amenable to such treatment, but with the development and licensing of azithromycin, uncomplicated lower genital tract chlamydial infection can also be effectively treated with single-dose therapy.[1]

There are three reasons why accurate diagnosis and effective treatment of STIs are important: reducing the spread of STIs, preventing associated morbidity and reducing the transmission of the human immunodeficiency virus (HIV), which remains an incurable infection. Single-dose therapy has an important role to play in achieving these aims. The main advantage with directly observed therapy is that compliance is virtually absolute. In core groups with high rates of STIs, mass treatment with single-dose therapy may be considered and may rapidly reduce prevalence rates. However, this must not be at the expense of reduced effectiveness or efficiency, tolerability or safety, or prohibitive cost. These factors must be considered in addition to other aspects of effective STI treatment, including sexual health education, facilitation of partner notification, and sexual abstinence until treatment of both the patient and their partner is complete.

Single-dose therapy is not an option for viral STIs, such as herpes simplex virus and human papillomavirus infection, which are highly prevalent among sexually active individuals, and an eradicative treatment for these infections remains elusive.

1. Compliance

It is apparent that patients often fail to take their medication as prescribed. Attempts have been made to quantify levels of compliance with short- and long-term medications in different settings. Methods of assessing compliance include self-reporting, tablet counts, medication event monitoring system (MEMS) caps on tablet bottles (which report how often the bottle is opened) and therapeutic drug monitoring. One study assessing compliance with antidepressants compared these methods and found that the MEMS system and self-report scores were useful systems for identifying non-compliant patients.[2] Compliance rates were found to be 79.5% after 6 weeks. Compliance of children with inhaled asthma medication has also been assessed and was found to reduce steadily over time, with adherence rates of 40 to 47% after 27 months.[3] A study of adherence in patients with epilepsy using MEMS caps found adherence levels with anticonvulsant therapy linked to the dosage frequency of the medication,[4] with average compliance rates of 87% for once daily regimens falling to 39% for regimens requiring dose administration four times a day.

In the genitourinary (GU) medicine setting, adherence with tetracycline and erythromycin therapy for chlamydial urethritis and cervicitis has been assessed. In one study 90% of patients reported taking their medication as prescribed but according to MEMS caps only 16% of them actually had.[5] A similar study assessing compliance by MEMS caps found the rate of strict compliance to be 25% and non-compliance 24%, with the remaining 51% of patients taking an intermediate level of medication.[6] A further study assessing adherence with these antibacterials by self-report judged 63.4% of patients to be compliant with their treatment regimen.[7] Those who were younger, contacts of infection or who experienced adverse effects of the medication were more likely to be non-compliant, but there was no association with race, gender or symptoms.[6,7] A further drawback

of poor adherence is that left-over medication may be kept and taken incorrectly at a later date without medical guidance, so contributing to the problems of inappropriate antibacterial use and the potential for developing bacterial resistance to these agents.

Lack of adherence confounds assessment of treatment efficacy, and under, over or erratic dose administration may contribute to reduced drug efficacy or safety. A highly effective way of overcoming these problems is by single-dose, directly observed therapy.

In the setting of GU Medicine clinics in the United Kingdom (UK), treatment is provided free of charge at the point of contact. In our own clinic this is administered on site by the nursing staff and is directly observed in most patients. Parenteral therapy, such as penicillin injections for the treatment of syphilis, is by definition directly observed and thus ensures compliance. This is one of the reasons that therapy for syphilis is administered this way. When not directly observed, single-dose therapy obviously introduces the risk of non-compliance, even with a very simple regimen, and thus supports the administration of directly observed therapy by clinic staff.

2. Effectiveness and Acceptability

Two studies have compared compliance and treatment failure rates with single-dose oral azithromycin and multi-dose oral tetracycline treatment for chlamydial infections.[5,8] Both studies had few treatment failures despite poor compliance rates. Among the patients with apparent treatment failure were those with behavioural risks of re-infection. This means that despite poor compliance, most patients took enough medication to treat their infection. The minimum dose of antibacterial required to achieve microbiological clearance of chlamydial infection remains unknown and, therefore, the true effect of compliance uncertain.

Further issues to be considered include the effect of single-dose therapy on patient follow-up and partner attendance rates. These were assessed in a study of men attending a GU Medicine clinic with non-gonococcal urethritis (NGU).[9] Those who received single-dose oral azithromycin as opposed to multi-dose oral therapies were more likely to attend for follow-up themselves and had higher rates of sexual contact attendance. They were no more likely to require further treatment because of re-infection from an untreated partner than those receiving multi-dose regimens. In addition, over 70% expressed a preference for single-dose therapy. Follow-up remains an essential part of STI management, and is particularly pertinent as *C. trachomatis* resistant to doxycycline, azithromycin and ofloxacin has now been reported in association with clinical failure.[10]

A single dose of 2.4 million units of benzathine benzylpenicillin by intramuscular injection was recommended as the treatment of choice for early syphilis in the 1998 US Centers for Disease Control and Prevention (CDC) guidelines.[11] In the UK the recommended regimen is daily intramuscular procaine penicillin for 10 to 21 days.[12] It has been argued that such a regimen is much less acceptable to patients than the single-dose therapy, but a study in East London, UK, showed this to be a well-accepted regimen with a high compliance of 88% and minimal adverse effects.[13] Intramuscular benzathine benzylpenicillin may be declined by patients who do not wish to have injections in favour of prolonged oral course treatment and this may compromise compliance. Single-dose benzathine benzylpenicillin is also a recommended treatment for early syphilis in pregnancy.[11] However, compared with two or three weekly injections, this is associated with lower birth weight, immaturity, prematurity, and increased perinatal mortality and total pregnancy loss.[14] HIV co-infection also complicates syphilis treatment and has been associated with an increased risk of progression to neurosyphilis, despite treatment with benzathine benzylpenicillin.[15] Conversely, a randomised, controlled trial of benzathine benzylpenicillin treatment with and without additional amoxicillin in HIV-positive and -negative patients found that single-dose therapy was adequate for most patients regardless of HIV status.[16]

Single-dose therapy for gonorrhoea is highly effective and well established.[17] However, efficacy does depend on the susceptibility of the organisms to the chosen antibacterial agent. This is of increasing relevance as gonococcal resistance to penicillin, fluoroquinolones and tetracyclines is becoming more prevalent in the UK.[18] Oral ciprofloxacin remains the agent of choice within most GU Medicine clinics in the UK with oral amoxicillin and probenecid as an alternative for pregnant women, dependant on the regional prevalence of penicillin-resistant *N. gonorrhoeae*. Intramuscular ceftriaxone is an appropriate choice for most strains demonstrating resistance to these agents,[17,18] and an alternative oral agent is cefixime. Both are administered as a single dose. Cefixime is the first choice agent of the 1998 US CDC guidelines and there are no safety issues in pregnancy; however, it may not eliminate pharyngeal carriage of the organism.[11] Single-dose oral ciprofloxacin has also been shown to have comparable efficacy to a 7-day course of erythromycin for the treatment of chancroid.[19]

T. vaginalis infection is treated with oral metronidazole as a single 2g dose or in divided doses for 5 days. The single-dose regimen optimises compliance but there is evidence suggesting a higher failure rate, particularly if partners do not receive concurrent treatment.[20] However, other studies report comparable cure rates and minimal adverse effect profiles with both regimens, recommending the single-dose regimen on the basis of ease and reduced cost.[21,22]

Bacterial vaginosis occurs when there is a shift in the vaginal microbial flora characterised by a loss of the vaginal lactobacilli and an overgrowth of other micro-organisms such as *Gardnerella vaginalis*. It is not regarded as a STI, there is no equivalent condition in men and there is no benefit in treating the male partners of women with bacterial vaginosis.[23] First-line oral therapy is metronidazole 400mg twice daily for 5 to 7 days or as a single 2g dose.[24] Although the single-dose regimen maximises compliance and is cheaper, it has been found to be slightly less effective 1 week following treatment with a more marked difference at 4-week follow-up,[25] and it is also associated with an increased incidence of adverse events. Intravaginal multi-dose clindamycin or metronidazole preparations are suitable alternatives.[24]

Vulvovaginal candidiasis occurs as a result of *Candida albicans* infection in 80 to 92% of patients with the remainder due to non-albicans species such as *Candida glabrata*.[26] Single-dose topical or oral azole therapy is an established and effective first line treatment. Multiple doses may be required for patients with diabetes mellitus or those with immunodeficiency. They may also be indicated in pregnancy, where only topical treatments should be used. Amongst the *Candida* species, non-albicans types have a decreased susceptibility to the azole-derived antifungal agents. This differential activity, together with the increased use of single-dose azole preparations, has been postulated as a cause for the potential increase in the prevalence of non-albicans species in vulvovaginal candidiasis.[27] However, this hypothesis remains unproven, has been questioned by others,[28] and single-dose oral or topical azole therapy remains the treatment of choice.

3. Tolerability and Safety

An increase in gastrointestinal adverse effects is frequently noted when metronidazole is given as a higher single dose for treatment for bacterial vaginosis or *T. vaginalis* infection. These adverse effects seem to be less prevalent when lower divided doses are used. Azithromycin single-dose therapy is not currently licensed for use in pregnancy. However, it has been used in pregnancy with apparent safety, demonstrates high efficacy and appears to have a much more favourable safety profile than a 7-day course of erythromycin, particularly in pregnancy when nausea and vomiting can be troublesome.[29,30]

4. Cost Effectiveness

When assessing the cost effectiveness of treatment for STIs, one must consider not only the immediate reduction in morbidity but also the savings

from preventing future sequelae. This is particularly pertinent for chlamydial infections where future reproductive morbidity places considerable financial burden on healthcare resources. Single-dose oral azithromycin achieves higher compliance rates and so may be a more effective treatment in the prevention of future morbidity, but the cost of providing the treatment and the subsequent benefits gained are incurred by different components of the healthcare system.[31] However, a cost-benefit analysis of the treatment of men with NGU with single-dose oral azithromycin, which accounted for drug costs and the cost of additional hospital visits to GU Medicine, has been shown to clearly favour azithromycin as first line therapy.[9]

5. Single-Dose Therapy to Control Sexually Transmitted Infections and HIV

In recent years evidence has accumulated that genital tract infections, particularly those resulting in ulcerative lesions, facilitate the transmission of HIV.[32-37] Treatment and prevention of STIs has been proposed as a strategy to reduce HIV transmission, particularly in the developing countries of sub-Saharan Africa where STIs are endemic and HIV seropositivity rates high. Two randomised trials were conducted to test this hypothesis.

The first was conducted between 1991 and 1994 in the Mwanza region of Tanzania. It evaluated the intervention of training health workers in syndromic case management of STIs, village campaigns, and supervising healthcare facilities and treatment provision in the area. Analysis revealed that after adjustment for confounding factors, HIV-1 incidence was 38% lower in the intervention group than control communities, a highly significant finding.[38]

The second study was performed in the Rakai district of Uganda from 1994 to 1998. In this setting the use of single-dose, directly observed antimicrobial therapy delivered together with vitamins, minerals and anthelminthics to participants in their homes every 10 months, was compared to the use of vitamins, minerals and anthelminthics only.[39] At 20-month follow-up, the prevalences of syphilis and trichomoniasis were lower in the intervention group compared with the control group. In pregnant women, the follow-up prevalence of trichomoniasis, bacterial vaginosis, gonorrhoea and chlamydial infection were also significantly lower in the intervention group than the control group. Despite the effect on bacterial STIs, the trial was stopped prematurely after three rounds of treatment because no effect on HIV incidence was seen.

There are many reasons why the results from these trials appear discordant. These include the differing stages of the HIV epidemic in the populations at the time of the studies, differing trial design and analysis, and lack of consideration of viral STIs and bacterial vaginosis.[40] The HIV epidemic was at a mature stage in Rakai at the time the study was performed with a stable HIV seroprevalence rate of 16%. The epidemic in Mwanza was immature with an HIV seroprevalence rate of 4% and rising. Mathematical computer modeling using data from the Mwanza population indicates that mass treatment performed at that time in areas with a high prevalence of STIs would have had a substantial impact.[41] Although rounds of single-dose therapy appeared ineffective in Rakai, in that particular circumstance, as a strategy for STI or HIV control it may be appropriate in other settings and should not be entirely discounted.[40] When combined with subsequent sustained syndromic management, it may be particularly effective.

Antiretroviral therapy was first established as an effective intervention to prevent mother to child transmission of HIV in 1994.[42] However, a long and complicated course for the mother and baby was required, and this proved too complex and expensive for use in developing countries. Single-dose therapy with nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) given to the mother in labour and to the baby within 72 hours of birth has been shown to reduce the rate of mother to child transmission of HIV to 13.1%, despite breastfeeding.[43] This is in comparison to rates of up to 35% without treatment. However, its use is associated with rapid virus mutation such that 23% of the women studied developed the

Table I. Summary of single-dose regimens used in the treatment of sexually transmitted infections

Infection	Single-dose regimen	Disadvantages	Advantages	Recommendations	Use in pregnancy
Syphilis	Benzathine benzylpenicillin, IM injection, 2.4MU	May be less effective in: late or latent infection concurrent HIV infection in pregnancy	Optimises compliance Convenience	Use standard extended courses when possible, with single dose regimens if non-compliance suspected	Good safety but may be less effective
Gonorrhoea (uncomplicated, lower genital tract)	Ciprofloxacin 500mg Amoxicillin 3g + probenecid 1g	Knowledge of regional resistance data is required (see text)	Optimises compliance Convenience	Single dose regimens need to be modified in the light of local antimicrobial resistance patterns	Penicillins and cephalosporins have good safety profiles in pregnancy
Chlamydial infection (uncomplicated, lower genital tract)	Azithromycin 1g	Comparatively increased cost	Optimises compliance Convenience	Use of multi-dose regimen is reasonable if good compliance is expected. Use single dose if uncertain about compliance. Balance cost and compliance	Studies have demonstrated efficacy in pregnancy but currently unlicensed
Trichomonas vaginalis	Metronidazole 2g	Adverse effects Possibly reduced efficacy	Optimises compliance Convenience Reduced cost	Use of multi-dose regimen is desirable if good compliance is expected	Good safety and effective
Bacterial vaginosis	Metronidazole 2g	Adverse effects Possibly reduced efficacy	Optimises compliance Convenience Reduced cost	Use of multi-dose regimen is desirable if good compliance is expected	Good safety and effective
Candidiasis	Clotrimazole 500mg or Fenticonazole 600mg PV Fluconazole 150 mg	Possibly reduced efficacy in complicated infections or pregnancy	Optimises compliance Convenience	Single-dose regimens in uncomplicated infections	Topical azoles have good safety profiles for pregnancy and are effective. Oral therapy contraindicated
HIV vertical transmission	Nevirapine single dose to mother in labour and baby within 72h of delivery	Less effective than longer courses of other drugs High incidence of resistant mutations after use	Simple Cheaper than longer courses	May be appropriate in resource limited situations or when the mother presents for the first time in labour	Zidovudine the only licensed drug for this use, but other regimens commonly used

IM = intramuscular; **PV** = per vagina.

K103N NNRTI primary mutation after only one dose of nevirapine.[44] In addition, 44% of infected babies also had nevirapine resistant virus, again after only one dose.[44]

6. Conclusion

Single-dose, directly observed therapy has a pivotal role to play in the management of STIs, dealing with the crucial factor of patient compliance. However, consideration should be given to the limitations of such regimens, which include possibly reduced efficacy and safety, and increased cost to the healthcare provider. Table I summarises some of the single-dose regimens used in the treatment of STIs, their advantages, disadvantages and recommendations.

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