How do you treat syphilis with parenteral benzylpenicillins?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

Before using this Q&A, read the disclaimer at www.ukmi.nhs.uk/activities/medicinesQAs/default.asp

Date of publication: Aug 2013

Background

Syphilis is a systemic disease caused by the spirochaete bacteria Treponema pallidum. It can be congenital (through mother to child transmission during pregnancy) or acquired (through sex or blood transfusion) (1). It causes considerable morbidity and the presence of genital ulcers in primary syphilis increases the sexual transmission of HIV (2). The clinical presentation of both early and late syphilis is diverse and patients may present to a wide range of services and clinicians including General Practitioners (2). It is classified in terms of disease stages; primary, secondary, early latent, late latent and late symptomatic (or ‘tertiary’) syphilis (2). Symptoms of a primary infection include ulcers or chancres at the infection site and symptoms of a secondary infection include skin rashes, mucocutaneous lesions and lymphadenopathy (3). Latent infections lack clinical manifestations and tertiary infections include cardiac, neurological or ophthalmic manifestations, auditory abnormalities or gummatous (granulomatous) lesions (3). Syphilis remains a common infection worldwide with an estimated 10-12 million new infections each year (2). Since the late 1990s infectious early syphilis has re-emerged as an important disease in Western Europe and the United Kingdom (2).

Answer

Parenteral benzylpenicillin (also known as penicillin G) is the preferred drug treatment for all stages of syphilis (3). Parenteral rather than oral therapy has been the treatment of choice because therapy is supervised and bioavailability is guaranteed (4).

Parenteral benzylpenicillins for the treatment of syphilis include;

- **Benzathine benzylpenicillin**, a long acting form of benzylpenicillin administered by deep intramuscular injection (5). It is usually given as a single dose or weekly for the treatment of syphilis depending on the disease stage and guidelines used (3) (4). It is unlicensed in the UK, the brand available at the time of writing is Extencilline® (600,000 units, 1.2million units (MU) and 2.4MU) (5).

- **Procaine benzylpenicillin**, a long acting form of benzylpenicillin administered by deep intramuscular injection (6). It is usually given once daily to treat syphilis (6). It is unlicensed in the UK and currently available as the brand Farmaproina® (600,000 units and 1.2 MU) (6).

- **Aqueous crystalline benzylpenicillin** is administered by intravenous injection for neurosyphilis. It is short acting, with a half-life of 30 minutes, so it is given every four hours (7). It is licensed in the UK for congenital syphilis and neurosyphilis. It is available as the brand Crystapen ® (600mg and 1200mg) (7).

When administering benzathine benzylpenicillin, if the volume for administration is large, the dose may be split and given as two injections at separate sites (1). Benzathine benzylpenicillin intramuscular injection can be painful. A small study in paediatrics has shown that this can be improved by using lidocaine 1% as the diluent but the trial was too small to be conclusive (8). Practice may vary from clinic to clinic so local practice guidelines should be checked.

Parenteral benzylpenicillins have been used effectively for more than 50 years to treat syphilis but no comparative trials have been adequately conducted to guide the selection of an optimal penicillin regimen (3). As a result, there are many different guidelines and the dose, duration and preparation varies between them, depending on the stage and clinical manifestations of disease. It is important to differentiate between the various products (See table 1). Other factors such as clinical experience and local availability of medicines also affect the choice of regimen.

From the NHS Evidence website www.evidence.nhs.uk
Standard antisyphilis therapy rarely fails to cure the disease, and there doesn’t appear to be resistance (2). Early stages of syphilis are more infectious but respond better to treatment (1). A treponemicidal level of antimicrobials needs to be achieved in both the serum and cerebrospinal fluid (CSF) to provide effective treatment for syphilis (1). A penicillin level of greater than 0.018mg per litre is considered sufficient, and needs to be maintained for at least 7-10 days in early syphilis (1). A longer duration of treatment is given in late syphilis on the basis of more slowly dividing treponemes (4).

**Table 1. Dosage regimens for treating syphilis with parenteral benzylpenicillins**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Early syphilis (primary, secondary and early latent)</th>
<th>Late latent, cardiovascular and gummatous syphilis</th>
<th>Neurosyphilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK National Guidelines on the Management of Syphilis 2008 (BASHH guidelines) (4)</td>
<td>Intramuscular Benzathine benzylpenicillin 2.4 MU as a single dose Or Intramuscular Procaine benzylpenicillin 600 000 units daily for 10 days</td>
<td>Intramuscular Benzathine benzylpenicillin 2.4 MU once weekly for 3 consecutive weeks Or Intramuscular Procaine benzylpenicillin 600 000 units daily for 17 days</td>
<td>Intramuscular Procaine benzylpenicillin 1.8MU to 2.4MU daily plus probenecid 500mg po qds for 17 days Or Intravenous Aqueous crystalline benzylpenicillin 3-4MU every four hours for 17 days</td>
</tr>
<tr>
<td>Centre for Disease Control and Prevention Guidelines (USA) 2006 (3)</td>
<td>Intramuscular Benzathine benzylpenicillin 2.4 MU as a single dose</td>
<td>Intramuscular Benzathine benzylpenicillin 2.4MU once weekly for 3 consecutive weeks</td>
<td>Intravenous Aqueous crystalline benzylpenicillin 3-4MU every four hours or continuous infusion for 10 – 14 days Or, Intramuscular Procaine benzylpenicillin 2.4MU daily plus probenecid 500mg po qds for 10-14 days</td>
</tr>
<tr>
<td>World Health Organization Guidelines 2003 (1)</td>
<td>Intramuscular Benzathine benzylpenicillin 2.4MU as a single dose Or, Intramuscular Procaine benzylpenicillin 1.2MU daily for 10 days</td>
<td>Intramuscular Benzathine benzylpenicillin 2.4MU once weekly for 3 consecutive weeks Or, Intramuscular Procaine benzylpenicillin 1.2MU daily for 20 days</td>
<td>Intravenous Aqueous crystalline benzylpenicillin 2-4MU every four hours for 14 days Or, Intramuscular Procaine benzylpenicillin 1.2MU daily plus probenecid 500mg orally qds for 10-14 days</td>
</tr>
</tbody>
</table>

**Alternative non parenteral treatments and regimens for penicillin allergic patients**

If patients refuse parenteral treatment, or if they are penicillin allergic, alternative regimens may be sought. There are substantially fewer clinical trial data available for non-penicillin regimens (3). Oral doxycycline, erythromycin and azithromycin have been evaluated (4). Erythromycin is the least effective and does not penetrate the CSF or placental barrier well (4). Doxycycline has superceded...
the older tetracyclines (4). Azithromycin has shown efficacy in early syphilis equivalent to benzathine benzylpenicillin but there are concerns regarding azithromycin treatment failure which appears to be intrinsic macrolide resistance in some strains of *Treponema pallidum* (4)(9). In small studies a number of ceftriaxone regimens have been shown to be effective (4).

Treatment regimens vary according to different guidelines. The UK National Guidelines on the Management of Syphilis 2008 advise (4):

- **Early syphilis:**
  1. Doxycycline 100mg bd orally for 14 days
  2. Azithromycin 2g stat orally, or azithromycin 500mg daily for 10 days
  3. Erythromycin 500mg qds orally for 14 days
  4. Ceftriaxone 500mg IM daily for 10 days (if no anaphylaxis to penicillin)
  5. Amoxicillin 500mg qds orally plus probenecid 500mg qds for 14 days

- **Late latent syphilis:**
  1. Doxycycline 100mg bd orally for 28 days
  2. Amoxicillin 2g tds orally plus probenecid 500mg qds orally for 28 days

- **Neurosyphilis:**
  1. Doxycycline 200mg bd orally for 28 days
  2. Amoxicillin 2g tds orally plus probenecid 500mg qds orally for 28 days
  3. Ceftriaxone 2g IM (with lidocaine as diluent) or IV (with water for injections as diluent) for 10 to 14 days (if no anaphylaxis to penicillin)

**Reactions to treatment**

Patients should be warned of possible reactions to treatments. These include the Jarisch-Herxheimer reaction, or reactions to either procaine, penicillin, or both.

a) Jarisch-Herxheimer is an acute febrile illness with headache, myalgia, chills and rigors usually occurring after the first dose of therapy and resolving within 24 hours (4). It is most common in early syphilis but is usually not important unless there is neurological or ophthalmic involvement or in pregnancy (4). It is uncommon in late syphilis but can potentially be life threatening if there is cardiological/neurological involvement (4).

b) A reaction to procaine is usually due to inadvertent IV injection of procaine benzylpenicillin (4). It is characterised by fear of impending death and may cause hallucinations or fits immediately after injection and lasting less than 20 minutes (4). Calm and verbal reassurance is required and rectal diazepam may be used if the patient is fitting (4). Remind prescribers and staff administering procaine benzylpenicillin that it must be given by intramuscular injection.

c) Anaphylaxis may occur in patients who are allergic to penicillin (4). Always check patient’s allergy status prior to administration.

**Special considerations**

HIV infected patients with early syphilis are more likely to have multiple, large and deep genital ulcers and the risk of neurological complications may be higher in HIV positive patients with early syphilis (4). Treatment should be appropriate for the stage of infection; that is HIV positive individuals should be given the same treatment regimens as HIV negative individuals. Some experts believe that HIV patients with syphilis should be treated as for neurosyphilis to prevent the development of neurological involvement, but hard evidence for this policy is lacking (4)(10).

**Summary**

- Parenteral benzylpenicillin (also known as penicillin G) is the preferred drug treatment for all stages of syphilis (3). The long acting forms of benzylpenicillin used to treat syphilis are procaine benzylpenicillin and benzathine benzylpenicillin. They are administered by deep intramuscular injection (5)(6).
- Procaine benzylpenicillin is usually given once daily in syphilis where as benzathine benzylpenicillin is given once weekly or as a single dose. The dose, duration and preparation vary according to the stage of disease and different guidelines (See table 1).
- Patients should be informed about possible adverse reactions such as the Jarisch-Herxheimer reaction, a reaction to procaine, or penicillin or both.
Alternative oral antibiotics are available for penicillin allergic patients, and patients refusing parenteral therapy. Special consideration should be given to HIV-infected persons, who have a greater risk of neurological complications (4), and late syphilis may develop more rapidly in HIV positive positive individuals (1).

Limitations
This Q&A does not cover treatment of syphilis in pregnancy and congenital syphilis in newborns. Information can be found in current guidelines.

http://www.bashh.org/guidelines
www.cdc.gov/std/treatment/

References

Quality Assurance

Prepared by
Varinder Rai, Medicines Information Pharmacist, London MI Service (Northwick Park), based on a previous Q&A written by Caroline Taylor, LMIS.

Date Prepared
July 2013

Checked by
Alexandra Denby, Regional MI Manager, London MI Service (Northwick Park)

Date of check
23rd July 2013

Search strategy

- Embase (search strategy = syphilis +penicillin derivative/im,iv, since 2011)
- Medline (syphilis + penicillins + intramuscular or intravenous injections, since 2011)
- NHS Evidence (syphilis)