Guidance on the use of Diphtheria Anti-toxin
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Diphtheria Anti-toxin (DAT)

Two diphtheria anti-toxin (equine) products, are currently being supplied in the UK.

The first product, Antidiphtheria Serum bull Bio, made be BB-NCIPD Ltd is supplied in 10ml ampoules containing 5,000 IU per ampoule in not more than 5 ml of serum.

The second product, made by the Institute of Immunology, Croatia is dispensed in 10ml ampoule containing 10,000 IU per ampoule in 10ml of serum.

Indications

1. For treatment of suspected diphtheria cases*
2. For treatment of confirmed infections, where clinically appropriate, due to toxigenic Corynebacteria ulcerans or C diphtheriae

*As defined in National Guidelines¹:

Notes:

- diphtheria anti-toxin should not be used for diphtheria prophylaxis.
- unimmunised contacts should be given diphtheria-containing vaccine and antibiotic prophylaxis in line with National Guidelines¹

Dosage

Dosage for diphtheria anti-toxin is determined by the severity and duration of the disease as shown in the table below. The dose is the same for adults and children, and the number of ampoules required should be calculated for the relevant product being used.

<table>
<thead>
<tr>
<th>Type of diphtheria</th>
<th>Dosage adults and children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe diphtheria e.g. extensive membrane and /or severe oedema ('bull neck')</td>
<td>100,000 IU</td>
</tr>
<tr>
<td>Laryngeal OR pharyngeal OR nasopharyngeal disease of more than 48hrs</td>
<td>100,000 IU</td>
</tr>
<tr>
<td>Laryngeal OR pharyngeal disease OR nasopharyngeal disease of less than 48 hours</td>
<td>60,000 IU</td>
</tr>
<tr>
<td>Skin lesions only¹</td>
<td>40,000 IU</td>
</tr>
</tbody>
</table>
WHO\(^2\) state that antitoxin is of limited value in cutaneous disease. In most cutaneous infections, large-scale toxin absorption is unlikely and therefore the risk of giving anti-toxin is usually considered substantially greater than any benefit. Nevertheless, if the cutaneous ulcer is sufficiently large (i.e. more than 2cm\(^2\)) and membranous, then anti-toxin may be justified.

Please note this guidance will differ from the dosage and administration instructions in the SmPC distributed with the product. In this instance this guidance document should be followed.

Please read ‘Administration’ section carefully prior to giving anti-toxin.

Administration

Precautions for Administration:

Prior to administration, a detailed history should be taken including:

- previous administration of equine anti-toxin
- known allergy (e.g. allergic rhinitis) following exposure to horses or other animals

Route

The IV route is the preferred route of administration of DAT, especially in severe cases. The antitoxin dose should be mixed in 250 –500 mL of normal saline (i.e. sodium chloride 0.9% injection) and administered slowly over 2 – 4 hours, closely monitoring for anaphylaxis.

Temperature

Antitoxin should be warmed to 32 – 34°C (90 – 95°F) before injection. Warming above the recommended temperature should be carefully avoided because the DAT proteins will denature.

Dosage

1. Perform sensitivity tests, and desensitisation if necessary.
2. Give the entire treatment dose of antitoxin IV in a single administration (except for series of injections needed for desensitisation).
Figure 1: Summary of DAT administration according to patient history and sensitivity testing

**Sensitivity Testing**

In persons with a **negative history** for animal allergy and no prior exposure to animal serum:

1. Inject ~0.05ml of a 1:100 dilution of the serum (in normal saline: sodium chloride 0.9% injection) intradermally, to cause a ~5mm bleb, and wait 30 minutes

2. If no evidence of hypersensitivity reaction (erythema, itch), repeat intradermal injection using a 1:10 dilution of the serum (in normal saline) and wait 30 minutes

3. If no evidence of hypersensitivity reaction, proceed with a slow IV infusion of full recommended dose. The antitoxin should be mixed in 250 – 500 mL of normal saline and administered slowly over 2 – 4 hours, with close monitoring for anaphylaxis.

4. If intradermal testing is positive or equivocal, then the schedule of desensitisation should be followed.

**DESENSITISATION PROTOCOL (IV)**

<table>
<thead>
<tr>
<th>Dose No.</th>
<th>Dilution of DAT in Saline</th>
<th>Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1,000</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>1:1,000</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>1:1,000</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>1:100</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>1:100</td>
<td>0.3</td>
</tr>
<tr>
<td>6</td>
<td>1:100</td>
<td>0.6</td>
</tr>
<tr>
<td>7</td>
<td>1:10</td>
<td>0.1</td>
</tr>
<tr>
<td>8</td>
<td>1:10</td>
<td>0.3</td>
</tr>
<tr>
<td>9</td>
<td>1:10</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>undiluted</td>
<td>0.1</td>
</tr>
<tr>
<td>11</td>
<td>undiluted</td>
<td>0.2</td>
</tr>
<tr>
<td>12</td>
<td>undiluted</td>
<td>0.6</td>
</tr>
<tr>
<td>13</td>
<td>undiluted</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Monitor patient carefully for anaphylaxis and/or serum sickness.
In patients with a *positive history for animal allergy or prior exposure to animal serum suggesting increased risk*:

1. Inject ~0.05ml of a 1:1000 dilution of the serum (in normal saline) intradermally, and wait 30 minutes
2. If no evidence of hypersensitivity reaction, repeat intradermal injection using a 1:100 dilution of the serum (in normal saline) and wait 30 minutes
3. If no evidence of hypersensitivity reaction, repeat intradermal injection using a 1:10 dilution of the serum (in normal saline) and wait 30 minutes
4. If no evidence of hypersensitivity reaction, proceed with a slow IV infusion of full recommended dose. The antitoxin should be mixed in 250 –500 mL of normal saline and administered slowly over 2 – 4 hours, with close monitoring for anaphylaxis.
5. If intradermal testing is positive or equivocal, then the schedule of desensitisation should be followed.

To dilute for intradermal testing, make serial dilutions as follows:

- 0.1ml of serum + 0.9ml normal saline = 1:10 dilution
- 0.1ml of 1:10 dilution + 0.9ml normal saline = 1:100 dilution
- 0.1ml of 1:100 dilution + 0.9ml normal saline = 1:1000 dilution

Recent use of an antihistamine (in last 48-72 hours) – including antihistamines present in over-the-counter preparations such as cough remedies – may interfere with the intradermal test. In this case, either seek the advice of a specialist in allergy to undertake screening using a positive (histamine) and negative (saline) control, or follow the desensitisation protocol for someone with a positive intradermal test.

**Monitor the patient carefully during treatment and ensure facilities for treating anaphylaxis (including 1:1000 adrenaline for injection) are readily available.**

**Desensitisation to DAT**

Patients with positive sensitivity testing to DAT or with a history suggesting increased risk from DAT administration (even with a negative or equivocal intradermal test) should undergo desensitization, as shown in the table below. The IV route is considered safer because it offers better control.³
Desensitization to DAT - Intravenous Route

<table>
<thead>
<tr>
<th>Dose Number*</th>
<th>Dilution of DAT in Normal Saline</th>
<th>Amount of Injection (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1000**</td>
<td>0.1</td>
</tr>
<tr>
<td>2</td>
<td>1:1000</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>1:1000</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>1:100**</td>
<td>0.1</td>
</tr>
<tr>
<td>5</td>
<td>1:100</td>
<td>0.3</td>
</tr>
<tr>
<td>6</td>
<td>1:100</td>
<td>0.6</td>
</tr>
<tr>
<td>7</td>
<td>1:10**</td>
<td>0.1</td>
</tr>
<tr>
<td>8</td>
<td>1:10</td>
<td>0.3</td>
</tr>
<tr>
<td>9</td>
<td>1:10</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>undiluted</td>
<td>0.1</td>
</tr>
<tr>
<td>11</td>
<td>undiluted</td>
<td>0.2</td>
</tr>
<tr>
<td>12</td>
<td>undiluted</td>
<td>0.6</td>
</tr>
<tr>
<td>13</td>
<td>undiluted</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Administer at 15 minute intervals

**1 ml (antitoxin) + 9.0 ml of saline (sodium chloride 0.9% injection) = 1:10 dilution
1 ml (1:10 dilution) + 9.0 ml of saline = 1:100 dilution
0.1 ml (1:10 dilution) + 9.9 ml saline = 1:1000 dilution
[1 ml (1:100 dilution) + 9 ml saline = 1:1000 dilution]

The protection from anaphylaxis afforded by giving DAT according to this desensitisation protocol requires that no interruption occur in the sequence of administration of doses; if an interruption occurs the protection is lost.
If no hypersensitivity reaction occurs, administer remaining quantity of anti-toxin as above.

Antimicrobial therapy

Appropriate antimicrobial agents in full therapeutic dosages should be started in line with national guidelines.

Pregnancy

Diphtheria anti-toxin (equine) should be used cautiously during pregnancy.

Side Effects

Administration of diphtheria equine anti-toxin may cause hypersensitivity reactions including anaphylaxis. Reactions occur in individuals previously sensitized to equine
anti-toxin or horse proteins either through previous administration on in some other way. Reactions to the anti-toxin may manifest as an anaphylactic reaction and/or serum sickness.

Anaphylaxis usually occurs within 1-2 hours of administration. The dose of adrenaline for anaphylaxis in teenagers and adults is 0.5ml of 1:1000 adrenaline given intramuscularly, every 5 minutes. In the event of severe anaphylaxis (no response to 2+ IM injections of adrenaline), an adrenaline infusion may be needed – call for specialist support.

Serum sickness can occur in up to 5% of patients according to historic data, usually around 7-12 days after the first injection although accelerated reactions have been reported in patients who have previously received equine anti-toxin preparations, with onset within days or even hours. Symptoms include more generalised erythema, urticaria, itching, and occasionally fever, pain and oedema of the joints and lymph nodes. Treatment is supportive, with anti-inflammatory preparations and antihistamine to provide symptomatic relief; systemic steroids may be needed in more severe cases.

Storage

Store at 2º to 8º C. Once the ampoule is opened, the preparation must be used immediately.

References

