September 5th 2022
km/22-02418

Review concerning veterinary medicines containing procaine benzylpenicillin for injection

Background

It has been noticed that the authorised durations of treatment vary between the different products containing procaine benzylpenicillin and based on available data not all of them might be appropriate to treat all claimed indications effectively. This could lead to a risk of development of antimicrobial resistance.

In accordance with Article 83(1) of Regulation (EU) 2019/6**,** all interested parties are invited to submit information, addressing the Committee for Veterinary Medicinal Products (CVMP) list of questions regarding information or data which could be relevant to evaluate the established dosage regimen of veterinary medicinal products containing **procaine benzylpenicillin** presented as suspension for injection.

Response from the Danish Veterinary Association (DVA)

Procaine penicillin is a time-dependent antibiotic, which is why the plasma concentration must be above the MIC for the longest possible time in the dosing interval to achieve a bactericidal effect. For gram-positive infections it is necessary for at least 50% of the time and for gram-negative infections at least 80% of the time.

In practice, significantly higher doses and/or more frequent dosing intervals than listed in the SPC are used for the most common products containing benzylpenicillin.

For example, the SPC specifies a dose of 1 ml/20 kg for Ethacellin, which is equivalent to 15 mg/kg and for Penovet the dose is 1 ml/15-30 kg (10-20 mg/kg) - but up to 30 mg/kg (equivalent to 1 ml/10 kg) is needed to treat certain infections in pigs and cattle.

When procaine penicillin is used for treatment of infections in **horses** (Ethacillin, Penovet or Primopen), dosing twice a day is necessary to secure sufficient MIC. Studies of pharmacokinetics and pharmacodynamics in horses have led to recommendations of a dose of 22,000 IU/kg (equivalent to 22 mg/kg) (Sullins, Messer & Nelson. 1984[1], Uboh et al. 2000[2]). Unfortunately, the SPC prescribes a dose of between 12-20 mg/kg and only one administration per day, which is insufficient.

---

[1] Sullins, Messer & Nelson. 1984. Serum concentration of penicillin in the horse after repeated intramuscular injections of procaine penicillin G alone or in combination with benzathine penicillin and/or phenylbutazone. *Am J Vet Res.* 45, ss 1003–1007.

[2] Uboh et al. 2000. Pharmacokinetics of penicillin G procaine versus penicillin G potassium and procainehydrochloride in horses. *Am. J. Vet. Res.* 61, ss. 811–815.

Den Danske Dyrlægeforening | Danish Veterinary Association | Amager Strandvej 60 | DK-2300 København S | +45 3871 0888
E-mail: ddd@ddd.dk | www.ddd.dk

For the treatment of lung- or joint infections in **calves and pigs**, a dose up to 1 ml/5 kg (60 mg/kg) is often used (=3 to 4 times the dosage listed in the SPC). This is, according to empirical knowledge, able to maintain a sufficient concentration for the individual to fight the infection. By doing so, veterinarians can use this narrow-spectrum penicillin with a short half-life instead of broad-spectrum agents that have a longer half-life (e.g. florfenicols, tetracyclines or macrolides).

In a Swedish study, the efficacy of procaine penicillin (administered dose 21 mg/kg) was inferior to tetracycline and quinolones when a strain of *Actinobacillus pleuropneumoniae* with a MIC of 0.5 microgram/ml was used as challenge (Sjølund et al. 2009[3]). This documents insufficient treatment with penicillin at the indicated dose once a day, which is in accordance with empirical knowledge.

Despite having used a treatment strategy (high dose for individual treatments against pleuropneumonia caused by *Actinobacillus pleuropneumonia*) with procaine penicillin for years in **pigs**, the MIC values for the bacteria remains low in Danish pig farms (personal information from L&F laboratory for Pig Diseases, Kjellerup), compared to other European countries.

Laboratory reported MIC values for *Actinobacillus pleuropneumoniae* to penicillin (from pigs with pleuropneumonia) are listed below (**2008-2012)**:

Year	% sensitive	% resistant	Number
2008	100	0	157
2009	99.4	0.6	157
2010	100	0	177
2011	97.9	2.1	142
2012 -> October 16th	100	0	118

From January 1st **2011** to October 16th **2012** the MIC-distributions were:

MIC µg/ml	<0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	>8
Number isolates	1	1	18	96	100	25	2	0	0	3

The latest data from **2021** (shown below) for MIC distribution for *Actinobacillus pleuropneumonia*-isolates from diseased lungs (L&F laboratory, Kjellerup) demonstrates a small shift towards higher MIC. However, methods have changed since 2012, which might have influenced the MIC detection limits.

MIC µg/ml	<0.06	0.12	0.25	0.5	1	2	4	>8
Number isolates	5	21	47	97	4	1	0	2

[3] Responses of pigs to a re-challenge with Actinobacillus pleuropneumoniae after being treated with different antimicrobials following their initial exposure - PubMed (nih.gov)

The MIC values are still low for most isolates and well below the expected pulmonary concentration of penicillin. In our opinion, this will make procaine penicillin the "drug of choice" if the dose is increased compared to the one in the current SPC.

- ➔ As the MIC value remains low, the DVA find that use of procaine penicillin in a higher dose can be continued without risk of insufficient response to treatment or further development of resistant strains of *Actinobacillus pleuropneumonia*.

Also, a **recent study** showed that an increased dosage of penicillin in the treatment of *Actinobacillus pleuropneumoniae* was clearly better than the prescribed dosage according to the SPC Exposure to benzylpenicillin after different dosage regimens in growing pigs (biomedcentral.com)

- ➔ The DVA therefore support when treating infections with *staphylococc*i or *streptococci*, which have low MIC values, low dosages may be sufficient, but for bacteria that have slightly higher MIC values, such as *Pasteurella*, *Actinobacillus* or *Mannheimia*, higher doses are needed.

The alternative is increased use of broad-spectrum preparations, which is not desired.

The adjustment to a higher dose in the SPC will indeed cost in numbers of ADD registered, as the veterinarian cannot reduce the treatment period accordingly.

Please contact us if you have any further questions.

Karin Melsen, Policy advisor, DVM
km@ddd.dk.
The Danish Veterinary Association