Guideline to collect, archive, handle and analyse pharmacokinetic data for VetCAST

Introduction

The purpose of this Guideline document is to provide proposals to facilitate standardisation of the processes of collection, archiving and analysis of individual pharmacokinetic (PK) data by VetCAST. This guideline describes:

- The collection, archiving, handling and analysis of PK data
- The building of population PK (PPK) models and reporting parameter estimates
- The use of the PPK data in Monte Carlo simulations for the calculation of PK-PD breakpoint values, with the objective of determining clinical breakpoints for Antimicrobial Susceptibility Testing (AST) of antimicrobial drugs used in veterinary medicine
- The provisions made to guarantee the confidentiality and safety of data shared by drug companies volunteering to help VetCAST.

Collection of individual pharmacokinetic data

The individual animal plasma concentration-time curves will be submitted to VetCAST in Excel spreadsheets (updated version, decimal point, in English, valid IS units, without any computation function to avoid transcription errors). The spreadsheet template will contain the following information, columns/header, including any useful comments:

- Origin of the data (Marketing authorisation holder of the exact VMP) and contact person
- Veterinary medicinal product administered (trade name) and its specific Marketing authorisation number
- Active ingredient(s)- quantitative and qualitative (names in internationally agreed form, e.g. INN, including the specification of the salt, ester and amount)
- Excipients (as listed in the product SPC)
- Pharmaceutical form: e.g. suspension for injection, tablets, concentrate for oral solution etc. European Pharmacopeia terms are recommended to be followed
- Batch number
- Date of drug administration
- Dose in mg/kg body weight/day (or other relevant interval e.g. 12 hours, if twice daily) or IU/kg body weight/day. Active ingredient should be specified as base/salt (accordingly with the composition of the product administered)
- Route (and site) of administration Route (- e.g. IM, IV, SC etc.), site (e.g. neck in the case of IM) and modality of administrations (in the case of oral administration e.g. by gavage, to have exactly specified dose obtained by the animals)
Guideline VetCAST PK analysis
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- For the IV route: bolus or infusion; indwelling catheter or not;
- Individual animal identification (ID)
- Breed
- Sex
- Age (in months or in years)
- Body weight (in kg)
- Feed, unfed, and nature of feed/food/milk....
- Health status (healthy vs diseased). If diseased, specify if there was concomitant medication that could have interfered with the PK of observed substance.
- Time of sampling, starting at time of dosing (min, h, days)
- Sampling modalities (sampling site, catheter or direct puncture, slaughter...)
- Sample storage conditions (temperature and time) with evidence supporting stability in frozen samples.
- Measured analyte(s) (e.g. prodrug, ester)
- Plasma or serum concentration with units, including, if available, total and free concentrations if systemic effect. If effect in a local compartment (e.g. in gut, with no systemic absorption), drug concentration in the relevant target tissue)
- Tabular presentation with appropriate format cells (text, numerical, appropriate number of decimal places...)
  - Numerical value or Below the Limit of Quantification (BLQ)
- GLP status of the study

Other useful information will be supplied as free text, as appropriate.

For each submission, a description of the analytical method will be required and should include:

- Detection mode: LC/MS, HPLC fluorometric, UPLC UV, or other
- Lower and upper limits of quantification (LLOQ and ULOQ) and Limit of Detection (LOD)
- Precision (CV% for intra- and inter- day variability)
- Whether there are metabolites that interfere with the quantification of the antimicrobial drug and any additional information, as appropriate
- Validation of the methods

Archiving of individual animal pharmacokinetic data

The data will be safely archived in a password protected hard drive, which will be the property of VetCAST. The raw PK information will not be divulged to external persons or bodies, but aggregated PK parameter estimates of data pooled from different sources will be made available on the EUCAST website. These aggregated data will be in line with the information already made publicly available in the Summary of Product Characteristics.
Analysis of individual animal pharmacokinetic data

1. Generating the database
Data will be initially scrutinised and graphical assessment will be performed to identify potential problems, errors or outliers. Plasma/serum concentrations below the lower limit of quantification (BLQ) will be retained in the dataset and flagged as BLQ.

Before data analysis by VETCAST, the consolidated Excel sheet, as prepared by VETCAST as “long-skinny” data sets i.e. ready for a contextual mapping in a population modelling program, will be reviewed by the data owner (e.g. company, university) and validated for that purpose.

Software
The VETCAST modellers will use suitable software for PK/PD modelling and Monte Carlo simulations, following population estimations. VETCAST will use Phoenix NLME. If necessary, another simulation program with the required specifications (spreadsheet-based application for predictive modelling, forecasting and simulation) will be used for other Monte Carlo simulations when required.

2. Population analysis
The goal of the population analysis is (1) to generate, by Monte Carlo Simulation, a population disposition curve and (2) to determine corresponding Probability of Target Attainment (quantiles) for the selected PK/PD index.

For PK analysis and reporting, VETCAST will follow general guidance, as described in the VETCAST position paper. Briefly, the development of a PK base model will include two steps: a Structural model development and a Statistical model development. In most instances, the final structural model will be kept as simple as possible. It will not include covariates for the fixed effects, because the ultimate objective is to determine a single PK/PD breakpoint, covering all types of animals for a given species. However, if possible from the data provided, some covariates will be explored to assess whether or not a single breakpoint value is acceptable for the establishment of a single clinical breakpoint for the investigated AST. These include demographic variables (e.g. breed for dogs or cattle, indicators of physiological status, e.g. pre-ruminant vs. ruminant, or health status, e.g. if the drug is intended for metaphylaxis vs curative treatment). In addition, relevance or not of a covariate will be considered for the writing of experts rules that will be released to assist clinical microbiologist in preparing their report to ensure the adequate and contextually correct interpretation of AST results.

Monte Carlo simulations (MCS)
Monte Carlo simulations will be performed for the proposed dose/dosage regimen, in the animal species of interest, to evaluate the expected Probability of Target Attainment (PTA %) taking into account the selected PK/PD index (T>MIC or AUC/MIC) and its breakpoint value(s). The PTAs will be computed by running at least 5,000 simulations, with a given initial seed, for each possible reported MIC value of the Wild-Type (sensitive) bacterial population. The PK/PD breakpoint will be set as the highest MIC value of the prediction interval for which PTA > 90%, and will be reported in the rationale document (see below).
1. Availability and reliability of MIC distributions from the VetCAST library
The MIC distribution will be statistically separated into wild-type distribution and resistant
distribution and the Epidemiological Cut-Off (ECOFF) will be determined using a published statistical
method (Turnidge, Kahlmeter et al., 2006). Company-generated MIC data will be collated, if
available.

2. Availability of plasma/serum protein binding data
Protein binding data over the range of plasma/serum concentrations encountered with clinical doses
will be required to bridge in vitro MICs and in vivo plasma/serum concentration data.

Reporting by VetCAST of the PK/PD breakpoint value supporting
the selection of the veterinary-specific clinical breakpoints in a
rationale document

For each antimicrobial drug catalogued by EUCAST, there is a linked document entitled “Rationale
for the EUCAST clinical breakpoints”. This document contains tables related to 1) dosages, 2) MIC
distributions, 3) breakpoints prior to harmonisation, 4) Pharmacokinetics, 5) Pharmacodynamics, 6)
Monte Carlo simulation and PK/PD breakpoints, 7) Clinical data, 8) Clinical Breakpoint. It is the intent
of VetCAST to produce similar rationale documents. Snapshots from the EUCAST rationale
documents are inserted below for illustrative purposes.

1. Dosage
In all cases, VetCAST will report the range of dosages used in different member states, following the
model set by EUCAST below. There is no confidentiality breach in publishing these data available in
the public domain.

Figure 1: most common disease, maximal dose and available formulation of a given antimicrobial
drug in 6 member states (BSAC: UK / CA-SFM: France / CRG: Netherlands / DIN: Germany / NWGA:
Norway / SRGA: Sweden).

<table>
<thead>
<tr>
<th>Dosage</th>
<th>BSAC UK</th>
<th>CA-SFM France</th>
<th>CRG Netherlands</th>
<th>DIN Germany</th>
<th>NWGA Norway</th>
<th>SRGA Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common dose</td>
<td>500 x 2 oral</td>
<td>500 x 2 oral</td>
<td>250 x 2 oral</td>
<td>600 x 2 oral</td>
<td>200-400 x 2 oral</td>
<td>500 x 2 oral</td>
</tr>
<tr>
<td></td>
<td>400 x 2 iv</td>
<td>200 x 2 iv</td>
<td>200 x 2 iv</td>
<td>200 x 2 iv</td>
<td>400 x 2 iv</td>
<td>400 x 2 iv</td>
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<tr>
<td>Maximum dose schedule</td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
<td>750 x 2 oral</td>
<td>tbc</td>
<td>750 x 2 oral</td>
</tr>
<tr>
<td></td>
<td>400 x 3 iv</td>
<td>400 x 3 iv</td>
<td>400 x 3 iv</td>
<td>400 x 2 iv</td>
<td></td>
<td>400 x 3 iv</td>
</tr>
<tr>
<td>Available formulations</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
<td>oral, iv</td>
</tr>
</tbody>
</table>
2. Aggregated susceptibility data

In each case, VetCAST will report the aggregated susceptibility data, as set by EUCAST below. The origin of the supplying laboratories will be kept anonymous, and there is no confidentiality breach in publishing these data.

Figure 2: MIC distributions and Epidemiological Cut-Off (ECOFF) for a sample of bacterial species for cefotaxime.

3. Aggregated pharmacokinetic summary data

In each case, VetCAST will report the aggregated PK summary based on the model set by EUCAST below. There is no confidentiality breach in publishing these data.

Figure 3: summary pharmacokinetic parameter estimates for cefotaxime published on the EUCAST website. Note that there is no display of individual plasma concentrations or data related to individual formulations.

4. Pharmacokinetics

| Dosage (mg) | 1000 x 3 iv |
| Cmax (mg/L) | 25-80 |
| Cmin (mg/L) | |
| Total body clearance (L/h) | |
| T ½ (h), mean (range) | 1-1.2 |
| AUC24h (mg.h.L) | 40-70 |
| Fraction unbound (%) | 60-67 |
| Volume of distribution (L/kg) | 0.2-0.3 |

Comments
- Two values are given where references differ. Cells are left empty when data are not readily available.
- The metabolite desacetylcefotaxime has 10% antimicrobial activity of the parent compound and has a half life of 2-4 hours.
- Peak serum concentrations are achieved in 30-60 min.

References
- Bryskier A. In Antimicrobial Agents 2005; ASM: 174
- Finch R. In Antibiotic and Chemotherapy 1997; Churchill-Livingstone: 235-6
- Kemenich et al., J Antimicrob Chemother 1983; 83: 425
- Standford et al., Rev Inf Dis 1982; 4 Suppl: S585
4. Monte Carlo simulation

The Probability of Target Attainment (%) for a given PK/PD index (e.g. the percentage of time during the inter-dosing interval for which free plasma/serum concentration remains above possible MICs) will be plotted against MIC possible values to permit graphical evaluation of the data. There is no confidentiality breach in publishing these data.

Figure 4: graphical representation of mean and 95% confidence interval of proportion of the inter-dosing interval for which plasma concentration exceeds MIC. A 2 log drop in viable Gram-negative organisms in animal model infections requires 40-50% fT>MIC. The 95% confidence interval of the 1 g dose administered by bolus intravenous injection results in a breakpoint of 1 mg/L.

References


