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Paracetamol Bioavailability Data Analysis

Practical 9 - Dataset-based practical

Aim

To calculate dose-normalised paracetamol bioavailability from a supplied animal-study teaching dataset.

Principle

Noncompartmental analysis estimates exposure from the concentration-time profile without first assuming a fixed compartmental structure. Terminal extrapolation requires a defensible terminal phase. IVIVC additionally needs an appropriate relationship between in-vitro release and in-vivo input or response; two similar-looking curves do not establish it.

Keep the supplied data, transformations, software version, analysis settings and complete output together. Record units explicitly and distinguish assumptions from observations.

Materials and Requirements

- Supplied concentration-time data, dose, route and subject identifiers
- Dissolution profiles where an IVIVC investigation is intended
- Spreadsheet or institution-approved analysis software
- Raw-data dictionary and analysis worksheet

Procedure

1. Define the analysis question and the variables, units, identifiers and missing-data conventions in the dataset.
2. Import a working copy and check values against the original file. Inspect ranges, duplicates, timing and unit consistency.
3. Map concentration, time, dose and subject columns and select the intended route and exposure calculation.
4. Inspect the profile and choose the integration method, terminal observations and treatment of below-quantitation values through the stated analysis plan.
5. Calculate Cmax, Tmax, AUC, terminal rate where justified, half-life and extrapolated fraction. Review terminal-fit diagnostics.
6. In WinNonlin or the selected implementation, preserve the model and settings report. For IVIVC, identify the development and validation datasets and the appropriate input-estimation method.
7. Retain diagnostics, intermediate calculations and the selected analysis settings. Explain exclusions and sensitivity checks.
8. Write a conclusion that addresses the stated question and the limitations of the design rather than relying on one fitted statistic.

Observations and Record

Enter actual measurements or the supplied teaching data. Record the method, material identity, conditions and units.

Parameter	Input or method	Calculated value	Diagnostic / units
Cmax and Tmax	Observed profile	Record	State units
AUC	Selected integration	Record	Check sampling
Terminal slope	Justified points	Record	Review fit

Parameter	Input or method	Calculated value	Diagnostic / units
IVIVC	Development and validation design	Record	State evidence

Calculations

- Linear trapezoid area = (C1 + C2)/2 x (t2 - t1)
- AUC_infinity = AUC_last + C_last/lambda_z, where terminal extrapolation is justified
- Half-life = ln(2)/lambda_z
- After extravascular dosing, dose/AUC estimates CL/F rather than true clearance unless F is known.

Worked Example

Illustrative oral profile: times 0, 1, 2, 4, 6 and 8 h; concentrations 0, 8, 4, 2, 1 and 0.5 mg/L.

Linear trapezoidal AUC to 8 h is 20.5 mg.h/L. The illustrated terminal decline from 2 to 8 h halves every 2 h, giving lambda_z = 0.3466 h^-1.

Tail area = 0.5/0.3466 = 1.443 mg.h/L; AUC_infinity is about 21.943 mg.h/L and half-life is 2.00 h.

A formal analysis uses adequate observations, prespecified methods and appropriate terminal-fit assessment.

Bioavailability record

- Use institution-supplied or explicitly simulated concentration-time data; the record does not require student animal dosing.
- Record study approvals, species, preparation, dose units, sampling plan and validated analytical method when reviewing a real authorised study.
- Illustrative dose-normalised AUC values are 0.18 and 0.24 exposure units per dose unit for oral and intravenous routes. Absolute bioavailability = 0.18/0.24 x 100 = 75.0%.

Result and Interpretation

- Report the exposure parameters and their data basis. Evaluate extrapolated exposure and the adequacy of terminal sampling.
- State separately whether an IVIVC was developed, tested or only proposed.

Precautions

- Do not mix concentration or time units.
- Distinguish observed from model-derived values.
- A regression between dissolution and plasma concentration is not automatically a validated Level A IVIVC.
- Preserve the original dataset and a reproducible record of the analysis.

Viva Questions and Answers

Why select the terminal phase carefully?

The selected slope affects half-life and extrapolated exposure.

What is CL/F?

Apparent clearance after an extravascular dose when absolute bioavailability is not established.

Why use separate IVIVC validation evidence?

The fitted relationship must predict data beyond the observations used to develop it.

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