# Reproducibility of Pharmacokinetic Parameters Using Different Input Functions in a Multi-Center Non-Expert Phase I Oncology Clinical Trial

V. Sharoyan[1], D. White[1], R. Sivaramakrishna[1], S. Galbraith[2], A. Guermazi[1], C. Reinhold[1], A. Padhani[1,3]

[1]Synarc, Inc., San Francisco, California, United States, [2]Bristol Myers Squibb Company, Princeton, New Jersey, United States, [3]Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, Middlesex, United Kingdom

**Introduction:** Quantitative modeling parameters such as transfer constant ($K^{trans}$) and IAUGC (initial area under the Gd-DTPA curve), rate constant ($k_{ep}$) and leakage space ($v_e$) are key pharmacodynamic indices that are measured in phase I studies of antiangiogenesis drugs using dynamic contrast enhanced MRI (DCE-MRI) [1]. These parameters are typically obtained using a multi-compartmental model analysis to the changing tissue contrast agent concentration. Knowledge of measurement reproducibility of these parameters is a requirement when assessing drug effects, so that true changes due to drug can be separated from spurious non-drug related changes. Reproducibility can be best assessed by measuring and comparing parameter values before treatment begins. The assessment of reproducibility is particularly important in multi-center studies because one can expect a wider variation in image quality, than from single-center data. The input plasma clearance function plays an important role in defining the reproducibility of these parameters. While individualized input functions offer the advantage of normalizing for variations in cardiac output they also have the disadvantage of being difficult to measure consistently. The purpose of this study was to compare the reproducibility of DCE-MRI kinetic parameters in a typical non-expert multi-center setting, using three vascular input functions (individualized input function derived from skeletal muscle, Fritz-Hansen coefficients, Weinmann coefficients) [2-4].

**Materials and Methods:** The data consisted of 6 pairs of pre-treatment DCE-MRI data from an ongoing multi-center phase I clinical trial. Three centers used 1.5T MR systems and similar measurement approaches: multi-slice $T_1$weighted dynamic scans with apre-contrast proton density reference image and 0.1mmol/kg Gd-DTPA injected iv. Quality assurance and quality control procedures were specified by an imaging clinical research organisation and were identical for all centers. ROIs were traced manually around the tumor using subtraction images appropriately windowed to display clearly enhancing tumor edges. ROIs were also placed in skeletal muscle close to the tumor at near-identical anatomical locations on each patient's paired dataset.

The pharmacokinetic (PK) analysis was performed by specifying input plasma clearance coefficients for three independent scenarios: (a) Individualized values deconvolved from the muscle ROI as described by Kovar et al [4], which were generated with Weinmann default inputs. This scenario is referred to as "muscle-normalized"; (b) Default values in accordance with data reported by Fritz-Hansen; and (c) Default values in accordance with data reported by Weinmann [2,3].

The Bland-Altman approach [5,6] was used to assess the repeatability of PK parameters for the three scenarios. The following statistics were generated: overall mean for averaged data, repeatability coefficient (r) in % which represents the range beyond which differences are considered statistically significant and within patient coefficient of variability (wCV).

**Results:** The tables below indicate the reproducibility statistics for the different PK parameters for the 3 scenarios. The results indicate that (b) and (c) scenarios have a smaller repeatability range and wCV values compared to those for scenario (a). For $K^{trans}$ and $k_{ep}$, the r% mean range for (b) is substantially smaller than that for (c). For $v_e$ and IAUGC, the r% mean range values are comparable. The

| Plasma input function coefficient measurement | $K^{trans}$ ($min^{-1}$) | | | $k_{ep}$ ($min^{-1}$) | | | $v_e$ (%) | | | IAUGC ($mMols.sec^{-1}$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | mean | r% mean | wCV | Mean | r% mean | wCV | mean | r% mean | wCV | mean | r% mean | wCV |
| (a) Muscle normalized[4] | 0.719 | -91.5 - 1074.8 | 143.4% | 1.511 | -88.9 - 802.1 | 121.2% | 0.453 | ±71.2 | 25.7 | 18.872 | ±61.6 | 22.2% |
| (b) Fritz-Hansen[3] | 0.483 | -63.1 - 171.2 | 43.4% | 0.846 | -66.5 - 198.3 | 48.4% | 0.588 | ±27.0 | 9.8% | 17.473 | ±53.6 | 19.4% |
| (c) Weinmann[2] | 1.573 | -79.1 - 377.9 | 75.9% | 2.907 | -79.3 - 383.6 | 76.6% | 0.548 | ±26.7 | 9.6% | 16.349 | ±48.1 | 17.4% |

same is observed for wCV values. This suggests that both scenarios (b) and (c) will be preferable for analysis compared to scenario (a). Furthermore, scenario (b) appears to be preferable over scenario (c).

**Conclusion** Our analysis indicates that Fritz-Hansen coefficients demonstrate the best reproducibility compared to Weinmann coefficients and muscle normalization in the clinical setting of a multicenter clinical trial. We are unable to show an advantage for individual vascular input function using muscle as the source for normalisation. The benefit of using the Fritz Hansen approach may be in part due to a more physiological description of the vascular input function. We are currently investigating whether the sensitivity to treatment related change is altered by employing the Fritz Hansen approach.

**References**

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