Single and multi-centre DCE-MRI reproducibility in Phase I clinical trials

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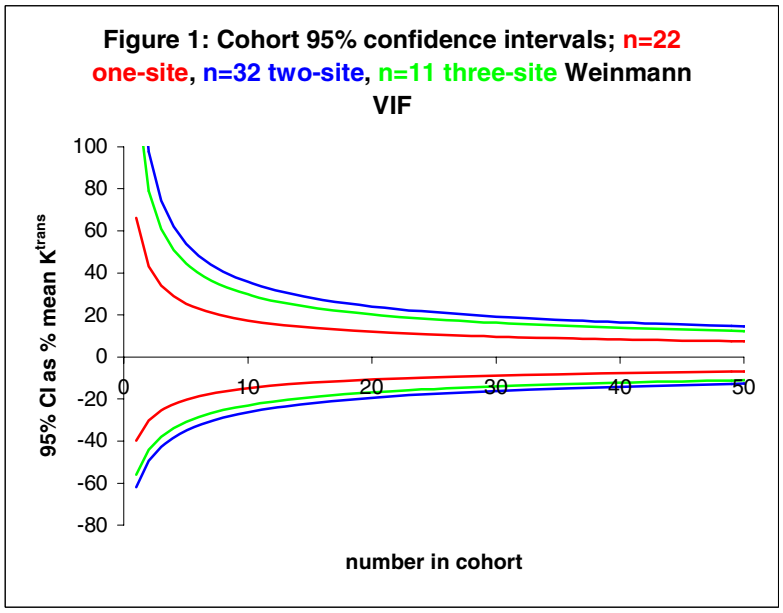
Introduction: The measurement of test-retest variability is an integral part of phase I study design where dynamic contrast enhanced MRI (DCE-MRI) is used to evaluate the effect of antiangiogenesis and angiolytic drugs on tumour vasculature [1]. The key recommended primary kinetic parameters in this evaluation are transfer constant (K^{trans}) and initial area under the gadolinium curve (IAUGC). The measurement of kinetic parameter reproducibility enables investigators to define the level of change that would be statistically significant (for a single patient and for dosing cohorts). This information can then be used to identify a biologically active dose to take into clinical studies with efficacy endpoints. Literature reproducibility data show wide variability, part of which is ascribed to the number and experience of the imaging centres. In this study, we compared single and multiple centres performing DCE-MRI studies. The primary motivation for this study was to identify the change in K^{trans} that would be significant for a single patient and for typical Phase I dosing cohort sizes of 3 and 6 patients.



Number of patients	1 centre (study A)	2 centres (Study B)	3 centres (Study C)
1	-39.8 to 66.0%	-61.9 to 162.2%	-55.7 to 125.7%
3	-25.4 to 34.0%	-42.7 to 74.4%	-37.8 to 60.8%
6	-20.3 to 25.4%	-32.5 to 48.2%	-28.5 to 39.9%

Table 1: K^{trans} 95% confidence intervals for cohorts of 1,3 and 6 patients for studies A, B and C

Methods and results: The data from DCE-MRI reproducibility studies carried out as part of Phase I clinical trials of antiangiogenesis drugs were evaluated. The following datasets were examined: Single-centre study with 22 patients (study A); two-centre study with 32 patients (study B) and three-centre study performed in 11 patients (study C). All centres used 1.5T MR systems and similar measurement approaches; multi-slice T_1weighted dynamic scans with a proton density reference image and 0.1mmol/kg Gd-DTPA. The quality assurance and quality control procedures were identical for 3 studies. Regions of interest were drawn by an experienced observer working independently (for study B; an additional experienced radiologist performed some of the ROI drawings). All data were analysed with MRIW software (ICR, London) using the pharmacokinetic model of Tofts with the vascular input function described by Weinmann et al. [2,3]. Tumour data were acquired on two occasions pre-treatment and used to calculate transfer constants (K^{trans}) for the whole tumour ROI from 3-4 slices. Data were transformed by natural logarithm when the mean difference between each pair of examinations was proportional to their means [4]. Using the actual values from each study we were able to compute the repeatability parameter (r) (expressed as a % of the mean) and the 95% CI for change in *n* patients for increasing number of patients [5]. This is shown in Figure 1. The 95% CI values for typical cohort sizes of 1, 3 and 6 are given in the Table.

We noted that the performance of study A was better than study B or C. The % fall in K^{trans} that is significant was least for the single centre study. There were no significant differences between the performance of studies B and C. Although the study centres are not specifically identified for this evaluation it should be noted that the study A centre did take part in study B but study C did not include either of the study A or B centres.

Discussion: This study has compared "real world" DCE-MRI reproducibility data performed in support of Phase I clinical trials of antiangiogenesis/angiolytic drugs and we have shown greater variability when the number of imaging centres increases. This apparent deterioration is expected in multicentre studies due to a number of complex factors relating to patient selection, quality control and quality assurance procedures. This degree of variability should be taken into account when planning Phase I clinical trials which employ an escalating dosing schedule for toxicity determination because the numbers of patients scanned at a given dose level is often very small (typically 3 per dosing cohort in single centre and 6 in multicentre) due to ethical considerations. If the magnitude of change in blood flow for an antiangiogenesis/angiolytic drug is expected to be small then single centre studies are recommended where possible. For multi-centre studies, high-quality QA and QC procedures are essential to minimise variability.

References

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