^{19}F MRS measurement of tumour pharmacokinetics of SR4554, a 2-nitroimidazole hypoxia probe.

Seddon BM[1], Maxwell RJ[2], Honess DJ[2], Grimshaw, R[1], Raynaud, F[1], Workman P[1].
[1]CRC Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, [2]Gray Laboratory Cancer Research Trust, Northwood, Middlesex, UK.

Introduction

Tumour hypoxia is known to predict for poor outcome in clinical studies of tumour treatment. Ability to identify tumour hypoxia is therefore important for determination of prognosis and for patient selection for hypoxia-modifying/dependent therapeutic strategies. SR 4554, a novel fluorinated 2-nitroimidazole compound, has been developed for use as a non-invasive probe for detection of hypoxic cells by ^{19}F MRS.

We describe a pharmacokinetic study performed to investigate the variation over time in MRS-detected fluorine signal obtained from tumour (indicating presence of SR 4554) following systemic administration of SR 4554. Concentrations of SR 4554 in tumour derived spectroscopically, and in plasma and tumour detected by HPLC analysis, are compared. A parameter of tumour hypoxia, the fluorine retention index, is calculated. We have used the relatively well oxygenated P22 carcinosarcoma tumour model to provide a reasonable approximation to the oxygenation status of human tumours (known to be less hypoxic than rodent tumours and human tumour xenografts).

Methods

Tumour-bearing mice (n=5) were injected with SR 4554 intraperitoneally at a dose of 180mg/kg. Animals were non-anaesthetised, and were restrained in plastic jigs. A surface coil (13mm diameter) was positioned over the tumour, and the animal was placed in a 4.7T MR spectrometer (Varian). A reference bulb containing 3-trimethylsilyl tetra-deutero-sodium proprionate and 5-fluorotryptophan was placed adjacent to the tumour.

Signal was acquired continuously for up to 5 hours using a pulse-acquire sequence with a TR of 4 seconds in blocks of 64 averages. Signal intensity was calculated (using 128 averages over 8.5 minutes) to produce a time course of the ^{19}F signal variation over time. Concentration of SR 4554 in the tumour was estimated by use of a double-tuned (^{19}F/^{2}H) circuit technique, comparing natural abundance deuterium signal from tumour with deuterium signal from the reference bulb, and fluorine signal from the tumour with fluorine signal from the reference bulb.

Simultaneously, tumour-bearing animals received SR 4554 at a dose of 180mg/kg and were placed in jigs. Animals were sacrificed at time points of 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7 and 24 hours; tumours and plasma were rapidly removed and immediately frozen at -70°c. HPLC analysis was performed on these samples to determine the concentration of SR 4554 present in tumour and plasma (4 – 6 animals per time point).

Results

The MRS time course shows that the mean (+/-SD) peak concentration of SR 4554 in tumour following intraperitoneal injection is 0.39 (+/-0.12) mM, occurring at a mean (+/-SD) time of 72 (+/-17) minutes. The mean (+/- SD) half-life is 80 (+/-39) minutes. Highest measured plasma levels of SR 4554 (detected by HPLC analysis) are observed at the 30 minute time point and fall to less than 5% of the peak value by 3 hours.

A fluorine retention index (FRI), indicating degree of retention of SR 4554 by tumour and therefore degree of tumour hypoxia, can be derived by calculating the ratio of concentration of SR 4554 present at a particular time point to the concentration of SR 4554 present at 45 minutes. The mean 2 hour, 3 hour and 4 hour FRIs are 0.89, 0.45 and 0.40 respectively. Examination of individual FRIs indicates variability of SR 4554 retention in this tumour model.

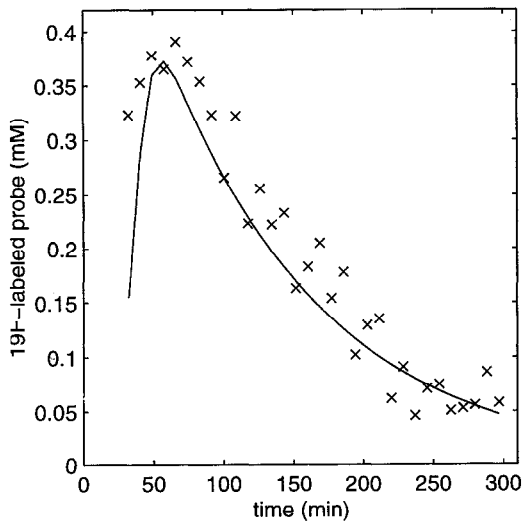

Figure 1. Pharmacokinetics of SR-4554 in P22 adenosarcoma.

Discussion

This study has demonstrated the ^{19}F MRS tumour time course of fluorine signal from SR-4554 in non-anaesthetised mice bearing the P22 carcinosarcoma, a tumour model closely resembling human tumours in terms of its oxygenation profile. Retention indices have been derived at a number of time points. This information will be used in the planning of a phase I study of SR 4554 in humans .

References

1. Aboagye, E.O. et al., Cancer Res. **57,** 3314-3318 (1997)