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SHORT COMMUNICATION

SOLLID – a single centre study to develop methods to investigate the effects of low radiation doses within nuclear medicine, to enable multicentre epidemiological investigations

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ABSTRACT

There is continuing debate concerning the risks of secondary malignancies from low levels of radiation exposure. The current model used for radiation protection is predicated on the assumption that even very low levels of exposure may entail risk. This has profound implications for medical procedures involving ionising radiation as radiation doses must be carefully monitored, and for diagnostic procedures are minimised as far as possible. This incurs considerable expense. The SOLLID study (ClinicalTrials.gov Identifier: NCT03580161) aims to develop the methodology to enable a large-scale epidemiological investigation of the effect of radiopharmaceutical administrations to patients undergoing diagnostic nuclear medicine procedures. Patients will undergo a series of scans in addition to that acquired as standard of care to enable the radiation doses delivered to healthy organs to be accurately calculated. Detailed analysis will be performed to determine the uncertainty in the radiation dose calculations as a function of the number and type of scans acquired. It is intended that this will inform a subsequent long-term multicentre epidemiological study that would address the question definitively. Secondary aims of the study are to evaluate the range of absorbed doses that are delivered from diagnostic nuclear medicine procedures and to use current risk models to ascertain the relative risks from these administrations.

INTRODUCTION

There remains considerable debate concerning the risks of malignancies from low levels of radiation exposure, whether from occupational exposures, nuclear incidents or from medical exposures.[1,2] The current paradigm for all medical, occupational or public exposures is to maintain radiation doses 'as low as reasonably achievable, economic and societal factors being taken into account' (ALARA), based on the 'Linear-no-Threshold' model for radiation protection.[3] This assumes that even very low levels of radiation exposure can cause secondary malignancies. This model has significant implications for diagnostic medical procedures involving radiation due to the potential health risks to patients, the obligation to communicate that risk, the costs of providing radiation protection and the impact on optimising the balance between the levels of activity administered and the duration of scans. Although studies have investigated risks from low levels of exposure over previous decades[4] no studies have as yet investigated the risk within the context of nuclear medicine across multiple centres.

The Simplification of Low Level Internal Dosimetry (SOLLID) study is a single centre, prospective, non-interventional pilot study. The overall aim is to evaluate the potential to investigate this issue within nuclear medicine. Over 600,000 diagnostic and therapeutic nuclear medicine oncological and non-oncological procedures are performed each year in England.[5] Procedures are performed following administrations of standard levels of radiotracers that may

be modified by patient weight. Average radiation absorbed doses delivered in these procedures are available from International Commission on Radiological Protection (ICRP) publications.[6,7] These are calculated using kinetic models derived from limited data, often obtained from a very small cohort of patients or from animal studies. While these values are sufficient to satisfy regulations, there is abundant evidence from dosimetry studies with therapeutic radiopharmaceuticals that the interpatient variation in the absorbed doses delivered to healthy organs from a fixed level administration of a radionuclide can vary by up to 2 orders of magnitude.[8] It is a reasonable assumption that a similar range of radiation dose levels will exist for diagnostic studies although it is accepted that data are scarce.[7,9] The effective dose delivered from an administration of ^{18}F-FDG has been shown to range from 0.0132 to 0.0291 mSv/MBq.[10] The effective dose delivered from a ^{68}Ga-PSMA scan has been reported as ranging from 0.0108 to 0.0246 mSv/MBq.[11] To our knowledge, the range of absorbed doses delivered from ^{99m}Tc MDP scans has not been calculated.

TRIAL DESIGN

The aim of the SOLLID study is to develop the methodology to enable a large-scale epidemiological investigation of the effect of radiopharmaceutical administrations to patients undergoing diagnostic nuclear medicine. Radiation dosimetry will be performed from a series of scans following administration in addition to the standard of care scan that is routinely acquired. This will enable the effective half-life of decay to be measured. The primary end point of the study is to determine the uncertainty on the absorbed doses calculated to normal organs and the whole-body (WB) as a function of the number of scans and WB counts acquired.

The secondary end points are to determine the range of doses delivered to normal organs. Seven diagnostic procedures will be studied: ^{99m}Tc-MDP bone imaging, ^{99m}Tc-DMSA kidney function, MAG3 renograms, ^{99m}Tc-Pertechnetate thyroid imaging and PET imaging using ^{18}F-FDG, ^{68}GaPSMA and ^{68}Ga DOTATATE (Table 1). Five patients will be recruited for each procedure, totalling 35 patients. A further exploratory end point is to determine the range of risk estimates for the development of secondary cancers associated with these procedures, based on the absorbed doses delivered.

Imaging regimens for SOLLID were developed to obtain the optimum information on tracer kinetics. For PET investigations, patients are imaged up to five times following intravenous injection of the PET tracer. A single bed position dynamic PET/CT image of the myocardium is acquired for 4 min, followed by a 40 min half-body dynamic whole body scan. WB measurements using a ceiling-mounted scintillation detector are acquired to determine radioactive excretion from the first and subsequent bladder voids. The clinical PET/CT scan is acquired at 1 h followed by further imaging at 2 and 4 h post-administration.

The most demanding imaging regimen is the Tc99m-MDP bone scan, for which patients are imaged up to seven times following intravenous injection of the tracer. A single field-of-view (FOV) dynamic image of the pelvis and kidneys is acquired for 30 min, followed by WB counting pre- and post-bladder voiding. WB imaging is performed at 1, 2, 3, 4, 5 and 24 h and a WB single photon emission tomography (SPECT)/CT performed at 3.5 h. Between each WB acquisition, further WB counting is performed to determine tracer excretion.

DOSIMETRY DATA

Organ segmentation is performed using the CT images. Quantification of SPECT and PET data is performed using recovery coefficients derived from phantom experiments, whereby known concentrations of activity for each of the radionuclides under investigation are imaged in a series of spheres of increasing diameters. This approach has been used successfully for a multicentre trial to evaluate the absorbed doses delivered to patients undergoing radioiodine treatments for thyroid cancer.[12] Radioisotope concentration in the relevant organs is plotted as a function of time and exponential functions are fitted to the data to model the biokinetics using non-linear regression and F-Test statistics. Time integrated activity for each organ is determined by

Table 1. Scanning procedures for the SOLLID study

	Tc-99m MDP	Tc-99m DMSA	MAG3 (renogram)	Tc-99m Pertechnetate	F-18 FDG	Ga-68 DOTATATE	Ga-68 PSMA
Use	Bone imaging	Kidney Imaging	Kidney Imaging	Thyroid imaging	Disease metabolism	Neuroendocrine tumour imaging	Metastatic Prostate Cancer imaging
Dynamic imaging	30 min over pelvis		30 min over kidneys and bladder		4 min over heart	4 min over heart	4 min over heart
Static γ camera imaging	5 WB sweeps up to 24 hours p.i.	Five images of abdomen up to 24 hours p.i.	Five images of abdomen up to 24 hours p.i.	5 WB sweeps up to 24 hours p.i.			
Tomographic imaging	SPECT/CT at 3 h p.i.	SPECT/CT at 2 h p.i.	SPECT/CT at 2 h p.i.	SPECT/CT at 3 h p.i.	6 x PET/CT up to 4 hours p.i.	6 x PET/CT up to 4 hours p.i..	6 x PET/CT up to 4 hours p.i.

DMSA, dimercaptosuccinic acid; PET, photon emission tomography; SOLLID, Simplification of Low Level Internal Dosimetry; SPECT, single photon emission tomography; WB, whole-body.

integrating the fitted functions. Patient-specific organ absorbed doses are then generated using the MIRD schema and reference S-values from OLINDA/EXM and IDAC dosimetry software.[13,14] Patient-specific organ S values will also be determined using mass-adjusted values.[15] Uncertainty analysis, subject to increasing research,[16] will be based on European Association of Nuclear Medicine (EANM) guidelines.[17] The variation in absorbed doses calculated using different subsets of scan acquisitions will be investigated to identify the minimum number of scans required to achieve statistically significant results.

STUDY POPULATION

Trial subjects will be over 18 years and male or female. Pregnant females will be excluded. Each subject will have been referred for the relevant nuclear medicine scans and must have satisfied the inclusion criteria for those scans. They must also be willing and able to undergo the extra procedures necessary to acquire sufficient data for the dosimetry calculations. This may entail up to 7 nuclear medicine scans and 10 activity retention measurements in the 24 h following administration of the radiopharmaceutical.

PUBLIC PATIENT INVOLVEMENT (PPI)

To obtain the most accurate dosimetry in a small patient cohort, a relatively demanding scanning schedule is asked of patients. In addition, the effects of radiation are often poorly understood and risks from exposure may be greatly under- or overestimated.[18] PPI is therefore a key element in all aspects of the study and imaging protocols were developed with the involvement of patient representatives. A patient forum was organised to discuss the methodology of the study, to consider how best to communicate the rationale and hypotheses underlying the study, and to ascertain the impact of the scanning schedules required. The trial was costed in line with INVOLVE guidelines.[19] Prior to the study commencing a patient volunteer was asked to undergo the full procedure without an administration in a 'dummy run', to identify any details to be addressed. Patients enrolled on the study are asked to complete a questionnaire to record their comments and suggestions. These data will inform future study design.

OUTCOMES AND FUTURE AIMS

For each of the seven imaging procedures, the following will be calculated: (i) effective dose to whole body (mSv), with associated uncertainties, (ii) the absorbed dose delivered to individual organs (mGy), with associated uncertainties, (iii) the increased uncertainty as a function of the extent of data acquisition.The trial will identify the minimum number of scans and measurements required to enable accurate dosimetry to be performed and will highlight particular studies that will be more or less suitable for continued investigation. Taken in conjunction with patient feedback a protocol for a large-scale multicentre epidemiological study will be developed, focussed on nuclear medicine diagnostic imaging.

DISCUSSION

The European Basic Safety Standards directive, incorporated into national regulations including the UK Ionising Radiation (Medical Exposure) Regulations (IR(ME)ER), mandate communication of risk to patients from diagnostic exposures.[20,21] Current risk estimates from medical examinations involving ionising radiation have been extrapolated from data obtained from the nuclear bombs dropped in WW2 and from nuclear incidents, which entailed high levels of exposure.[22] There are increasing arguments that the LNT model may overestimate the effect of low levels of radiation.[23]

The CT component of the procedures will enable attenuation corrected organ dosimetry with anatomical outlining. These will deliver radiation doses that may be of the order of those delivered from the SPECT and PET scans and must be taken into account for the calculation of effective doses.

It is intended that this study will inform a subsequent multicentre epidemiological investigation into the effects of low levels of radiation exposure by evaluation of the absorbed doses delivered and by monitoring primary and secondary outcomes. In recent years, two networks have been developed to perform multicentre studies of quantitative imaging of I-131 for the treatment of thyroid cancer. The 'Selimetry' study has investigated the use of the MEK inhibitor selumetinib to enable possible re-treatment of iodine refractory patients in eight UK centres[12,24–26] and the EU funded 'Medirad' study is currently underway in four centres in Germany, France and the UK.[27] Both studies have entailed characterisation of γ cameras for sensitivity, recovery coefficients and dead-time using phantom studies and site visits. Data transfer, archiving, and centralised image processing have been set up to ensure that dosimetry data may be acquired and collated from different centres. An improved understanding of the effect of low levels of radiation exposure will lead to more cost-effective practice in radiation protection.This would enable optimised activities to be used for nuclear medicine procedures that may in turn improve diagnostic accuracy.

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