Dosimetric Assessment of ^{51}Mn- and ^{52}Mn-chloride as Potential Tracers in Multimodality Imaging (MMI)

L. De Nardo[1,2], A. Zorz[2,5], M. Paiusco[2,5], D. Cecchin[2,6], M. Bello[1,3], N. Uzunov[3,4], J. Esposito[3], L. Meléndez-Alafort [5]

1 Dipartimento di Fisica e Astronomia, Università di Padova, Padova, Italy.
2 INFN, Sezione di Padova, Padova, Italy. 3 INFN, Laboratori Nazionali di Legnaro, Legnaro (Padova), Italy.
4 Faculty of Natural Sciences, University of Shumen, Shumen, Bulgaria.
5 Istituto Oncologico Veneto IOV-IRCCS, Padova, Italy. 6 Dipartimento di Medicina dell'Università di Padova, Padova, Italy.

INTRODUCTION

Multimodality imaging (MMI), a combination of several imaging modalities using different physical techniques, is becoming increasingly common in medical physics, as it may help to overcome the limitations of the single methods. For example, when combining PET (*Positron Emission Tomography)* or SPECT (Single Photon Emission Computed Tomography) and CT (*Computed Tomography)* imaging, the low resolution of the PET or SPECT image is compensated with the high resolution of CT image. Besides, MMI allow to pair functional and molecular information, obtained by PET or SPECT, with anatomical information acquired using imaging techniques such as CT and MRI. While functional imaging through PET or SPECT always requires the administration of a radiolabeled tracer, anatomical imaging through MRI or CT involves administration of a contrast agent to achieve the highest signal to noise ratio. However, so far radiolabeled tracer and contrast agent have always different chemical composition and therefore different biological pathways which could lead to an imaging mismatch. To achieve a genuine fusion between functional and anatomical imaging, the contrast and radioactive agents should be chemically identical. It is therefore interesting to seek for an element possessing paramagnetic properties, useful as an MRI contrast agent, and at the same time having radioactive isotopes suitable for PET imaging. These requirements are met by the transition element manganese, possessing both paramagnetic properties and β^+-emitting radioisotopes, such as ^{52}Mn ($t_{1/2}$= 5.591 d, β^+= 29.6%, $E(\beta^+)_{avg}$= 244.6 keV), ^{52m}Mn ($t_{1/2}$= 21.1 min, β^+=96.6%, $E(\beta^+)_{avg}$ = 1179 keV) and ^{51}Mn ($t_{1/2}$= 45.59 min, β^+=97.1%, $E(\beta^+)_{avg}$ = 970.2 keV). For this reason, experimental studies concerning ^{52}Mn/^{51}Mn production by cyclotrons were prompted within the framework of the Multimodal PET/MR Imaging with Cyclotron-produced $^{52/51}$Mn and stable paramagnetic Mn iSotopes (METRICS) research project, led by the Legnaro National Laboratories at the National Institute for Nuclear Physics, Italy (LNL-INFN). Aim of this project is the investigation of different production routes for these radioisotopes and the optimization of the proper radiochemical separation methods, but also the development of new Mn(II)-complexes to be employed both for PET and MRI. Main goal of this work is to investigate the suitability of $MnCl_2$ for diagnostic imaging, based on internal dose calculations due to injection of this radiopharmaceutical as pure inorganic compound, marked with both ^{52}Mn and ^{51}Mn radioisotopes.

MATERIALS AND METHODS

Biodistribution data in healthy mice after $^{52}MnCl_2$ injection reported by Hernandez et al. [1] as percent of injected activity per gram of tissue in major sources organs (heart, liver, kidneys, muscle, pancreas and salivary gland) as function of the time (from 1 to 13 days) appear the most complete between those published so far in literature and were used to calculate the organ doses and the effective dose potentially received by a human subject after injection of radioactive $MnCl_2$. These data were scaled from mice to human through the relative mass scaling method [2], plotted as function of the time post injection and fitted by a tri-exponential equation to obtain the organ activity curves. The number of disintegrations in the source organs was then calculated by integration of these curves using CoKiMo software [3] and taking into account the physical half-lives of ^{52}Mn and ^{51}Mn. Activity in the non-source organs was obtained by subtracting the number of disintegrations in the source organs to the total number of disintegrations in the body caused by the $MnCl_2$ injection. The total number of disintegrations in the body was calculated in two different ways, by a conservative estimation, assuming only radioactive decay, and with an estimation based on the human biological clearance (BC) stated by Mahoney et al. [4] after intravenously injecting ^{54}Mn in man. Mahoney found that Mn is cleared from the body by two exponential components: about 70% of the injected material was eliminated by a "slow" pathway with a biological half-time of 45 days and the rest through a "fast" pathway, with a half-time of 4 days. Dose calculations based on the RADAR method [5] have been performed with the OLINDA (Organ Level INternal Dose Assessment) 1.1 and 2.0 software codes [6-7]. The OLINDA code version 1.1 makes use of anthropomorphic phantoms based on the Oak Ridge models, which employ geometrical shapes to define the organs and calculates the effective dose equivalent (EDE) and the effective dose (ED) using the tissue weighting factors recommended by ICRP 26 [8] and ICRP 60 [9], respectively. In version 2.0, the geometrical models were replaced by the realistic

NURBS-type models, based on the recent standardized masses defined by the ICRP 89 [10], and the ED is calculated using the new tissue weighting factors recommended by ICRP 103 [11].

Table 1. Values of EDE and ED (mSv/MBq) calculated for $^{51}MnCl_2$ and $^{52}MnCl_2$ with the OLINDA v1.1 and v2.0 software for male and female ORNL and ICRP 89 phantoms and based on the ICRP 26, 60 and 103 (BC= biological clearance).

		Male		Female	
		Without BC	**With BC**	**Without BC**	**With BC**
$^{51}MnCl_2$	**EDE (ICRP26)**	1.65 E-02	1.65 E-02	2.13 E-02	2.12 E-02
	ED (ICRP60)	1.10 E-02	1.09 E-02	1.41 E-02	1.41 E-02
	ED (ICRP103)	1.03 E-02	1.03 E-02	1.38 E-02	1.38 E-02
$^{52}MnCl_2$	**EDE (ICRP26)**	2.32	1.79	2.81	2.18
	ED (ICRP60)	2.15	1.62	2.58	1.95
	ED (ICRP103)	1.74	1.35	2.31	1.79

RESULTS

Due to the short physical half-life of ^{51}Mn, absorbed doses originating from $^{51}MnCl_2$ calculated with the two different hypotheses concerning the activity in the remaining organs are very similar (Table 1). As regards to the dose received by the main organs, it was established that the critical organs are the kidneys, followed by the pancreas and the liver, both for male and female phantoms. In the case of ^{52}Mn, organ absorbed doses calculated without BC were 15 to 35% higher than the values obtained contemplating BC. Therefore, ED values for both male and female models increase about 30% when biological removal was not considered. In the case of ^{52}Mn, the critical organ was the pancreas, followed by the kidneys and liver. For both isotopes ED values calculated with Olinda 1.1 using the ORNL phantoms, were higher than the ED calculated with Olinda 2.0 using the ICRP 89 phantoms, especially for males. This result can be explained by the fact that the adult male ORNL phantom is indeed hermaphroditic [12]; then, the presence of female organs such as ovaries, uterus, and breasts in the ORNL phantom can contribute to the increment of effective dose values when Olinda 1.1 is used. The female effective doses calculated for both isotopes (^{51}Mn and ^{52}Mn) are indeed about 30% higher than male ED. This result is in agreement with those reported for other radiopharmaceuticals [13].

CONCLUSIONS

This work demonstrates that the biological half-life of manganese radioisotopes has a significant impact on their effective half-life and a strong influence on the dose assessment in the case of radioisotopes with a long physical half-life, like ^{52}Mn. It was also shown that, for an accurate radiopharmaceutical dose assessment, it is crucial to use the most improved human phantoms currently available and to apply the latest tissue-weighting factors.

This work demonstrates that, while for ^{51}Mn ED is comparable to that of ^{18}FDG (0.0192 mSv/MBq; gender-averaged value)[5], the calculated ED value corresponding to ^{52}Mn is about two orders of magnitude higher, due to the large ratio of high-energy gamma emissions (744 keV, 936 keV, and 1434 keV) per each β^+ particle. However, it has to be outlined that the effective dose due to ^{52}Mn-chloride is not quite different from the one reported for ^{89}Zr ($t_{1/2}$ = 3.3 d; 23% positron emissions: $E(\beta^+)_{avg}$ =396.9 keV; spontaneous gamma decay= 908.97 keV) which, conjugated to the trastuzumab protein, is currently being used in clinical studies [14-15], as well as for ^{124}I ($t_{1/2}$ =4.2 d; 23% positron emission: $E(\beta^+)_{avg}$=819 keV; 602 keV gamma emission) [16]. Besides, ^{52}Mn has the advantage over ^{51}Mn to provide higher PET image resolution (0.63 mm vs. 2.9 mm) [17] due to the lower positron energy. This potentiality should be exploited by labelling receptor-specific molecules that could improve its pharmacokinetic properties. Such preliminary work is the starting step towards future dosimetric assessment studies on new (and more interesting) Mn-carriers now under developments.

[1] R. Hernandez et al., Diabetes 66, (2017) 2163.
[2] Sparks, R., Aydogan, B., Sixth International Radiopharmaceutical Dosimetry Symposium (1999) 705
[3] L. Meléndez-Alafort et al., Comptes Rendus L'Academie Bulg. des Sci. 70 (2017) 1649
[4] J.P.Mahoney, W.J. Small, J. Clin. Invest. 47 (1968) 643
[5] M.Stabin, J.A. Siegel, J. Nucl. Med. 59 (2017) 154.
[6] M.Stabin, A.Farmer, J. Nucl. Med. 53(2012)585.
[7] M.Stabin, R.B.Sparks, E.Crowe, J Nucl Med 46 (2005) 1023.
[8] ICRP Publication 26 (1977)
[9] ICRP Publication 60 (1991)
[10] ICRP Publication 89 (2002)
[11] ICRP Publication 103 (2007)
[12] M.Cristy, K.F. Eckerman, Ornl/Tm-8381 V1-V7 (1987)
[13] M.G.Stabin, Environ Health Perspect 105 (1997) 1403.
[14] F.Bensch et al., Eur. J. Nucl. Med.Mol.Imag.45 (2018) 2300.
[15] R.Laforest et al., Mol Imaging Biol 18(2016) 952.
[16] C.A.Foss et al., J Nucl Med 59 (2018) 1751.
[17] M.Pagani et al., Eur J Nucl Med 24 (1997) 1301.