NUCLEAR MEDICINE IN THE MANAGEMENT OF (NEURO)ENDOCRINE TUMOURS

K.Peremans, C.Van de Wiele

Faculty of Veterinary Medicine, Ugent, Salisburylaan 133, 9890 Merelbeke, Belgium

Kathelijne.peremans@ugent.be

University Hospital, Ugent, Ghent, Belgium

Christophe.vandewiele@ugent.be

Several imaging techniques may be involved in both diagnosis and staging of (neuro)endocrine tumours, each with competing or complementary diagnostic power. Nuclear imaging modalities have the capacity to evaluate viability and metabolism of tissue and offer the possibility to image the whole body in search of metastases in a relative short acquisition time. Depending on the decay mode of the injected radionuclide (positron emitting or gamma photon emitting radioisotopes) single or multiple head gamma cameras or PET (positron emitting tomography) cameras are used for imaging purposes. A specific class of radionuclides, which decay with emission of particle radiation (Auger or conversion electrons, alpha and beta particle emission), is used for therapeutic purposes.

Uptake and accumulation of radiopharmaceuticals depend on several physiological processes. First, perfusion has to be intact to give the tracer access to certain organs. Once on the spot, the uptake by cells will depend on simple or facilitated diffusion, active transport (via the ATP-ase dependent Na/K pumps or utilization of an electrochemical gradient) or binding to antigens or receptors. When the radiopharmaceutical is inside the cell, accumulation may occur through binding with intracellular organelles, incorporation in vesicles or cellular molecules, or by enzymatic conversion to an irreversible trapped compound. Uptake and retention of the radiopharmaceutical in tumour cells is altered compared to normal cells, due to altered perfusion within the tumour, increased rate of proliferation and metabolism, altered membrane transport and increased expression of specific receptors or specific tumour antigens. This results in different uptake of radioactive markers in tumour tissue compared to normal cells allowing recognition of the latter on images. It has to be born in mind that all radiopharmaceuticals follow a physiological distribution and elimination pathway which must be known in order to differentiate physiological organ uptake versus uptake in pathological tissue. This has also as a consequence that uptake in tumours localized in organs with high physiological uptake, may be difficult to detect.

2-^{18}F-fluoro-2-deoxy-D-glucose (FDG) can be used to determine enhanced glucose uptake in malignancies including endocrine tumours. However, its use in neuroendocrine tumors is limited because this type of tumours generally do not have a high metabolic rate. During the last decades, the potential diagnostic use of several naturally occurring labelled aminoacids as markers for tumour proliferation and increased metabolism has been investigated {Vallabhajosula, 2001 1548 /id}. Preliminary results with labelled phenylalanine in human endocrine tumours have been favourable {Hoegerle, 2001 1570 /id}. Pertechnetate and radioiodide accumulate in normal thyroid tissue by an active transport mechanism. The degree of pertechnetate or radioiodine uptake will depend on the functional status of the tumour. Although no association could be made between intensity of uptake and histological grading of the tumour, poorly circumscribed, heterogeneous uptake was associated with capsular invasion in the dog (N=29) {Marks, 1994 1617 /id}. Radioiodide, ^{123}I (gamma emitter) and ^{131}I (gamma and beta particle emitter) can evaluate thyroid organification and is more reliable than pertechnetate to evaluate thyroid uptake pre-therapeutically and to detect metastases {Broome, 1992 137 /id;Campbell, 1990 1618 /id}. Unfortunately, ^{123}I is very expensive. ^{131}I has a long half-life (8.1d), delivers a high radiation dose to the thyroid (resulting from the beta particle emission), has high energy photons (364keV) and is therefore less

than optimal for routine imaging with conventional gamma cameras. For these reasons, ^{131}I is mainly used for therapy of thyroid cancer in both man and animals. Concerning thyroid carcinoma, apart from anaplastic and medullary carcinomas that do not concentrate iodine, radioiodine can be used in combination with or without thyroidectomy, for recurrent disease or to treat distant metastases. The main drawback of radioiodine therapy is the radioprotection issue. High amounts of radioactivity are used and animals have to be hospitalized. Stimulating radioiodine uptake may decrease the ablative dose. Recent studies in man on the use of recombinant human TSH (rhTSH) to enhance radioiodine uptake in differentiated thyroid tumours and non toxic nodular goiter, have reported promising results {Nieuwlaat, 2003 1583 /id} . Current research is also focussed on gene therapy to increase the expression of Na-I symporters in tumors that have dedifferentiated. Sestamibi and tetrofosmine can be used as general tumour markers for dedifferentiated thyroid and parathyroid tumours. They bind to mitochondria and are also substrate for the P-gp, overexpressed in multi drug resistant (MDR) tumours. These tracers may therefore be valuable tools to determine in vivo which tumour will be drug resistant and which patients need a change of chemotherapeutic strategy or might benefit from P-gp inhibitors {Vallabhajosula, 2001 1548 /id}. Somatostatin receptor scintigraphy (SRS) has been the preferred technique to localise neuroendocrine tumours and tumours derived from the central nervous system in man {Pauwels, 1998 1552 /id}. Radioligands have been developed, albeit with different affinities for the different subtypes of somatostatine receptors. The overexpression of certain SSTR subtypes in some tumours with low affinity for the used synthetic somatostatin analogue may render false negative results . In veterinary medicine, normal distribution of radiolabelled octreotide (^{111}In-DTPA-D-Phe^{1}-octreotide) was investigated in dogs with SPECT and compared with autoradiography {Robben, 2003 1584 /id}. The same group used this radiopharmaceutical successfully to stage insulinoma in 6 dogs {Robben, 1997 3 /id}. Uptake in the primary tumour and its metastases was demonstrated in a dog, suspected of a gastrinoma, with ^{111}In-pentetreotide {Altschul, 1997 1588 /id}. Somatostatine ligands can also be used for therapy when labelled with radiotoxic radionuclides. Promising research is performed on gene transfer to increase the expression of specific receptor subtypes not only to improve detection capacity but also to increase the uptake of radiotoxic markers {Rogers, 2000 1551 /id}. MIBG is structurally similar to the neurotransmitter norepinephrine and the adrenergic neuron blocker guanethidine. This compound is transferred by a transporter system in the pre-synaptic cell, where it accumulates in catecholamine storing granules. This radiopharmaceutical is mainly used in the imaging of neuroblastoma, phaeochromocytoma, thyroid medullary carcinoma and other tumours arising from the neural crest for identification of the primary tumour, staging and therapy prediction {Pauwels, 1998 1552 /id}. ^{131}I-MIBG can also be used for therapy of MIBG avid tumours. Both ^{123}I and ^{18}F labelled guanidine derivatives correctly identified pheochromocytoma in dogs with adrenal masses, respectively in one and two dogs {Berry, 2002 1589 /id;Berry, 1993 23 /id}. Intense uptake in the area of the adrenal gland was seen in all dogs. Limitations for use in veterinary medicine are the high cost of the radiopharmaceutical. Several other receptor markers, including labelled neuropeptides, are currently under investigation but clinical evaluation of most of them is still limited {Pauwels, 1998 1552 /id}.

Conflicts of interest: none