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Biodistribution of radioiodinated Nalepride: assessment of a promising dopamine D2 receptor radioligand

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Aims : [123I]nalepride is predicted to be an excellent SPECT imaging agent for dopamine D2 receptors due to the presence of the allyl group, which produce more favorable pharmacokinetic parameters than those of epidepride. For lack of 123I in China, aim of the study was on the investigation of the in-vitro stability, biodistribution and brain-uptake of 5-(131)I-Nalepride in ICR mice. **Methods :** Nalepride, (S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-iodo-2,3-dimethoxybenzamide was synthesized according to our modified route. Preparation of 5-(131)I-Nalepride at high specific activity was achieved by iododestannylation of the corresponding tributyltinbenzamide. After intravenous injection, blood and tissue samples, taken at designated time intervals, were collected for analysis. To assess the effect of spiperone and tributyltin precursor, 10mg/Kg spiperone and tributyltin precursor were administered intravenously 30min prior to the tail vein administration of 5-10µCi 5-(131)I-Nalepride. **Results :** The yield of nalepride from 5-iodo-2,3-dimethoxybenzoic acid and (S)-N-[(1-allyl-2-aminomethyl]pyrrolidine is 50%. The radiochemical purity of 5-(131)I-Nalepride was over 95% measured by TLC. The saline solution of 5-(131)I-Nalepride was stable at least 7days at 4 and 37 centigrade. 5-(131)I-Nalepride was rapidly cleared from blood. Highest uptake was observed in liver and small intestine ,then kidney and urinary bladder at 5 min p.i.. 5-(131)I-Nalepride displayed high rapid uptake and fast clearance in the brain. Striatal uptake peaked at 8.85 ± 0.52% ID/g at 45min p.i., then declined slowly to 2.02 ± 0.38% ID/g at 24h. The striatal-to-cerebellum ratio increased with time (2 at 5min,35 at 45min, 268 at 6h,341 at 8h and 416 at 12h). Coinjection with spiperone could displace striatal specific binding of 5-(131)I-Nalepride while tributin precursor was no significant effect to that. **Conclusions :** Radioiodinated Nalepride is an excellent dopamine D2 receptor imaging agent.

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Radiopharmacy/Radiochemistry: Technetium

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A Sensitive, Rapid and Inexpensive Method to Assess Aluminium Ions (III) in Technetium eluates

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Aluminium ions (Al 3+) can adversely affect some labelling operations and alter the biodistribution of the radiopharmaceuticals. Therefore, Al determination is recommended in every eluate. We have developed a spot test employing the method originally proposed by Nadzhafova et al. (J Anal Chem 2001;56:178) for the determination of Al ions in water. Materials & Methods Briefly, we first put a cellulose filter-paper in a solution of a nonionic surfactant, and then into a 0.2% solution of 1,10 phenantroline, then impregnated with a 0.05% Chrome Azurol solution, it was finally treated with a 20% solution of hexamethylentetramine; we used water distilled twice for the solutions. The paper was dried and 5µL aliquot of the testing solution was dropped onto it. The reagent strips were tested with different concentration of Al from 0 up to 95.4 µg/mL. To validate the measurements, the test was performed in parallel employing Aluminon and Ascorbic Acid in solution and the results were evaluated by spectrophotometry at 525 nm absorbance. Some dried paper strips were stored in a cool dry place for further evaluation. Results. We observed a blue coloration whose intensity was proportional to the amount of aluminium in the solution. Blue spots were clearly recognized up to a concentrations of 2.5 µg/mL, while a concentration of about 1 µg/mL gave only a pale, but still recognizable, colour . The entire operation takes only a few minutes. There is a strict correlation between test paper and assay in solution. Test performance was non affected by storage of the impregnated cellulose strip for some weeks. Conclusion. This approach easily recognized concentrations which are about one third of the upper limit of 5 µg/mL stated by the European Pharmacopeia and showed a sensitivity superior to commercially available spot system. The entire procedure is time saving and the cost of the reagent per test is less than 0.50 euro.

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Isocyanide-carbonyl complexes of Tc-99m/Re-188 for possible radiopharmaceutical applications

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Co-ordination chemistry of technetium and rhenium attracts considerable interest due to the nuclear medicine applications of their radionuclides. ^{99m}Tc (*γ*-emitter) is the most popular radioisotope used in diagnostic nuclear medicine with more than 85 percent of routine analyses. The β^--emitting rhenium isotopes, ^{186}Re and ^{188}Re, are used in radioimmunotherapy. The co-ordination behaviour of tricarbonylmetal(I) with chelating ligands, important for designing new metal-based radiopharmaceuticals, has been intensively studied by numerous authors. Particularly stable bonds have been found between the $[M(CO)_3]^+$ core (M = Re^I, Tc^I) and aromatic nitrogen donor atoms of multidentate ligands [1]. In this paper we report the n.c.a scale complex formation of the tricarbonyltechnetium(I)/rhenium(I) moiety with mono- and bidentate ligands using the [2+1] approach. In the general formula of the investigated complexes $[M^I(CO)_3L_1L_2]$ M^I denotes $^{99m}Tc^I$ (**1**) or $^{188}Re^I$(**2**), L_1 - the bidentate N-methyl-2-pyridinecarboxyamide ligand and L_2 - monodentate ligand (water (**1a**, **2a**) or *tert*-Butyl 3-isocyanopropionate (**1b**, **2b**) molecule). The latter complexes were obtained from their tricarbonyl precursors *fac*-$[M^I(CO)_3(H_2O)_3]^+$ [1,2] in the consecutive ligand exchange reactions with L_1 and L_2. Stability of the complexes (isolated by semipreparative HPLC) in a function of time and under conditions of the challenge experiments (i.e. exccess of histidine or cysteine) has been investigated. Lipophilicity, log P, of **1a, 2a, 1b** and **2b** was characterized by their partition coefficients, P, in the physiological-like conditions (*n*-octanol/0.9% NaCl aqueous solution or *n*-octanol/PBS buffer pH=7.4). The structures of the investigated complexes are discussed basing on quantum chemical calculations (B3LYP method) for **2a** and **2b** as well as on the experimental and theoretical results obtained previously for "cold refernce compound" $Re^I(CO)_3L_1Cl$ [3]. The biomolecule (BM) labelling procedure with ^{99m}Tc coupled with bidentate ligand [2^{BM}+1] or monodentate isocyanide ligand [2+1^{BM}] were studied and compared. Histidine and cysteine challenge experiments showed the higher complex stability of **1b** and **2b** than **1a** and **2a**. Substitution of the last water molecule in [2^{BM}+1] approach by the isocyanide ligand results stabilization of the conjugate Acknowledgements The authors thank the BIKER LTD (Warsaw, Poland) for the ^{99m}Tc generators and the Institute of Atomic Energy Radioisotope Centre POLATOM (Swierk-Otwock, Poland) for the ^{188}Re generator. [1] R. Alberto, R. Schibli, A. Egli, A. P. Schubiger, *J. Am. Chem.Soc.* **1998**, *120*, 7987. [2] S. H. Park, S. Seifert, H-J. Pietzsch, *Bioconjugate Chem.*, **2006**, 17, 223. [3] L. Fuks, E. Gniazdowska, J. Mieczkowski, N. Sadlej-Sosnowska, *Polyhedron*, **2008**, 27, 1353.

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DTPA-Liposome and PEG-DTPA-Liposome: Comparison of Radiolabelling, In-vitro Stability, Biodistribution and Imaging in Normal an Tumor Model

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Liposomes constitute drug delivery nanosystems so the tumor can be reached by passive diffusion due to their size. Our aim was to study and compare the usefulness of DTPA-liposome and PEG-DTPA -liposome in tumor scintigraphy by studying its stability, biodistribution and accumulation in melanoma tumor after radiolabelling with Technetium-99m. DTPA-Liposomes were compounded by: phosphatidylcholine, cholesterol, 1,2- dimyristoyl-sn-glycero-3-phosphoetanolamine-N-DTPA (9:4:1 w/w). PEG-DTPA -Liposomes were compounded by: Phosphatidylcholine, cholesterol, 1,2- dimyristoyl-sn-glycero-3-phosphoetanolamine-N-DTPA and 1,2 dipalmitoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethilene glycol)-5000] (9:4:1:1 w/w). Both kind of liposomes were prepared by hand shaken method. Liposomes were labeled with Technetium-99m: 0.4 ml of $^{99m}TcO_4^-$ (15mCi/ml) was mixed with 0, 8 ml of liposome suspension. To this mixture, 0, 2 ml of SnF_2 solution (0, 69 mg/ml) was added and incubated for 20 minutes at room temperature. The labeling yield and radiochemical purity was estimated by ascending instant thing layer chromatography (ITLC), using 0,9 % saline and pyridine:acetic acid:water (3:5:1.5 v/v) as the mobile phases. In order to check the stability and strength of the binding of ^{99m}Tc with PEG-DTPA-liposomes as well as with DTPA-Liposomes, 0,5 ml of the labeled preparation was challenged against various concentrations of cysteine (0,1; 10; 30 and 50 mM) and incubated for 1 and 3 hours at 37 ºC. The effect of cysteine on labeling efficiency was evaluated by ITLC-SG using normal saline and acetone as the mobile phases. Biological distribution was studied in melanoma induced (B16 F-1 murine melanoma cell line) C57 black mice, weight 31,4 ± 2,0 (n = 4) at 4 h post iv injection. In the same model scintigraphy images were taken after 4 h of iv injection of 650 µCi ^{99m}Tc-liposomes. For both kind of liposomes, labeling efficiency was higher than 90%, and stability towards transchelation was good for all the cysteine concentrations except for 50 mM. At 3 h of incubation, both were stable with concentrations of 0,1 and 10 mM of cysteine. Biodistribution pattern of liposomes showed accumulation in liver and tumor. The scintigraphy images showed high uptake in tumor and liver for PEG-DTPA-liposomes and much less uptake in tumor for DTPA-liposomes. These results are encouraging to continue research of this potential diagnostic imaging agent for melanoma. Aknowledgement: Dinacyt

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Biodistribution of canine leukocytes labelled in whole blood with technetium-99m stannous fluoride colloid and their use in localising induced acute intradermally inflammation

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Objectives: The aims of this study were to assess the safety and biodistribution of canine leukocytes labelled in whole blood with ^{99m}Tc stannous fluoride colloid (^{99m}Tc-SnC) in healthy dogs, and to determine the ability of this radiopharmaceutical to detect inflammation in dogs. **Methods:** A 10 mL jugular venous blood sample was collected from each of seven healthy dogs. Each sample was incubated with 600 MBq of ^{99m}Tc-SnC for 1 hr at room temperature followed by intravenous injection of the autologous radiolabelled blood sample. Each dog underwent a whole body scintigraphic scan at 10 and 30 min and 2, 4, 6 and 24 hrs post-injection using a gamma camera. An additional seven healthy dogs were injected intradermally with 60 ng of human recombinant tumour necrosis factor (TNF-α) suspended in 0.1 mL sterile saline into one thigh. Similar volume of sterile saline was injected into contralateral thigh. Three hours later, 10 mL of autologous radiolabelled blood were injected into each dog and hindquarter scans were performed at 30 min and 2, 4, 6 and 24 hrs post-injection of the radiolabelled leukocytes. Cutaneous injection sites were biopsied post-scan and histologically examined. **Results:** In healthy dogs, rapid clearance of pulmonary uptake was observed by 30 min post-injection. Persistent high uptake by liver and spleen, mild to moderate uptake by bone marrow and no bowel uptake was noted in all scans. No adverse side effects were observed in any dog. In dogs injected with TNF-α, cutaneous inflammation was identifiable scintigraphically by 30 min post-injection of radiolabelled leukocytes and confirmed histologically. Control injection sites were scintigraphically and histologically normal. **Conclusion:** The current study showed that intravenous injection of autologous leukocytes radiolabelled with ^{99m}Tc-SnC is a safe technique in dogs. The technique showed high sensitivity and specificity in detecting mild acute inflammation

Poster Presentation