^{99m}Tc exametazime (HMPAO) leukocytes

1. Indications

^{99m}Tc exametazime (HMPAO or hexamethylpropyleneamine oxime) labelled leukocytes or labelled white blood cells are prepared using a registered kit Ceretec®. ^{99m}Tc exametazime leukocytes can be used to detect and localise sites of infection and to detect and determine the extent of inflammatory conditions not associated with infection. A complete list of indications is given in chapter *'Leucocyte scintigraphy'*.

Compared with ^{111}In oxine leukocytes, scintigraphy with ^{99m}Tc exametazime leukocytes is preferred for most indications, because the advantage of earlier and shorter imaging times and lower radiation dose. ^{111}In oxine leukocytes scintigraphy is preferred in patients with inflammatory bowel disease and kidney infections because, unlike ^{99m}Tc exametazime leukocytes, there is normally no excretion into gastrointestinal or urinary tracts. Also in more chronic processes, where late imaging is needed, ^{111}In oxine leukocytes can be used.

2. Preparation

The preparation of ^{99m}Tc exametazime leukocytes is described in the the SmPC and guidelines. The preparation can be summarized in the following steps:

a. Fill a syringe with anticoagulant (ACD-A) and sedimentation agent (HES)
b. Collect blood using a needle with an inner diameter of 19 G. Needles with a smaller inner diameter will damage the cells. Make sure that the blood is well mixed with the anticoagulant
c. Bring either the blood-mixture over in a tube or turn the syringe with the plunger facing downwards
d. Allow the red cells to sediment for 45-60 min
e. Separate the leukocyte rich and platelet rich plasma (LRPRP) upper layer from the layer of red cells
f. Centrifuge the LRPRP at 150 g for 5 min
g. Separate the platelet rich plasma (PRP) upper layer from the layer of the leukocytes
h. Centrifuge the PRP at 1500 g for 10 min
i. Separate the cell free plasma upper layer from the platelets
j. Re-suspend the leukocytes in cell free plasma
k. Reconstitute a vial of exametazime using fresh ^{99m}Tc pertechnetate eluate. The generator used should be eluted less than 24 h ago. The eluate should obtained less than 2 h ago
l. Add the ^{99m}Tc exametazime to the suspended leukocytes
m. Incubate for 10 min at room temperature
n. Centrifuge for 5 min at 150 g
o. Remove the supernatant and keep for determination of labelling efficiency
p. Re-suspend the radiolabelled cells in cell free plasma
q. Draw the needed activity of ^{99m}Tc exametazime leukocytes for the patient dose

Special considerations:

- Working with blood can introduce risks to both the operator and the patient. The department labelling the cells should comply with all regulations. Adequate facilities, equipment, procedures and training for operators should be present. Additional the risks for blood contamination should be recognizes and precautionary measures should be implemented to minimise those risks.
- Sedimentation may be affected by a variety of factors such as number of cells and certain diseases like sickle cell anaemia.
- Once reconstituted the shelf life of the ^{99m}Tc exametazime kit is 30 min. The obtained ^{99m}Tc exametazime will need to be used for the labelling within those 30 min.
- In some countries Hydroxyethyl-starch (HES) solutions might not be available. The reason for this is the endorsement of the EMA to allow the use of HES only in restricted patient populations. In the case HES is no longer available, alternatives like succinylated gelatin and methyl cellulose could be considered.

3. Quality control

- Before the blood cell labelling is started and throughout the procedure a check on the absence of blood clots needs to be performed.
- Before adding the reconstituted ^{99m}Tc exametazime to the leukocytes, the radiochemical purity will need to be determined as described in the SmPC. A minimum radiochemical purity of 80% is expected.
- The labelling efficiency of the ^{99m}Tc exametazime labelled leukocytes should be determined after labelling. The labelling efficiency of the ^{99m}Tc exametazime leukocytes is defined as the total radioactivity measured in the cells as a percentage of the total radioactivity measured in both the cells and the supernatant. The method is described in the SmPC. A labelling efficiency around 55% might be expected. Although labelling efficiency of the radiolabeled leukocytes have been reported from approximately 35-90% or more. The labelling efficiency depends on several aspects such as: presence of disease in patient, concentration and number of cells, cell damage, plasma concentration in the labelling medium, pH, concentration of ligand and radionuclide, temperature, operator inter-variability and drugs (see 'interactions').

Several other quality control tests have been described. Some of these tests are time-consuming. The following tests are recommended to be performed periodically of for validation purposes:

- Tryptan blue exclusion test, clumping and cell counting
- Cell subset recovery test
- Measurement of cell efflux of ^{99m}Tc
- In vivo in lung uptake
- In vivo liver-to-spleen ratio

The tests are described in the EANM guidelines

4. Interactions, contraindications & adverse reactions

Interactions

The following drugs could alter chemotaxis of the leukocytes and thereby interfere with the leukocyte labelling. This might cause less uptake of ^{99m}Tc exametazime in the leukocytes and a disturbed imaging.

- Azathioprine
- Cephalosporins
- Cyclosporine
- Cyclophosphamide
- Epinephrine (Adrenalin)
- Heparin
- Iron preparations
- Interferons
- Interleukin-2
- Lidocaine
- Low molecular weight heparins (LMWHs)
- Mesalazine (Mesalamine, 5-ASA)
- Methotrexate
- Nifedipine
- Paracetamol (Acetaminophen)
- Prednisolone
- Radiotherapy
- Ranitidine
- Sulfasalazine
- Total parenteral nutrition (TPN)

For those drugs, with the exception of nifedipine and ranitidine, a possible effect in images should be taken into account. Nifedipine should be discontinued 12 h before the study (32 h for sustained release/retard preparations). Ranitidine should be discontinued 10 h for the study.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Adverse reactions

- Hypersensitivity (including rash, erythema, urticaria, angiooedema, pruritus, anaphylactoid reaction or anaphylactoid shock)
- Headache, dizziness, paraesthesia
- Flushing
- Nausea, vomiting
- Asthenic conditions (e.g., malaise, fatigue)

5. Biodistribution & pharmacokinetics

The blood clearance half-life of ^{99m}Tc exametazime leukocytes is about 4 h. During the first hour after intravenous administration of ^{99m}Tc exametazime leukocytes, activity is seen in lungs, liver, spleen, blood pool, bone marrow and bladder. Bowel activity is routinely visualized by 3-4 h and increases with time. For labelled leukocytes, about 15-30% of the administrated activity is excreted renally in 24 h and about 6% is eliminated via the bowel in 48 h.

6. Stability

It has been reported that the loss of label for ^{99m}Tc exametazime leukocytes is 9% during one hour of incubation. It is essential that cells are viable when returned to the patient. Labelled cells may be damanged from the collection and labelling procedures. Re-suspension of cells in cell free plasma optimises their viability. The SmPC states that

the ^{99m}Tc exametazime labelled leukocytes should be injected after labelling. A specific maximum shelf live is not mentioned. In practice, longer periods of time between blood being taken from a patient and the cells being re-injected have provided no evidence of problems. However it is recommended to re-inject as soon as possible, preferably within 1-2 h after labelling.

7. Literature

- Ceretec [SmPC]. Eindhoven: GE Healthcare; 2013.
- De Vries EF, Roca M, Jamar F, Israel O, Signore A. Guidelines for the labelling of leucocytes with 99mTc-HMPAO. Eur J Nucl Med Mol Imaging 2010:37:842-8.
- Palestro CJ, Brown ML, Forstrom LA, et al. Society of Nuclear Medicine Procedure Guideline for 99mTC-Exametazime (HMPAO)-Labeled Leukocyte Scintigraphy for Suspected Infection/Inflammation. The Society of Nuclear Medicine, Version 3.
- Peters AM. Imaging Inflammation: current role of labelled autologous leukocytes. J Nucl Med. 1992;33:65-7.
- Guidelines for the safe prepraration of radiolabelled blood cells. UK Radiopharmacy Group. 2009.
- Hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients - CMDh endorses PRAC recommendations. EMA. 25 October 2013.
- Solanki C, Li DJ, Wong A, Miles KA, Sampson CB. Multidose use of exametazine for leukocyte labelling: a new approach using tin enhancement. Nucl Med Commun 1993:14(11):1035-40.
- Danpure HJ, Osman S, Carroll S. The development of a clinical protocol for the radiolabelling of mixed leucocytes with 99Tcm-hexamethylpropyleneamine oxime. Nucl Med Commun 1988:9(6):465-75.
- Peters AM, Osman S, Henderson BL, et al. Clinical Experience with 99mTc-hexamethylpropyleneaminooxime for labelling leucocytes and imaging inflammation 1986:328:946-9.
- Ellis BL, Sampson CB. Radiolabelling of blood cells-Theory and practice. In: Sampson CB, ed.Textbook of radiopharmacy theory and practice. Amsterdam: Gordon and Breach Science Publishers; 1999: 83-104.
- Schreuder N. Radiofarmaca Medicatiebewaking. Zwolle: Probook Media; 2013. p52.
- E. Lazzeri, A. Signore, P.A. Erba, et al. Radionuclide Imaging of Infection and Inflammation: A Pictorial Case-Based Atlas. Milan: Springer; 2013. p11.
- Smith BT, Weatherman KD. Diagnostic Imagaing for pharmacists. Washington D.C.: APhA; 2012;89-90.