^{13}N ammonia

^{13}N-NH_3

1. Indications

Evaluation of myocardial perfusion in patients with suspected or existing coronary artery disease

2. Preparation

^{13}N-NH_3 will be formed by radiation of the ^{13}N target with protons in an area containing 1,8 ml of 5 mmol/L ethanol in water. ^{13}N-NH_3 is formed during that reaction. To avoid the formation of nitrite and nitrate the ethanol is added in the solution.

The nuclear reaction: ^{16}O (p,α) ^{13}N

After radiation around 1,8 ml of the radiated solution will be transported into another LAF-closet. With the help of a QMA SepPak Cartridge the solution is placed into a sterile 25 ml vial which contains 10 ml 0,9% NaCl. Thereafter a sterile 10 ml syringe is filled with the resulted solution.

3. Quality control

^{13}N-NH_3	NGMB requirement	Release requirement	Frequency	Ph. Eur. 8,2
Appearance	Clear, colorless	No	Every patient	Clear, colorless
pH	6-8	Yes	Every patient	5,5-8,5
Bubble point test GP-filter 1 (bar)	>3,7	No	Every patient	-
Bubble point test GP-filter 2 (bar)	>3,7	No	Every patient	-
Radiochemical purity (%) Impurities: [^{13}N]-NO_2- [^{13}N]-NO_3- [^{18}F]-F- [^{15}O]-H_2O	>99	No	1x per equal week if operational	> 99

Radionuclidic purity (%): gammaspectrum (keV) t1/2 (min)	>99 511, evt 1022 9-11	No	4x per year	>99 9-11
Ethanol (g/l) 2	<100	No	Only validation	-
Osmolarity (mosmol/kg) (for information only)	240-800	No	1x per equal week if operational	-
Sterility	Sterile	No	1x per equal week if operational	sterile
Endotoxins (EU/ml)	<2,5	No	1x per equal week if operational	<5,83
Plate count after 1 time gp filtration 4	Max. 1 kve/ml	No	Only validation	-
Plate count after 2 times gp filtration	0	No	Only validation	-
Al (ig/l)	<20005	No	Only validation	<2000

4. Interactions

At this moment, no cross interactions with other drug substances have been described. When the drug product is administered via a catheter, some retention of the drug substance in the catheter may occur. Lines should be as short as possible.

5. Contraindications

No contraindications have been reported nor observed yet.

6. Adverse reactions

In the UMCG, many clinical studies with ^{13}N-NH_3 have been performed in both healthy volunteers and different patient groups. 47 patients, 103 patients, 40 patients and 21 healthy volunteers, and 19 healthy volunteers have been injected with ^{13}N-NH_3. From 1995-2003 we injected ^{13}N-NH_3 in at least 480 patients. During the years 2006-2010, we conducted several studies for which we injected ^{13}N-NH_3 into at least 40 different patients safely. Please refer to Pubmed (^{13}N and ammonia, limited to humans 274 hits, October 20th, 2014) for published clinical studies in other institutions. Based on all these data, one may conclude that human exposure to ^{13}N-NH_3 is safe.

7. Biodistribution & pharmacokinetics

The radioactive half life of the isotope ^{13}N, and thus the tracer ^{13}N-NH_3 is 10 min. *Weiss et al*. developed a modeling approach for the analysis of the systemic kinetics of the tracer ^{13}N-NH_3 administered for dynamic liver scanning. The radioactive half life of the tracer limits the time span in which data are available in PET experimental setting. A circulatory pharmacokinetic model was applied to the metabolism of ^{13}N-NH_3 in anaesthetized pigs, which incorporated data from serial measurements of ^{13}N-NH_3 and ^{13}N-metabolite activity in arterial and portal venous blood together with blood flow rates through the portal vein and through the hepatic artery obtained over 20 min after intravenous injection of ^{13}N-NH_3. Models analysis showed that up to 20 min after injection the time course of ^{13}N-NH_3 concentration in arterial blood is primarily determined by distribution kinetics (steady-state volume of distribution 1856 ±531 ml/kg). Simultaneous fitting of arterial ^{13}N-NH_3 and metabolite blood concentrations allowed for estimation of the hepatic ^{13}N-NH_3 clearance (10,25 ±1,84 ml/min) which accounted for the formation of the circulating metabolites.

Several tracer kinetic methods have been proposed for quantification of regional myocardial blood flow (MBF) with ^{13}N-NH_3 and PET. *Choi et al.* compared six different commonly used models to characterize the accuracy of each approach. Studies which were used to compare the methods included studies with both animals (dogs) and humans (healthy volunteers and patients). They concluded that MBF can be measured accurately using ^{13}N-NH_3 PET and tracer kinetic methods. The results indicate that preference should be given to the two-parameter model, incorporating geometrical ROI representation among the compartment models, and to the graphical analysis among the non-compartmental approaches. Please refer to Pubmed for more information on pharmacokinetics of ^{13}N-NH_3 (^{13}N and ammonia/pharmacokinetics 40 hits, October 20th, 2014).

8. Stability

Physical half-life of ^{13}N-NH_3 is 10 min. The injection takes place as soon as possible after production. Therefore, there is no use for stability testing.

9. Literature

- UMCG investigational medicinal product dossier [^{13}N]-ammonia.
- Production protocol UMCG N-^{13}-NH_3.