Enhancement results of In-111-DTPA- Octreotide Therapy by Ultrasound microbubbles

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**Aim:** to estimate the uptake & distribution differentiation of In-111 Octreotide by somatostatin receptor positive tumors, when contrast micro bubbles & ultrasound are applied

**in order to:** to improve the action of Electron Emission of In-111-octreotide by increasing cell internalization after the sonoporation of the tumor

- Ultrasound interaction with microbubbles provokes them to oscillate, resonate and eventually to be disrupted by the ultrasound energy.
- Liver displays a strong affinity for taking up the microbubbles.
Method

• Patients, suffering of neuroendocrine tumors, were treated by In-111 Octreotide, through hepatic artery catheterization radionuclide infusion.

• Scintigraphic images of the tumor area were taken after the administration of the radiopharmaceutical.

• 18h post infusion 2,4ml contrast agent Sonovue was injected i.v. in a concentration of 45mgr per ml followed by flash of 5ml sodium chloride A 2nd dosage repeated 10 min later. Liver displays a strong affinity for taking up the microbubbles.

• Indium scans were repeated after sonoporation
Sonoporation

• Ultrasound creates transient permeability of cell membranes in the presence of microbubbles.
• This effect allows foreign molecules to enter cells.

- Ultrasound results in a great expansion of microbubbles prior to destruction (depending on frequency).
- Cell walls show small pores following application of ultrasound in the presence of microbubbles.

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Growth and Collapse of Microbubbles:

- The gas nuclei expand under the influence of the ultrasonic wave and detach to free micro bubbles in the liquid.
- The micro bubbles continue to adsorb energy from the wave and grow isothermally.
- When the micro bubbles reach a critical size (approximately 2 to 3 times the resonance radius) they implode violently.

- **Limiting microbubble concentrations reduces associated cell damage**
- **Membrane recovery time in healthy cells is shown to be as short as 3 to 10 seconds**

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Micrographs show bubble size to oscillate under ultrasound until disintegration occurs.

Recent research suggests a cascade of cavitations initiated by micro bubble collapse.

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Ultrasound interaction with bubbles results in increased membrane permeability by shear stress, temperature rise and activation of reactive oxygen species.

- a: transient holes induced by shear stress;
- b: increase in membrane fluidity
- c: endocytosis of micro bubbles
- d: fusion of the micro bubble membrane with the cell membrane
**SonoVue® microbubbles**

*Commonly used to improve contrast in diagnostic ultrasound*

- SonoVue, is an aqueous suspension of stabilized microbubbles.
- Size of microbubbles is between 1 and 10 μm
- No is between 200 and 500 / mL.
- Gas used is Sulphur HexaFluoride in a phospholipids surface layer encapsulated in sphere
- Bubbles behave isothermally, but their radius violently changes
- Their coating controls the way in which respond to ultrasound
Response of bubbles to ultrasound as function of Mechanical Index

In this study a maximal Mechanical Index 0.9-1 was used.
Ultrasound Parameters

- Ultrasound beam of an HDI-ATL 3000 system
- A broadband convex transducer 2-4 MHz frequency
- A max pulse repetition frequency 0.05%
- A maximal Mechanical Index 0.9-1
- Was applied externally to the treatment area for a total time of 12 to 20 minutes.

Restriction in the duration of ultrasound examination was necessary due to the In-111 radiation burden of the examiner.

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Micro bubbles sonoporation of Liver metastatic lesions

Ultrasound Blood perfusion study without contrast media

Ultrasound/sonovue application for 12 minutes-increased perfusion

After 80% of bubbles rupture
Perfusion back to normal
microbubbles sonoporation of Liver metastatic lesions

Ultrasound Blood perfusion study before contrast media application

Increased perfusion after 1 min of contrast media sonovue use. Application of ultrasound bubbles for 15 minutes

A series of corresponding scintigraphic images was obtained

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Uptake measurements were performed to the In111 scans taken before and after the ultrasound application and differences, on the relative activity and in the target area In-111 redistribution, were indicated.
**In111 Octreotide therapy**

Enhancement and pattern differentiation of the mean counts on tumor regions after sonoporation.

Induced acceleration of intracellular motion of the receptors in the tumor after the micro bubbles - ultrasound application is estimated by index TER.

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In111 Octreotide therapy

Enhancement and pattern differentiation of the mean counts on tumor regions after sonoporation.

Pre-ultrasound

Post-ultrasound treatment

Induced acceleration of intracellular motion of the receptors in the tumor after the micro bubbles - ultrasound application is estimated by index TER

T.E.R. = 3.75

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Results

• Uptake measurements were performed to the images taken before and after the Ultrasound-microbubbles application and the differences on the relative activity (tissue/background) on the target area, pre- and post-sonoporation, gave a Treatment Enhancement Ratio (TER) in a range 2.5-4 that shows a statistical significant peptide internalization increase in the combined treatment of In-111-Octreotide and Ultrasound micro-bubble contrast application.
Conclusion 1:

- Ultrasound-micro bubbles application increases and differentiates the uptake and distribution of In-Octreotide in somatostatin receptor positive tumours.

- After sonoporation, scintigraphic images analysis gives semi quantitative data and a Treatment Enhancement Ratio (TER) specific for tumour region.

- Radiopharmaceutical distribution pre and after micro bubbles application shows pattern differentiation of the mean counts on tumour selective regions.
Conclusion 2:

- The internalization increment seems to be directly analogue to the duration of the bubble treatment up to 20 minutes.

- Cell permeabilization enhancement by the ultrasound bubble contrast application leads to peptide internalization increase, in In-111 Octreotide infusion which becomes more effective for the benefit of the treated patient.