

Title: **Tentative Targeting of Pancreas with Particulate and Molecular MRI Contrast Agents.**

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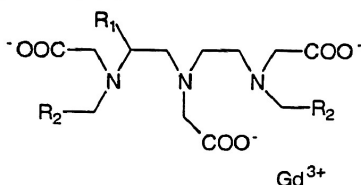
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Abstract: **PURPOSE.**

Imaging of the pancreas is not straightforward due to its diffuse tissue architecture. Contrast-enhanced MRI thus appears as an extremely valuable option. It has been reported that unspecific gadolinium complexes enhance normal pancreatic parenchyma after rapid bolus injection (1) and that administration of Mn-DPDP induces a prolonged and clinically useful enhancement of the tissue (2). The present animal study aims at evaluating the retention or the internalization of commercially available compounds and of new materials potentially exhibiting a pancreatic selectivity.

MATERIALS AND METHODS.

Contrast Media. Five paramagnetic complexes and two particulate contrast media were used: Gd-DTPA, Gd-EOB-DTPA, Gd-DTPA-BAlaA, Gd-DTPA-BisGlucosAmide, Mn-DPDP, Sinerem® (Guerbet) and MSM (Magnetic Starch Microspheres) (3).



Gd-DTPA : $R_1=H$, $R_2=COO^-$

Gd-EOB-DTPA : $R_1=p-C_6H_4OC_2H_5$, $R_2=COO^-$

Gd-DTPA-BAlaA : $R_1=H$, $R_2=CONHCH(CH_3)COO^-$

Gd-DTPA-BisGlucosAmide : $R_1=H$, $R_2=CONHC_6H_{11}O_5$

Animals. Male Wistar rats weighing 240 to 300 grams were used for the experiments. All the protocols fulfill the requirements of the Ethical Committee of our Institution.

Pancreatitis. The pathology was induced by the i.p. injection of caerulein (40 μ g/kg b.w.) 6 hours before the pancreas isolation surgery.

In vivo experiments. The contrast agents were administered through the femoral vein at the dose of 0.1 mM/kg of b.w.; the pancreas was excised one hour later and analyzed by relaxometry.

Perfused organs experiments. Pancreases were isolated and perfused as described in (4) at a constant flow rate of 4 ml/min. with a Krebs-Henseleit solution kept at 37°C. The perfusion protocol included a 20 min. stabilization period (open circuit) followed by the administration of the contrast media (20 min., closed circuit) and a wash-out phase (20 min., open circuit). For those contrast media studied within this protocol, the concentration in the perfusate was as follows: Gd-DTPA: 1 mM; Gd-EOB-DTPA: 1 mM; Mn-DPDP: 25 μ M; MSM: 134 μ M of iron; Sinerem®: 54 μ M of iron.

1H Relaxometry and ^{31}P Spectroscopy were respectively performed on a spin analyzer Bruker Minispec PC-110 and on a Bruker AMX-300 spectrometer.

RESULTS.

In vivo experiments. No significant change of water R_1 was noticed on the pancreas of healthy rats one hour after the administration of Gd-DTPA, Gd-EOB-DTPA, Gd-DTPA-BAlaA and Gd-DTPA-BisGlucosAmide.

In vitro experiments. Neither healthy nor pathological pancreases showed any significant capture of superparamagnetic materials (Sinerem® and MSM). The perfusion of Gd-DTPA and Gd-EOB-DTPA induced a transient increase of the tissue R_1 , which returned to its initial level after 10 minutes of wash-out. Only Mn-DPDP induced a sustained broadening of the β -ATP peak of the perfused organ.

CONCLUSION.

Our results indicate that, among the tested compounds, only Mn-DPDP leads to some persistent enhancement of the pancreas related to the internalization of a paramagnetic moiety. Gd-DTPA and Gd-EOB-DTPA influence the tissue relaxivity but only from an extracellular compartment. In spite of oedema and infiltration by macrophages induced by pancreatitis, no contrast was noticed after the perfusion of small or large superparamagnetic particles. Adjunction to DTPA of lipophilic groups or amino-acids and sugar residues which were hoped to promote binding to membrane receptors and therefore to facilitate the internalization of compounds did not modify the biodistribution of the paramagnetic complexes. Other vectors are currently under investigation.

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