Imaging of Experimental Colitis with a Radiolabeled Leukotriene B_4 Antagonist

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The use of radiolabeled leukocytes is considered the gold standard for scintigraphic imaging of inflammatory bowel disease. The disadvantages of ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO)-leukocytes, however, encourage the search for new imaging agents with at least similar diagnostic accuracy but without the laborious preparation and subsequent risk of contamination. In this study we investigated the imaging characteristics of a new imaging agent that specifically binds to the leukotriene B_4 (LTB_4) receptors expressed on neutrophils. Imaging characteristics of the ^{111}In-labeled LTB_4 antagonist (DPC11870) were compared with those of ^{18}F-FDG and ^{99m}Tc-HMPAO-granulocytes in a rabbit model of experimental colitis. **Methods:** Acute colitis was induced in New Zealand White (NZW) rabbits by infusion of trinitrobenzene sulfonic acid in the descending colon. Forty-eight hours after induction of colitis, all animals were injected intravenously with ^{99m}Tc-granulocytes, ^{18}F-FDG, or ^{111}In-DPC11870. The pharmacokinetics and biodistribution were studied by serial scintigraphic imaging and by ex vivo counting of dissected tissues. **Results:** All 3 radiopharmaceuticals showed the inflamed colon as early as 1 h after injection. However, compared with ^{99m}Tc-granulocytes, both ^{111}In-DPC11870 and ^{18}F-FDG were superior in revealing the inflamed lesions. The biodistribution data showed that uptake of ^{111}In-DPC11870 in the inflamed colon was highest (0.72 ± 0.18 percentage injected dose per gram [%ID/g]), followed by uptake of ^{99m}Tc-granulocytes (0.40 ± 0.11 %ID/g) and of ^{18}F-FDG (0.16 ± 0.04 %ID/g). Because of low activity concentrations in the noninflamed colon, the radiolabeled LTB_4 antagonist also revealed the highest ratio of affected colon to unaffected colon (11.6 for ^{111}In-DPC11870, 5.5 for ^{99m}Tc-granulocytes, and 4.1 for ^{18}F-FDG). **Conclusion:** The radiolabeled LTB_4 antagonist DPC11870 clearly delineated acute colitis lesions in NZW rabbits within 1 h after injection. Because of high uptake in the inflamed lesions and a low activity concentration in the noninflamed colon, images acquired with ^{111}In-DPC11870 were better than those acquired with ^{99m}Tc-granulocytes or ^{18}F-FDG.

Key Words: LTB_4 antagonist; infection imaging; inflammatory bowel disease; granulocytes; ^{18}F-FDG

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Several nuclear medicine imaging techniques are currently used as tools for diagnosis of inflammatory and infectious diseases. In general, scintigraphic imaging of inflammatory and infectious foci is performed using radiolabeled leukocytes. Especially in cases of inflammatory bowel disease, radiolabeled leukocytes are considered the best of the available scintigraphic imaging agents. ^{99m}Tc-Hexamethylpropyleneamine oxime (HMPAO)-leukocytes are a useful radiopharmaceutical for the management of patients with Crohn's disease. Uptake of radioactivity has shown a correlation with endoscopy and histology (*1*). Despite the fact that ^{111}In- or ^{99m}Tc-labeled leukocytes are considered adequate imaging agents, their laborious preparation and their requirement that potentially contaminated blood be handled has stimulated a search for an alternative radiopharmaceutical comprising the same imaging qualities.

Recent reports suggest that ^{18}F-FDG may be such an alternative (*2*,*3*). ^{18}F-FDG PET is a distinguished imaging tool in clinical oncology because of its ability to image the increased glucose uptake of tumor cells. Several studies have shown that increased glucose metabolism is not restricted to malignant cells (*4*). Increased ^{18}F-FDG accumulation also occurs in inflammatory cells (*5*,*6*).

Besides ^{18}F-FDG, chemokine receptor–binding agents may be used for the imaging of infection and inflammation (*7*,*8*). The use of radiolabeled chemotactic peptides (e.g., *N*-formyl-methionyl-leucyl-phenylalanine and chemokines) is based on the high-affinity interaction with their receptors specifically expressed on (activated) white blood cells. Because many of these leukocytes infiltrate at the site of inflammation, interaction with these receptors in vivo may lead to accumulation of the radiolabeled agent in the infectious or inflammatory foci. Compared with the radiopharmaceuticals currently used to image infectious and inflammatory lesions, these agents have additional advantages warranting their further investigation, including low molecular weight—leading to rapid penetration in the focus and fast clearance from the blood—and absence of the potential hazard associated with handling blood products (*9*).

Leukotriene B_4 (LTB_4) is a chemotactic molecule that could be studied for this purpose. LTB_4 activates granulo-

cytes and macrophages in reaction to an inflammatory response (*10*,*11*). Two types of LTB_4 receptors have been identified (*12*,*13*). The first receptor type, BLT1, is a high-affinity receptor expressed mainly on human neutrophils. The second receptor type, BLT2, is a low-affinity receptor expressed more ubiquitously, with high expression in spleen, leukocytes, ovary, and liver (*10*,*14*). The ^{99m}Tc-labeled LTB_4 antagonist RP517 was recently reported to bind to the neutrophil LTB_4 receptor and was also found capable of imaging myocardial inflammation caused by coronary artery occlusion and reperfusion in a dog model (*15*). We found that RP517 can rapidly reveal intramuscular *Escherichia coli* abscesses in rabbits (*16*). The high lipophilicity of RP517 results in predominantly hepatobiliary excretion, making imaging of infectious and inflammatory foci in the abdomen difficult.

The LTB_4 antagonist used in this study was DPC11870. DPC11870 is structurally related to RP517 but is made less lipophilic by the addition of pharmacokinetic modifying groups. We found that DPC11870 binds to human granulocytes with high affinity in vitro. Therefore, we hypothesized that in vivo interaction with granulocytes at the site of inflammation, combined with reduced uptake in the gastrointestinal tract, can lead to visualization of the inflamed colon. In this study we investigated the imaging characteristics of the ^{111}In-labeled LTB_4 antagonist DPC11870, ^{18}F-FDG, and ^{99m}Tc-leukocytes in a rabbit model of acute, chemically induced colitis.

MATERIALS AND METHODS

DPC11870

DPC11870 is a bivalent LTB_4 antagonist consisting of 2 identical LTB_4 receptor–binding moieties, conjugated with DTPA to allow radiolabeling with ^{111}In. The labeling of 20 μg DPC11870 and 75 MBq ^{111}In was performed in metal-free 0.25 mol/L ammonium acetate buffer, pH 5.5, during 30 min at room temperature (*17*). Radiochemical purity was checked by instant thin-layer chromatography on silica gel strips (Gelman Sciences, Inc.) in 0.1 mol/L sodium citrate buffer, pH 6.0, and by reversed-phase high-performance liquid chromatography (model 1100 system; Agilent Technologies S.A./N.V.) on a C18 column (Zorbax Rx-C18, 4.6 mm × 25 cm; Agilent), using a linear gradient from 100% NH_4Ac buffer, pH 7.0, to 100% acetonitrile in 50 min, at a flow rate of 1 mL/min. The specific activity of the ^{111}In-DPC11870 was 3.7 MBq/μg (12 MBq/nmol), and the chemical purity exceeded 95%.

Radiolabeling of Granulocytes

Because radiolabeled leukocytes obtained from infected donors showed better imaging characteristics than did leukocytes obtained from healthy donors (*18*), blood was obtained from a donor rabbit in which acute colitis had been induced 48 h before. The collection of 50 mL of blood and the purification and labeling of granulocytes with 185 MBq of ^{99m}Tc-HMPAO was performed as described previously (*19*). Labeling efficiency exceeded 80%.

^{18}F-FDG

^{18}FDG was commercially obtained (DRN 9957; Tyco Healthcare). The activity concentration was 1.22 GBq/11.3 mL at calibration time.

Animal Model

Fifteen female New Zealand White (NZW) rabbits weighing 2.3–2.8 kg were kept in cages (1 rabbit per cage) and fed standard laboratory chow and water ad libitum. Thirty minutes before the induction of colitis and during the imaging experiment, the animals were sedated with a subcutaneous injection of 0.7 mL Hypnorm (fentanyl, 0.315 mg/mL, and fluanisone, 10 mg/mL; Janssen Pharmaceutical). Colitis was induced as described previously, with minor modifications (*20*,*21*). A flexible silicone tube (2.6-mm diameter, 40-cm length) was inserted into the colon, with the tip placed 20 cm from the anal sphincter. Through the tube, 1 mL of 50% ethanol, followed by 1 mL of ethanol containing 25 mg of trinitrobenzene sulfonic acid (Sigma Chemicals) and 3 mL of ethanol, was injected into the colon. After the induction, animals had free access to the normal amount of food and water. All animal experiments were approved by the local Animal Welfare Committee in accordance with the Dutch legislation and were performed in accordance with their guidelines.

Imaging and Biodistribution

Forty-eight hours after the induction of colitis, the animals received an intravenous injection of 11 MBq of ^{111}In-DPC11870, 18.5 MBq of ^{99m}Tc-HMPAO-granulocytes, or 30 MBq of ^{18}F-FDG. For comparison, a healthy rabbit also was injected with 11 MBq ^{111}In-DPC11870. For scintigraphic imaging of ^{111}In-DPC11870 and ^{99m}Tc-granulocytes, the rabbits were immobilized in a mold and placed prone on a γ-camera (Orbiter; Siemens) using a low-energy (^{99m}Tc-granulocytes) or medium-energy (^{111}In-DPC11870) parallel-hole collimator. Images of 300,000 counts each were obtained at various times after injection and stored in a 256 × 256 matrix. All images were windowed identically, allowing a fair comparison among the experiments. For PET, the animals were imaged for 16 min starting 1 h after injection, using a rotated half-ring dedicated PET scanner (ECAT ART; Siemens/CTI) and a scan distance of 28.35 cm (38% transmission). The animals were euthanized after the last image was acquired. A blood sample was drawn by cardiac puncture. Tissues were dissected and weighed. The amount of radioactivity in the tissues was measured in a shielded well-type γ-counter (Wizard; Canberra Packard) together with the injection standards and was expressed as percentage injected dose per gram (%ID/g). The ratio of affected colon to unaffected colon was calculated for each inflamed colonic segment, using uptake of the compound in an unaffected segment at the proximal end as the reference value. The mean and SD of the individual ratios were calculated for each radiolabeled compound. The time at which biodistribution was performed was considered the optimal time point for each radiolabeled compound. Imaging beyond 1 h after injection of ^{18}F-FDG is hardly feasible because of its short biologic and physical half-life. In the case of ^{99m}Tc-HMPAO-granulocytes, leakage of ^{99m}Tc-HMPAO and subsequent excretion to the gallbladder and intestine restricts the maximum imaging and evaluation time (*19*,*22*).

Statistical Analysis

All mean values are presented as mean ± SD. Statistical analysis was performed using ANOVA. The level of significance was set at 0.05.

RESULTS

Two days after the induction of colitis, all animals had diarrhea. The rabbits ate less food, but their water intake and

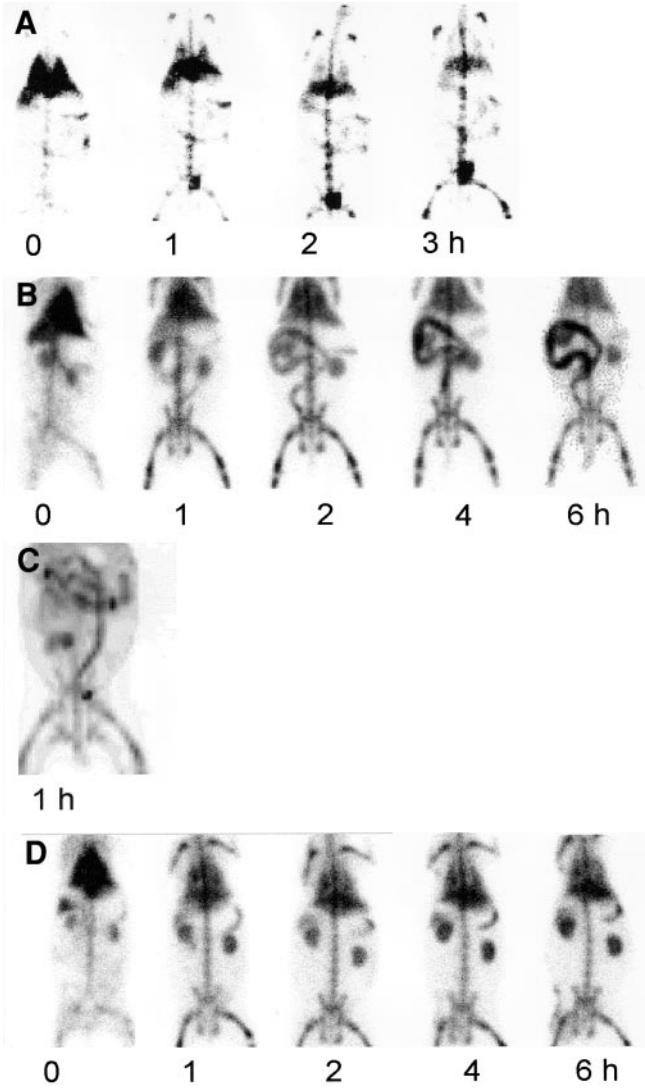

FIGURE 1. Anterior scintigraphic images of rabbits that were placed prone on γ-camera. (A) Images acquired 0, 1, 2, and 3 h after injection of 18.5 MBq ^{99m}Tc-granulocytes in rabbit with acute colitis. (B) Images acquired 0, 1, 2, 4, and 6 h after injection of 11 MBq ^{111}In-DPC11870 in rabbit with acute colitis. (C) 3-Dimensional representation of image acquired 1 h after injection of 30 MBq ^{18}F-FDG in rabbit with acute colitis. (D) Images acquired 0, 1, 2, 4, and 6 h after injection of 11 MBq ^{111}In-DPC11870 in healthy rabbit.

behavior were normal. Scintigraphic images acquired at several different times after injection are shown in Figure 1. Each of the 3 radiopharmaceuticals showed the inflamed colon at 1 h after injection. Uptake of radiolabeled granulocytes at the site of the inflamed colon was moderate, especially when compared with uptake of ^{111}In-DPC11870 at the same time points. Both ^{18}F-FDG and ^{111}In-DPC11870 clearly delineated the colitis and showed low uptake in noninflamed colon; however, ^{111}In-DPC11870 revealed the inflamed lesions better than did ^{18}F-FDG. The images acquired after injection of ^{111}In-DPC11870 in the healthy animal showed no accumulation of radioactivity in the abdominal area at any time point.

The general in vivo behavior of the 3 radiotracers was very different. Immediately after injection, ^{99m}Tc-granulocytes showed high uptake in lung and liver, and the activity concentration in both organs decreased with time. In all images, uptake of radioactivity was seen in the bone marrow. The pharmacokinetics of ^{111}In-DPC11870 were different from those of ^{99m}Tc-granulocytes. A few minutes after injection, the radiolabeled LTB_4 antagonist localized mainly in the circulation (heart), liver, and kidneys. At later times, radioactivity decreased in the circulation but accumulated in the bone marrow and inflamed colon. PET images acquired 1 h after ^{18}F-FDG injection revealed a high radioactivity concentration in the kidneys. Before PET scanning, the bladder was emptied by catheterization. Figure 2 summarizes the biodistribution data of ^{18}F-FDG at 1.5 h after injection, of ^{99m}Tc-granulocytes at 3 h after injection, and of ^{111}In-DPC11870 at 6 h after injection. These times were considered optimal for the individual radiopharmaceuticals. Uptake in the inflamed colon was highest for ^{111}In-DPC11870 and then for ^{99m}Tc-granulocytes (0.72 ± 0.18 %ID/g vs. 0.40 ± 0.11 %ID/g, respectively). Uptake of ^{18}F-FDG in the inflamed colon was relatively low (0.16 ± 0.04 %ID/g). Furthermore, the total %ID in the inflamed colon was significantly higher for ^{111}In-DPC11870 than for the other 2 radioactive tracers ($P < 0.004$), whereas there was no significant difference in colonic uptake between ^{99m}Tc-granulocytes and ^{18}F-FDG ($P > 0.6$). Although the radioactivity concentration in the unaffected part of the colon was highest in rabbits injected with ^{111}In-DPC11870, the ratio of affected colon to unaffected colon was nevertheless highest with this radiopharmaceutical (11.6 for ^{111}In-DPC11870, 5.5 for ^{99m}Tc-granulocytes, and 4.1 for ^{18}F-FDG; Fig. 3). After dissection of the tissues, activity in the

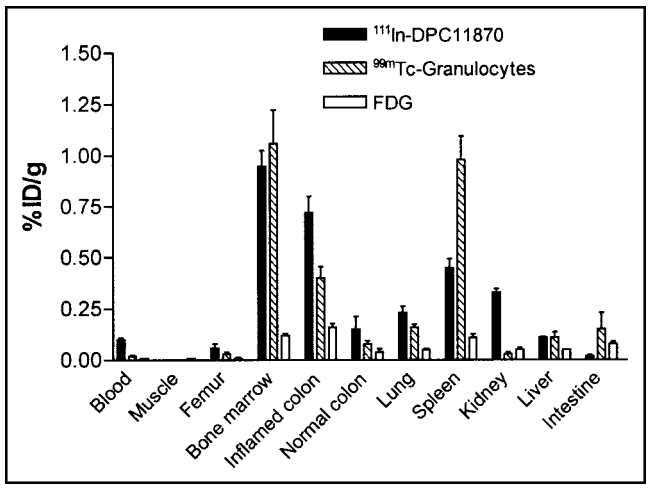

FIGURE 2. Biodistribution data of rabbits that received intravenous injections of ^{111}In-DPC11870, ^{99m}Tc-granulocytes, or ^{18}F-FDG. Uptake in organs and tissues is expressed as %ID/g. Each bar represents mean ± SD. Ex vivo biodistribution was determined 6 h after injection for ^{111}In-DPC11870, 3 h after injection for ^{99m}Tc-granulocytes, and 1 h after injection for ^{18}F-FDG.

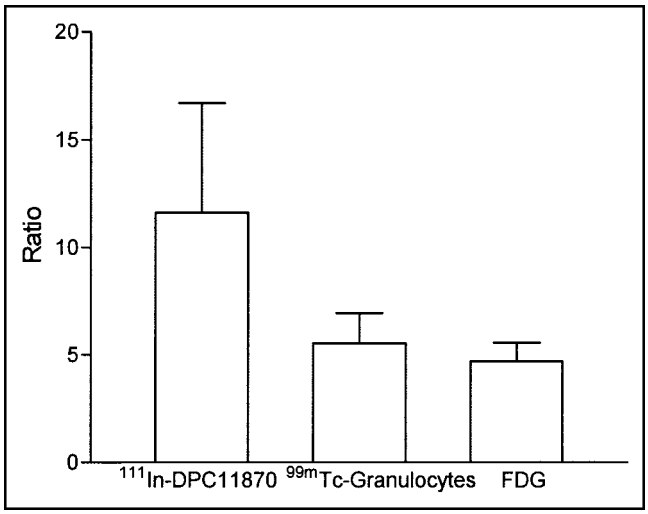

FIGURE 3. Mean ratios of affected colon to unaffected colon for ^{18}F-FDG, ^{99m}Tc-granulocytes, and ^{111}In-DPC11870 at 1, 3, and 6 h after injection, respectively. Ratios were derived from individual colonic segments taken at dissection.

colonic tissue and activity in the colonic content were measured separately. Each of the 3 radiolabeled compounds had low activity concentrations in the content of the colon, as shown in Figure 4. The radioactivity concentration in the colonic content did not significantly differ between the 3 agents ($P > 0.6$). For ^{99m}Tc-labeled granulocytes, the radioactivity concentration was high in spleen and bone marrow (0.98 ± 0.23 %ID/g and 1.06 ± 0.33 %ID/g, respectively). The ^{111}In-DPC11870 biodistribution data revealed a similar high uptake in bone marrow (0.95 ± 0.17 %ID/g), whereas uptake in the spleen was considerably lower (0.45 ± 0.10 %ID/g). For this agent, considerable activity localized in the kidneys (0.33 ± 0.04 %ID/g). Biodistribution data from animals injected with ^{18}F-FDG indicated that a large fraction of the injected dose had already been excreted from the body by 1 h after injection. Uptake of ^{18}F-FDG in all organs (except inflamed colon) was very low, and activity concentrations in the bone marrow and spleen were low (0.12 ± 0.02 %ID/g and 0.11 ± 0.03 %ID/g, respectively).

DISCUSSION

The present study demonstrated that both ^{111}In-DPC11870 and ^{18}F-FDG are excellent agents for imaging experimental colitis in NZW rabbits. Both agents are superior to ^{99m}Tc-leukocytes, the standard imaging agent for scintigraphic evaluation of inflammatory bowel disease in humans. Images acquired after injection of ^{111}In-DPC11870 showed the inflamed colon in as soon as 1 h. The activity concentration of radiolabeled DPC11870 in the colon at 6 h after injection was high, and visualization of inflamed lesions in the colon was better with ^{111}In-DPC11870 than with ^{18}F-FDG.

Numerous studies have focused on the role of leukotrienes and leukotriene antagonists as chemotactic compounds in the mediation of infection and inflammation (*10*,*23*). Because of the antiinflammatory effect of LTB_4 antagonists, the mechanism of interaction and the receptor specificity of these compounds have been studied extensively (*24*). Yokomizo et al. (*12*,*13*) reported that 2 different LTB_4 receptors could be identified. The high-affinity receptor BLT1 is expressed mainly on activated polymorphonuclear leukocytes at the site of infection or inflammation. Accumulation of ^{111}In-DPC11870 in inflamed colon is most likely due to interaction with the BLT1 receptor expressed on these infiltrated cells. In vitro binding studies showed that DPC11870 binds to purified human granulocytes with high affinity (*17*).

Recently, several investigators reported the applicability of ^{18}F-FDG for imaging of infection and inflammation. Animal models demonstrated that ^{18}F-FDG accumulates in both acute and chronic infectious lesions (*2*,*25*). The accumulation of ^{18}F-FDG in infectious and inflammatory lesions has been hypothesized to be a consequence of enhanced uptake of ^{18}F-FDG in neutrophils, macrophages, causative microorganisms, or granulation tissue (*5*,*26*). Uptake of ^{18}F-FDG in these cells is enhanced because of the increased glycolysis and the intensified stimulation of the hexose monophosphate shunt in these cells (*27*). In addition, activated inflammatory cells also have an increased expression of glucose transporters, and the affinity of glucose transporters (for deoxyglucose) is increased by several cytokines and growth factors (*28*,*29*). ^{18}F-FDG PET for visualization of infectious and inflammatory foci is now a frequent subject of clinical studies. Hannah et al. (*27*) were among the first investigators to describe a patient with increased ^{18}F-FDG uptake in the bowel, with the uptake probably being due to inflammation in the bowel wall. In a separate study of 5 patients diagnosed with colitis, Kresnik et al. (*30*) showed that ^{18}F-FDG PET detected colitis at an early clinical stage.

The results of the present study on rabbits with acute colitis confirmed this increased ^{18}F-FDG uptake in inflamed lesions in the colon. With ^{18}F-FDG PET, the inflamed colon

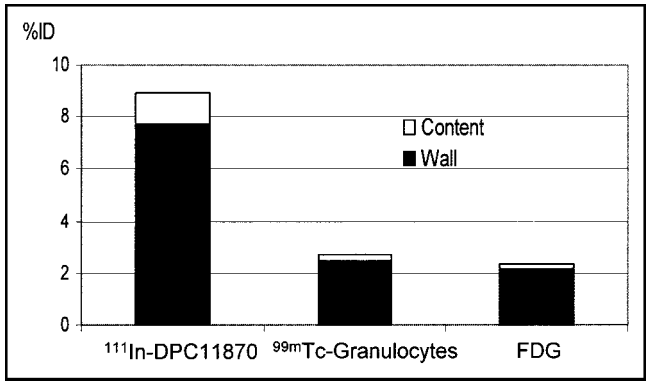

FIGURE 4. Amount of activity (%ID) found in colonic wall and in content of affected colon for the 3 radiopharmaceuticals: ^{111}In-DPC11870, ^{99m}Tc-granulocytes, and ^{18}F-FDG.

was rapidly revealed and, because of rapid and complete clearance of activity from the remainder of the body, was distinctly seen. Conventional ^{99m}Tc-granulocytes, a commonly used imaging agent in the management of patients with inflammatory bowel disease, showed that uptake of radioactivity in the colon was increased. However, because of relatively high background radioactivity, the inflamed colon was less evident than with ^{18}F-FDG and ^{111}In-DPC11870.

Differential counting of the colonic tissue and the colonic content indicated that each of the 3 agents almost exclusively localized in the inflamed colonic wall (91, 92, and 87 %ID for ^{99m}Tc-granulocytes, ^{18}F-FDG, and ^{111}In-DPC11870, respectively) rather than in the feces, indicating that radioactivity is cell associated. Occasionally, some local uptake in the stool was observed. Macroscopic examination of the colonic wall and the content of the colon indicated that this local uptake was observed mainly in regions with severe tissue damage and ulcers. This implies that occasional enhanced radioactivity in the feces may be caused by loss of cells from the lumen.

CONCLUSION

^{99m}Tc-granulocytes, ^{111}In-labeled LTB_4 antagonist DPC11870, and ^{18}F-FDG reveal acute colitis in NZW rabbits early after injection. We found that both ^{111}In-DPC11870 and ^{18}F-FDG were superior to ^{99m}Tc-granulocytes in allowing visualization of inflamed lesions. At later times, the quality of the images obtained with ^{111}In-DPC11870 continued improving because of ongoing accumulation of radioactivity at the site of inflammation and continuous clearance from the background.

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