Pretreatment with Diphenoxylate Hydrochloride/Atropine Sulfate (Lomotil) does not Decrease Physiologic Bowel FDG Activity on PET/CT Scans of the Abdomen and Pelvis

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Abstract

Purpose: Physiologic uptake of 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) by bowel can confound positron emission tomography/computed tomography (PET/CT) assessment for abdominal pathology, particularly within the bowel itself. We wished to determine if oral administration of the antimotility agent, Lomotil (5 mg diphenoxylate hydrochloride/0.05 mg atropine sulfate; G.D. Searle and Company, a division of Pfizer), prior to PET/CT scanning would reduce physiologic uptake of FDG by the small bowel and colon (lower gastrointestinal [GI] tract).

Procedures: Patients undergoing PET/CT scans for lymphoma were enrolled in a prospective, randomized, double-blinded study and received either 10 mL water (control group) or 10 mL Lomotil (experimental group) orally 30–60 min prior to scanning. Scans were reviewed independently by two blinded experienced readers and scored for the degree of FDG activity in the lower GI tract relative to liver activity.

Results: The administration of Lomotil prior to PET/CT scanning did not reduce physiologic FDG activity in the small bowel and colon. In contrast, increased radiotracer uptake by the lower GI tract was observed in the Lomotil group compared to the control group.

Conclusions: Pretreatment with Lomotil prior to PET/CT scanning confers no benefit toward the reduction of physiologic FDG uptake by the small bowel and colon.

Key words: Lomotil, Diphenoxylate/atropine, PET, Positron emission tomography

Introduction

2-[18F]-Fluoro-2-deoxy-D-glucose–positron emission tomography (FDG-PET) has proven to be a valuable clinical tool for the staging and surveillance of head/neck, thoracic, and abdominal/pelvic malignancies [1–3]. FDG is a glucose analog. Like glucose, it enters cells via a receptor-mediated process and is promptly phosphorylated in the cytoplasm. Unlike glucose, further metabolism is very slow, resulting in FDG accumulation within the cell. Any process that increases the metabolic activity of a tissue over the general background will result in relatively increased FDG radiotracer uptake and accumulation. It is up to the interpreting physician to determine if such increased uptake detected by PET scanning is due to neoplasm, infection, an inflammatory process, artifact, or represents normal activity for that tissue.

As expected, highly metabolic tissues such as skeletal muscle and brown fat may accumulate FDG [4–8] on PET/CT scans. Discrimination from pathology in these areas can usually be achieved by assessing for inflammation or mass lesions on coregistered CT images [9]. FDG also frequently
localizes to the lower gastrointestinal (GI) tract in a nonspecific manner [10–12]. The underlying etiology for such uptake remains unknown and is presumably either due to smooth muscle accumulation, mucosal accumulation, concentration of radiotracer within the bowel lumen, or a combination of these processes [12, 13]. Coregistered CT images are generally not helpful for differentiating nonspecific FDG uptake in the GI tract from true pathology such as adenomas or small malignancies. This often requires surgery or colonoscopy [14–16].

Reduction of physiologic bowel uptake would potentially allow for more specific identification of bowel pathology by PET/CT and thus decrease unnecessary diagnostic procedures and associated morbidity. Stahl and co-investigators noted decreased bowel uptake on PET after administration of the anticholinergic, N-butylscopolamine [17], presumably due to the inhibition of smooth muscle peristalsis and, therefore, decreasing the energy requirements of the bowel. This drug is not available in the United States. We wished to investigate this promising strategy further using the more readily available oral antiperistaltic medication (Lomotil) in a prospective, randomized, double-blind study involving patients undergoing PET/CT scans for lymphoma.

Materials and Methods

Sixty-nine patients undergoing routine clinical PET/CT scans for lymphoma were entered prospectively after informed written consent in an institutional review board-approved protocol. Thirty-four patients (average age 59±10 years; 29 males and five females) were randomized to receive a single 10-mL oral dose of Lomotil (5 mg diphenoxylate hydrochloride/0.05 mg atropine sulfate; G.D. Searle and Company, a division of Pfizer) 30 to 60 min before injection of approximately 740 MBq (20 mCi) of FDG. Thirty-four patients (average age 55±10 years; 24 males and ten females) were randomized to a control group to receive 10 mL of water in the same fashion. One patient was by chance enrolled twice in the study on separate visits to the clinic. This patient, a 58-year-old male, was initially scanned after pretreatment with water and scanned 4 months later after pretreatment with Lomotil. Thus, a total of 70 scans were acquired during the study (35 following administration of water; 35 following administration of Lomotil). With the exception of a single patient who had non-FDG-avid low-grade follicular lymphoma involving the duodenum, none of the enrolled patients had lymphoma involving the small bowel or colon at the time of the scan.

Sixty-three PET studies were performed as static 2D scans (5 min per bed position) with a slice thickness of 4.25 mm on a Discovery LS scanner (GE Medical Systems, Waukesha, WI, USA), and data were reconstructed with 2D OSEM (28 subsets, two iterations) into a 50-cm field of view with a postfilter resolution of 7.3 mm full width at half maximum. Seven PET studies were performed as static 2D scans (5 min per bed position) with a slice thickness of 3.27 mm intervals on a Discovery RX scanner (GE Medical Systems, Waukesha, WI, USA), and data were reconstructed with 2D OSEM (28 subsets, two iterations) into a 60-cm field of view with a postfilter resolution of 7.0 mm full width at half maximum. All PET data were corrected for scatter, random coincidences, and decay. Noncontrast CT was used for attenuation correction and anatomic coregistration.

Two nuclear medicine radiologists (MN, VL), blinded to the administration of Lomotil or placebo, read the scans independently and scored uptake in the small bowel and uptake in the large bowel of each patient either as 0 (no uptake), 1 (uptake less than liver), 2 (uptake equivalent to liver), or 3 (uptake greater than liver). The summed small bowel and large bowel data for each reader were compared between the placebo and Lomotil groups using an extension of Fisher’s exact test for ordered contingency tables [18, 19].

Results

Pretreatment with Lomotil prior to scanning resulted in no significant decrease of small bowel and colonic FDG activity scores (Table 1). In contrast, both reviewers noted statistically greater (p<0.05) small bowel uptake of FDG and an upward trend in colonic activity following the administration of Lomotil. Likewise, Lomotil resulted in statistically greater overall lower GI tract FDG uptake when the small bowel and colon were assessed as a single unit. Fig. 1 demonstrates sample coronal images from PET/CT scans of two randomized patients, one pretreated with Lomotil and the other pretreated with water. Bowel FDG uptake is noticeably higher in the patient who received Lomotil.

Table 1. Average FDG uptake by the small bowel and colon in patients pretreated with water (control) vs. Lomotil

<table>
<thead>
<tr>
<th></th>
<th>Reader</th>
<th>Control*</th>
<th>Lomotil*</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small bowel</td>
<td>VL</td>
<td>1.34±0.64</td>
<td>1.74±0.74</td>
<td>0.0197</td>
</tr>
<tr>
<td></td>
<td>MN</td>
<td>1.43±0.65</td>
<td>1.77±0.60</td>
<td>0.0485</td>
</tr>
<tr>
<td>Colon</td>
<td>VL</td>
<td>1.37±0.77</td>
<td>1.77±0.91</td>
<td>0.0567</td>
</tr>
<tr>
<td></td>
<td>MN</td>
<td>1.31±0.96</td>
<td>1.69±0.80</td>
<td>0.0906</td>
</tr>
<tr>
<td>Small bowel+colon</td>
<td>VL</td>
<td>1.36±0.58</td>
<td>1.76±0.63</td>
<td>0.0107</td>
</tr>
<tr>
<td></td>
<td>MN</td>
<td>1.37±0.48</td>
<td>1.73±0.55</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

Intraclass correlations for interrater reliability between VL and MN were 0.226 (fair) for the small bowel, 0.396 (fair) for the colon, and 0.445 (moderate) for the small bowel and colon combined

*p<0.05, significant difference between the control and Lomotil groups with 95% confidence

Averaged activity scores (+one standard deviation; 0=none, 1=less than liver, 2=same as liver, 3=greater than liver)
Discussion

Bowel FDG uptake is frequent and nonspecific, limiting the usefulness of PET/CT imaging for lower GI tract pathology [10–12]. Potential sources of radiotracer accumulation include physiologic processes, malignancy, inflammation, infection, and benign tumor [14–16, 13, 20]. In few situations, the pattern of uptake may suggest the presence of pathology vs. normal physiologic accumulation. For example, long stretches of colonic uptake can be indicative of colitis [13, 20]. However, most individuals demonstrate some degree of nonspecific FDG accumulation which is often localized to multiple short segments [13] and can be focally intense, particularly in the colon. The etiology of such uptake is not known and can confound scan interpretation.

Efforts at reducing nonspecific uptake have focused on the inhibition of smooth muscle peristalsis. Presumably, limiting muscle activity reduces metabolic activity, thus decreasing radiotracer uptake. Atropine, which inhibits smooth muscle peristalsis [21], did not decrease FDG bowel uptake in a study by Jadvar et al. [22]. However, the study was statistically underpowered due to the inclusion of only five patients. In contrast, Stahl et al. reported decreased bowel uptake in a larger study using the anticholinergic, N-butylscopolamine [17]. However, this agent is not available in the United States. We wished to determine if the more readily available antiperistaltic agent, Lomotil, would demonstrate the same effect. In contrast to N-butylscopolamine, our results show that administration of Lomotil prior to PET/CT scanning does not significantly reduce FDG uptake in the lower GI tract. These disparate findings may be related to the different mechanisms of action of these agents. Diphenoxylate functions as an analog of Demerol (meperidine) and slows peristalsis of the GI tract by stimulating mu and delta opiate receptors [23]. A subtherapeutic dose of atropine is included in the preparation to discourage self-administration of large amounts of diphenoxylate for its potential central nervous system effects; at recommended doses of Lomotil, atropine has no effect. N-butylscopolamine func-

Fig. 1. Selected coregistered coronal CT, PET, and fused images of the abdomen and pelvis in a patient pretreated with Lomotil (row a) and in a different patient pretreated with water (row b) prior to scanning.
tions as an anticholinergic, thus inhibiting glandular secretions and smooth muscle contraction by opposing the muscarinic functions of acetylcholine [23]. These findings suggest that FDG uptake by the bowel may be predominantly determined by secretory activity rather than peristalsis. Alternatively, these agents may differentially target as of yet undescribed visceral pathways affecting bowel metabolic activity.

The maximum recommended single adult dose of Lomotil for the treatment of diarrhea is 5 mg diphenoxylate hydrochloride/0.05 mg atropine orally [23] and was thus chosen as the amount to be administered to patients in the experimental group prior to scanning. The initial patient chosen as the amount to be administered to patients in the initial patient observation period was 30 minutes with a peak plasma concentration at about 0.5 mg diphenoxylate hydrochloride/0.05 mg atropine orally [23, 24]. As a result, administration of Lomotil no less than 60 min prior to FDG injection was desired in this study to ensure sufficient time for drug effect. However, this required patients to arrive at the hospital at least 60 min prior to scanning. It is possible that different results may have been obtained if patients in the experimental group had been placed on multiple-dose therapy beginning several days prior to scanning. It is possible that different results may have been obtained if patients in the experimental group had been placed on multiple-dose therapy beginning several days prior to scanning. It is possible that different results may have been obtained if patients in the experimental group had been placed on multiple-dose therapy beginning several days prior to scan. Given the results observed in this study with single-dose therapy, however, more rigorous pretreatment may only worsen FDG uptake by bowel.

**Conclusion**

Some practices routinely pretreat patients with the antiperistaltic agent, Lomotil, in an effort to diminish confounding bowel activity on PET scans. Our investigation reveals no benefit to the usage of this drug for this purpose. Rather, background FDG uptake by the lower GI tract is increased. We conclude that Lomotil should not be routinely given prior to PET/CT scanning for the intent of lowering background bowel radiotracer uptake.

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**References**

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