A Randomised Controlled Trial Assessing the Effect of Oral Diazepam on $^{18}$F-FDG Uptake in the Neck and Upper Chest Region

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Abstract

Objective: A distinctive pattern of physiological symmetrical uptake of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) in the neck and upper chest region is a phenomenon that is sometimes observed on positron emission tomography (PET) scans of some oncologic patients. Initially, it was assumed to be muscle uptake secondary to patient anxiety or tension, which could be prevented by diazepam treatment. However, PET–computed tomography data have shown that $^{18}$F-FDG uptake is not restricted to the musculature but is also localised within the non-muscular soft tissue, such as brown adipose tissue. The efficacy of benzodiazepine treatment to reduce this uptake has not been well established. Therefore, a randomised controlled trial was conducted to decide whether diazepam would decrease physiological $^{18}$F-FDG uptake in the neck and upper chest region (FDG-NUC).

Methods: A randomised, double-blind, placebo-controlled trial was conducted to assess the effect on FDG-NUC of 5 mg diazepam, given orally 1 h before $^{18}$F-FDG injection. Patients younger than 40 years, having or suspected to have a malignancy, were eligible for inclusion. The primary endpoint was FDG-NUC, as assessed by visual analysis of whole-body PET scans by two independent observers. The secondary endpoint was clinical relevance of FDG-NUC.

Results: Fifty-two patients were included between September 2003 and January 2005. Twenty-eight patients (54%) received placebo; 24 (46%) received diazepam. FDG-NUC was seen in 25% of the patients in the diazepam group versus 29% in the placebo group. This difference was not statistically significant.

Conclusion: No beneficial effect of administration of diazepam could be established. Pre-medication with benzodiazepines to diminish physiological uptake of $^{18}$F-FDG in the neck and upper chest region is not indicated.

Key words: Positron emission tomography, $^{18}$F-FDG, Neck and upper chest region, Diazepam, Randomised controlled trial

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Introduction

Preparation of patients for 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) studies aims to eliminate or reduce patterns of physiological uptake that may interfere with image interpretation. Non-specific 18F-FDG uptake in the neck and mediastinal area, in the heart, bowel and urinary tract might lead to erroneous interpretation with potentially serious clinical consequences or useless scans. Fasting is the only universally accepted standard procedure before 18F-FDG injection, although the duration of fasting may vary. There is hardly any uniformity with respect to other procedures to reduce non-specific uptake. This is likely due to the lack of compelling evidence that interventions actually work.

Especially non-specific uptake of 18F-FDG in the neck and upper chest region can significantly interfere with image quality and image interpretation. At first, this distinctive pattern of physiological symmetrical uptake of 18F-FDG in the neck and upper chest region (FDG-NUC; Fig 1), predominantly seen in some oncologic patients, was thought to be muscle uptake secondary to patient anxiety or tension [1, 2]. However, PET–computed tomography (PET-CT) data have shown that 18F-FDG uptake is not only restricted to the musculature but is also localised within the non-muscular soft tissue, such as the brown adipose tissue (BAT) [3]. Recent literature suggests that pre-medications with beta blockers may diminish uptake of 18F-FDG in BAT [4, 5]. However, it is still relatively common to pre-medicate patients with benzodiazepines to reduce FDG-NUC. Since the efficacy of benzodiazepine treatment before administration of 18F-FDG has not been well established yet, a randomised controlled trial was conducted to decide whether oral administration of diazepam would decrease FDG-NUC in oncologic patients younger than 40 years.

Previously, retrospective analysis of PET images acquired in 192 patients at our centre revealed an overall prevalence of 31% [6]. In patients under 40 years, this percentage was 35. Multivariate logistic regression showed a strong inverse association between age and FDG-NUC. No association between low body mass index and FDG-NUC could be established. Both findings were also reported by Bar-Shalom et al. [7] and Truong et al. [8]. In our retrospective analysis, no protective effect of benzodiazepines could be determined. However, occasionally, benzodiazepines were administered only shortly before injection of 18F-FDG. Considering a time to maximum plasma concentration of at least 15 to 30 min, the drug may not have been effective during the early uptake period following injection of 18F-FDG [9].

Methods

Study Population

The study was conducted in two hospitals: a university medical centre and a general hospital in The Netherlands. Patients aged between 18 and 40 years who were referred for an oncologic 18F-FDG PET scan were eligible. Exclusion criteria were diabetes mellitus, myasthenia gravis, severe hepatic insufficiency, known allergy to benzodiazepines, driving on the day of the PET imaging, and use of a benzodiazepine within 7 days before the start of the study.

Study Design

The study was designed as a prospective, double-blind, multicenter, randomised, placebo-controlled clinical trial. The Internal Review Board of both participating hospitals

Fig. 1. Physiological uptake of FDG in the neck and upper chest region.
approved the protocol. Informed consent was obtained in all patients.

Randomisation in blocks of four and stratification according to centre and tumour was performed centrally by the Department of Pharmacy of the VU University Medical Center. Diazepam 5 mg (Stesolid®) tablets were obtained from Dumex, Hilversum, The Netherlands and placebo (albochin) tablets from Interpharm, Den Bosch, The Netherlands. The tablets were identical to ensure blinding. Study medication was packaged and blinded at the Department of Pharmacy of the VU University Medical Center.

Eligible patients were asked to participate by their own attending clinician, the nuclear medicine physician or by the principle investigator. If all inclusion criteria had been met and informed consent had been obtained, patients were randomised. Patients were instructed to take study medication 1 h before injection of 18F-FDG.

PET imaging was performed according to standard hospital procedure. All patients were injected after fasting for at least 6 h, although patients were allowed and encouraged to drink only water. All serum glucose levels were within normal range at time of PET scanning. During the whole procedure, room temperature was constant at about 20°C. The scans were obtained 1 h after intravenous injection of 370–500 MBq 18F-FDG. 18F-FDG was obtained from Tyco Mallinckrodt, Petten, The Netherlands.

Data Analysis

The primary endpoint was FDG-NUC prevalence, as assessed by visual analysis of whole-body PET scans by two independent experienced observers. Assessment of abnormal FDG-NUC was performed using a Likert scale (uptake absent, slight, moderate, and intense) to indicate the intensity. Moderate and intense uptake were considered positive for FDG-NUC, whereas absent and slight uptake were deemed negative. The secondary endpoint was whether FDG-NUC had any clinical relevance by interfering with scan interpretation, as assessed by the observers. Clinical relevance relates to the perceived probability of findings of FDG-NUC to be interpreted by the nuclear medicine physician as either false positive or false negative. This clinical relevance was scaled as not relevant, moderately or highly interfering with scan interpretation. In case of disagreement on either endpoint, a third observer would review the scan and serve as an arbiter.

Statistical Analysis

The number of patients needed was estimated from results of the retrospective analysis earlier performed at the VU University Medical Center [6]. The calculation was based on a risk of FDG-NUC in patients under 40 years of 35%, a drug-related improvement of 70%, which we thought was clinically relevant and was realistic given the data of Barrington et al. [1], a significance level of 0.05, a power of 80% and two-tailed analysis. The number of patients needed was calculated at 41 per treatment group.

Table 1. Patient characteristics

|                     | Placebo (n=28) | Diazepam (n=24) | p value |
|---------------------|---------------|-----------------|--------|
| Sex (M/F)           | 15/13         | 12/12           | 0.797  |
| Mean age (year)±SD  | 30.2±5.9      | 30.6±6.4        | 0.748  |
| Mean bodyweight (kg)±SD | 73.8±13.2     | 80.1±19.0       | 0.541  |
| Mean body mass index (kg/m²)±SD | 23.7±3.2     | 25.0±4.9        | 0.545  |
| Scan                | 20 (71)       | 12 (50)         | 0.113  |
| First (%)           | 8 (29)        | 12 (50)         |        |
| Second or later (%) |                |                 |        |
| Tumour              | 0 (0)         | 1 (4)           | 0.388  |
| Head and neck (%)   | 15 (54)       | 15 (63)         |        |
| Lymphoma (%)        | 13 (46)       | 8 (33)          |        |
| Other (%)           |                |                 |        |
| Centre              | VU University Medical Center, Amsterdam | 25 | 23 | 0.377 |
|                     | Catharina Hospital, Eindhoven | 3 | 1 | |
| Patients without co medication (%) | 14 (50) | 14 (58) | 0.548 |
Table 2. Physiological uptake of 18F-FDG in the neck and upper chest region

| Treatment group     | Placebo (n=28) | Diazepam (n=24) | p value |
|---------------------|----------------|----------------|---------|
| No FDG-NUC (%)      | 20 (71)        | 18 (75)        | 0.772   |
| FDG-NUC (%)         | 8 (29)         | 6 (25)         |         |

Statistical analysis (Fisher exact chi-square) was performed using SPSS 12.0, and p<0.05 was considered statistically significant. For FDG-NUC in both groups, 95% exact binomial confidence intervals (95% CI) were computed using STATA 8.0.

Results

Fifty-two patients were included in the study between September 2003 and January 2005. Twenty-eight patients (54%) received placebo and 24 (46%) diazepam (Fig. 2). There was no difference in patient characteristics in the two treatment groups (Table 1).

Six (25.0%; 95% CI, 9.8–46.7) patients in the diazepam group developed FDG-NUC versus eight (28.6%; 95% CI, 13.2–48.7) in the placebo group (Table 2). The percentage difference is not statistically significant (−3.6%; 95% CI, −0.26–0.20, p=0.77). Table 3 shows the clinical relevance of FDG-NUC in the patients. Since the calculated relative risk of FDG-NUC was 0.88, approximately 2,500 patients should be included to show a statistically significant difference between diazepam and placebo. Therefore, the study was stopped before inclusion was complete.

Co-medication was used by 14 of 28 (50%) patients in the placebo group and ten of 24 (42%) patients in the diazepam group (Table 4). Interactions between study medication and co-medication were not clinically relevant.

Discussion

In this randomised clinical trial, diazepam had no effect on the prevalence of FDG-NUC. In an earlier retrospective study, we found that 35% of patients with malignant lymphoma or malignancies of head and neck, thyroid or lung younger than 40 years had FDG-NUC. In this prospective study, the prevalence of FDG-NUC was slightly lower at 27%. This may be explained by the difference in patient population: For instance, patients with other tumour types were allowed to enroll, and there may have been a selection bias in favour of less anxious patients. Conceptually, this observed lack of a protective effect by diazepam is in accordance with the idea that uptake of 18F-FDG is primarily noted in non-muscular tissue, which might not be blocked by benzodiazepines. This is in keeping with the results of the preclinical studies described by Tatsumi et al. The use of the non-selective beta-blocker propranolol appeared to diminish uptake of 18F-FDG in BAT [4]. Furthermore, a case report has been published in which the beneficial effect of propranolol has been described [5].

One might argue that the dose of diazepam, 5 mg, was too low and therefore not effective. However, as none of the patients was a regular benzodiazepine user, it is unlikely that the low dose is the cause of the observed lack of effect in the present study. Furthermore, Barrington and Maisey [1] used doses ranging from 5 to 10 mg of diazepam as well.

An increasing number of institutions use PET-CT, with less interpretation problems in physiological cervical uptake due to the anatomical CT information. However, many hospitals still use stand-alone PET systems. In either case, it would be beneficial to be able to diminish physiological uptake of 18F-FDG in patients who are at risk for FDG-NUC. As we did not use a PET-CT combination, it was very difficult to differentiate between uptake of FDG in brown fat or muscle tissue. In most patients (12/14), the uptake was bilateral, symmetrical and diffuse, indicating that this may be in part muscle uptake [10]. The results of the present study clearly show that benzodiazepines cannot be used to

Table 3. Clinical relevance of FDG-NUC in patients showing physiological uptake in neck and upper chest region

| Treatment group     | Placebo (n=8) | Diazepam (n=6) | p value |
|---------------------|--------------|-------------|---------|
| Not relevant (%)    | 8 (100)      | 4 (67)      | 0.165   |
| Moderately relevant | 0 (0)        | 1 (17)      |         |
| Highly relevant (%) | 0 (0)        | 1 (17)      |         |
diminish FDG-NUC, regardless of the origin of the uptake. As benzodiazepines are muscle relaxants, these data also suggest that interventions should focus on reducing uptake of $^{18}$F-FDG in BAT, rather than in muscle. In our study, the rooms were adequately acclimatised and warm. To confirm the findings of Jacobsson et al. [5], it might be better to focus on other interventions such as pre-medication with beta blockers. Before such interventions can be implemented, randomised controlled trials are necessary to show the interventions to be effective on diminishing disturbing physiological $^{18}$F-FDG uptake.

In conclusion, pre-medication with diazepam did not reduce the prevalence of physiological uptake of $^{18}$F-FDG in the neck and upper chest region.

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