THE EFFECTIVENESS OF MEBEVERINE (DUSPATALIN) AND HYOSCINE-N-BUTYLBROMIDE (BUSCOPAN) IN REDUCTION OF PHYSIOLOGICAL BOWEL UPTAKE IN 18F-FDG PET-CT

By

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DECLARATION

I hereby declare that this research was sent to Universiti Sains Malaysia (USM) for the degree of Master of Medicine (Nuclear Medicine). It has not been sent to any other universities. With that, this research can be used for consultation and photocopied as a reference.

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DR MOHD FAHMI SHUKUR BIN RAMLI

P-IPM 0008/13

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In the name of Allah, the Most Gracious and Most Merciful.

I would like to express my gratitude to Allah for all the blessings over me. Peace and blessings be upon the Prophet Muhammad (peace be upon him), his family and companions.

I dedicate this book to my parent; Ramli Bin Safar and Ku Selasiah Binti Ku Sulaiman, my father and mother-in-law; Yahya Bin Pakih and Khamsiah Binti Hj Jahuri as well as to my beloved wife Noor Zakiah Binti Yahya. Without their support and prayers I would not be able to complete this journey. To my family and friends, thank you for your patience, encouragement and help that were given to me while preparing this dissertation.

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Dr Mohd Fahmi Shukur Bin Ramli

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ABBREVIATIONS

18F	Radioisotope Fluorine-18
cm	Centimetre
CT	Computed tomography
FDG	Fluorodeoxyglucose
keV	Kiloelectron volt
kV	Kilovolt
mA	Milliampere
mBq	Megabecquerel
mCi	Millicurie
mg	Milligram
mm	Millimetre
mmol/L	Millimol per litre
mSv	Millisievert
PET-CT	Positron Emission Tomography-Computed Tomography
s	Seconds
SUV	Standardised Uptake Value
SUV_{max}	Maximum standardised uptake value
SUV_{mean}	Mean standardised uptake value

ABSTRAK

Latar belakang: Pengagihan 18F-FDG dalam imbasan PET-CT adalah berdasarkan kepada keperluan glukosa oleh sel-sel. Pengambilan 18F-FDG yang banyak oleh sel-sel yang mempunyai metabolisma aktif seperti sel otot licin usus mampu menjejaskan tafsiran imej. Kajian ini menilai keberkesanan Mebeverine (Duspatalin) dan Hyoscine-n-butylbromide (Buscopan) dalam mengurangkan pengambilan 18F-FDG secara fisiologi oleh usus ketika imbasan 18F-FDG PET-CT dijalankan.

Kaedah: Sebuah kajian prospektif rawak telah dijalankan kepada 195 pesakit yang menjalani imbasan PET-CT di antara September 2016 hingga Februari 2017. Mereka dibahagikan kepada 3 kumpulan; 62 pesakit menerima 135mg ubat Mebeverine, 68 pesakit menerima 10mg ubat Hyoscine-n-butylbromide manakala 65 pesakit adalah kumpulan kawalan. Semua pesakit diimbas antara 45 minit ke 1 jam selepas suntikan 18F-FDG. Seorang pakar perubatan nuklear telah menganalisa imej imbasan; SUV_{mean} untuk usus dan nisbah SUV_{mean} usus : hati telah diperolehi untuk analisis statistik.

Keputusan: Nilai purata SUV_{mean} dan nisbah SUV_{mean} usus:hati di dalam ketiga-tiga kumpulan adalah hampir sama. Tiada perbezaan yang signifikan antara purata SUV_{mean} dan nisbah SUV_{mean} usus:hati di dalam ketiga-tiga kumpulan ($p>0.050$). Analisis kualitatif ke atas tahap pengambilan 18F-FDG oleh usus dan kesukaran mentafsir imej dalam ketiga-tiga kumpulan adalah tidak signifikan ($p=0.302$ dan $p=0.957$ masing-masing). Terdapat perkaitan yang positif antara tahap pengambilan 18F-FDG dan kesukaran mentafsir imej ($r=0.332$, $p<0.001$).

Kesimpulan: Tiada kesan yang signifikan oleh Mebeverine dan Hyoscine-n-butylbromide dalam pengurangan pengambilan 18F-FDG oleh usus secara fisiologi semasa imbasan PET-CT. Semakin tinggi tahap pengambilan 18F-FDG dalam usus, semakin sukar untuk menafsir imej imbasan.

Katakunci: 18F-FDG PET-CT, pengambilan 18F-FDG oleh usus, Mebeverine, Duspatalin, Hyoscine-n-butylbromide, Buscopan, kesan antispasmodik.

ABSTRACT

Background: 18F-FDG distibution in PET-CT scan is based on glucose avidity of the cells. Intense accumulation of 18F-FDG in in the cells with active metabolism like smooth muscles in the bowel can affect the image interpretation. The aim of this study is to determine the effects of Mebeverine (Duspatalin) and Hyoscine-n-butylbromide (Buscopan) in the reduction of physiological bowel uptake in 18F-FDG PET-CT scan.

Methodology: A prospective randomised controlled trial was conducted for 195 patients whom attended PET-CT scan between September 2016 and February 2017. They were divided into 3 groups; 62 patients received 135mg of oral Mebeverine, 68 patients received 10mg of oral Hyoscine-n-butylbromide and 65 patients were in the control group. All patients were scanned 45 minutes to 1 hour after injection of 18F-FDG. An independent experienced interpreter reviewed the images; SUV_{mean} of bowel and bowel-to-liver ratio were obtained for statistical analysis.

Results: There were almost equal values of mean SUV_{mean} of bowel and bowel-to-liver ratio in all groups. No significant different in mean SUV_{mean} of bowel and bowel-to-liver ratio among the three groups ($p>0.050$). There was no significant association of degree of bowel uptake and difficulty of image interpretation in all the three groups ($p=0.302$ and $p=0.957$ respectively). There was positive relationship between degree of bowel uptake and difficulty of image interpretation ($r=0.332$, $p<0.001$).

Conclusion: There was no significant effect of Mebeverine and Hyoscine-n-butylbromide to reduce physiological bowel uptake in 18F-FDG PET-CT. The higher the degree of bowel uptake, the more difficult for the interpreter to interpret the images.

Keywords: 18F-FDG PET-CT, physiological bowel uptake, Mebeverine, Duspatalin, Hyoscine-n-butylbromide, Buscopan, antispasmodic effect.

CHAPTER 1

INTRODUCTION

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INTRODUCTION

Positron Emission Tomography (PET) imaging was introduced in the field of nuclear medicine since 1974 with the capability of assessing functional/physiological status of a disease by using radioisotope. Over the years, its use especially in oncology cases has been widely accepted (Rohren et al, 2004). However, it was limited due to lack of anatomical identification (Lind et al, 2004). The difficulty in localisation of the 18F-FDG uptake in PET is due to poor spatial resolution (Townsend, 2004 and Moses, 2011).

Computed tomography on the other hand has the ability to demonstrate good anatomy but lack in functional evaluation. In view of that, new advancement has been introduced in 1998 by combining PET imaging and CT imaging to form a hybrid imaging called PET-CT. The ability of PET-CT imaging to evaluate the functional and anatomical findings has helped in improving diagnostic accuracy (Von Schulthess, 2006). Furthermore, PET-CT scan also able to evaluate physiological 18F-FDG uptake. This is important because some uptake appears to be physiological in PET but CT evaluation found pathology at the uptake site (Kostakoglu et al, 2004). The ability to evaluate pathological and physiological findings has helped to improve patient management (Bar-Shalom et al, 2003).

However, some 18F-FDG uptake is difficult to be interpreted such as physiological uptake in the smooth muscles of bowel. Gastrointestinal tract uptake among others is the commonest site of uptake in PET-CT. High 18F-FDG uptake in the bowel might be due to active bowel movement. In view of this, it may mask any underlying bowel related pathology.

It is more challenging to interpret the image when the primary lesion originated from the bowel or any organ adjacent to the bowel. As a result, the use of antispasmodic agent such as Mebeverine (Duspatalin) and Hyoscine-n-butylbromide (Buscopan) was introduced. Studies done looking into the use of these agents prior to PET-CT scan have noted reductions in the physiological 18F-FDG uptake in the bowel. However, there is no consensus as to which of this agent is to be used prior to the scan. Therefore, the aim of this study is to assess the effectiveness of both agents in reducing the physiological uptake in the bowel.

CHAPTER 2

LITERATURE REVIEW

CHAPTER 2

LITERATURE REVIEW

2.1 Brief background of PET-CT

PET imaging concept is based on detecting the distribution of radiotracer in the body. Since the day of PET was introduced, there are many types of radiotracer available. The distribution of the radiotracer reflects the physiology of the disease. For example, 18F-fluorodeoxyglucose, 18F-fluorothymidine, 11C-methionine, 11C-choline and 18F-fluoride. Commonly, the radioisotope is tagged to a molecule that undergoes metabolism within the cells. For example, radioisotope 18-Fluorine is a positron emitter. It is tagged to fluorodeoxyglucose (FDG) which is a glucose analogue that will be distributed in the body to areas in which there is high glucose consumption by the cells e.g. in inflammation, infection, physiological such as brain as well as cancer cells. 18F-FDG is transported into the cells via glucose transporter proteins (GLUT). Then, it will undergo a phosphorylation process by hexokinase (Figure 2.1.1). The end product of this is 18F-FDG-6-phospate. Phosphorylated 18F-FDG is chemically impermeable to cell membrane and therefore does not undergo further metabolism. It will remain trapped in the cell (Paulwels et al, 1998).

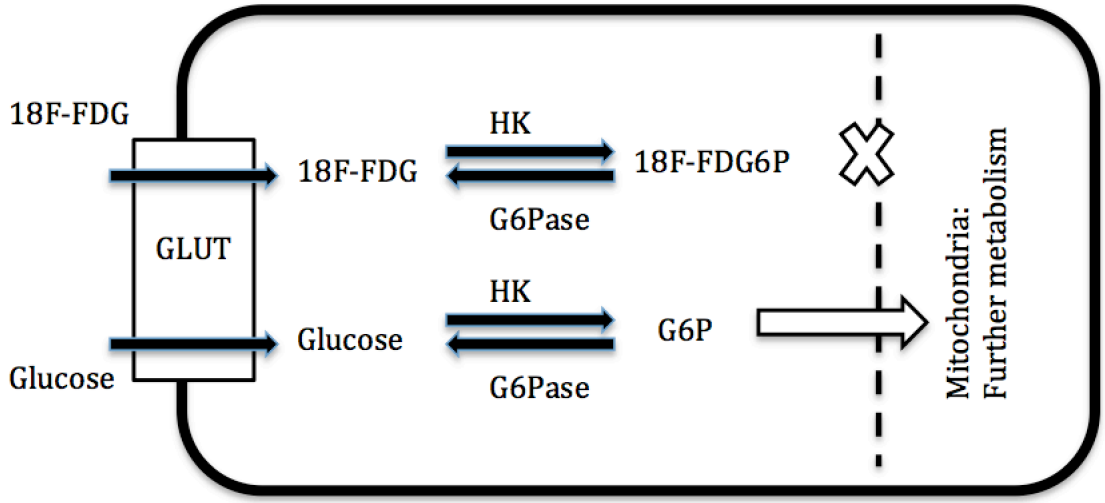

Figure 2.1.1: Schematic diagram on the metabolic trapping of 18F-FDG in the cells and glucose metabolism pathway. HK – hexokinase, G6Pase – glucose-6-phospatase, 18F-FDG6P – 18F-FDG-6-phospate, G6P – glucose-6-phospate

As 18-Fluorine decays, it emits positron, which will undergo annihilation process with electron. Annihilation of positron-electron produces two annihilation photons travelling back-to-back (Figure 2.1.2). The amount of energy of each photon is 511 keV. The PET scanning machine detects these photons and processes it to form PET images. The areas with high affinity to glucose will accumulate higher amount of 18F-FDG, thus the amount of annihilation photons is higher in this areas. As a result, areas of high 18F-FDG uptake will be seen in the image later. In the areas whereby there is high glucose metabolism, both physiological and pathological sites appear increased in uptake that requires precaution during image interpretation.

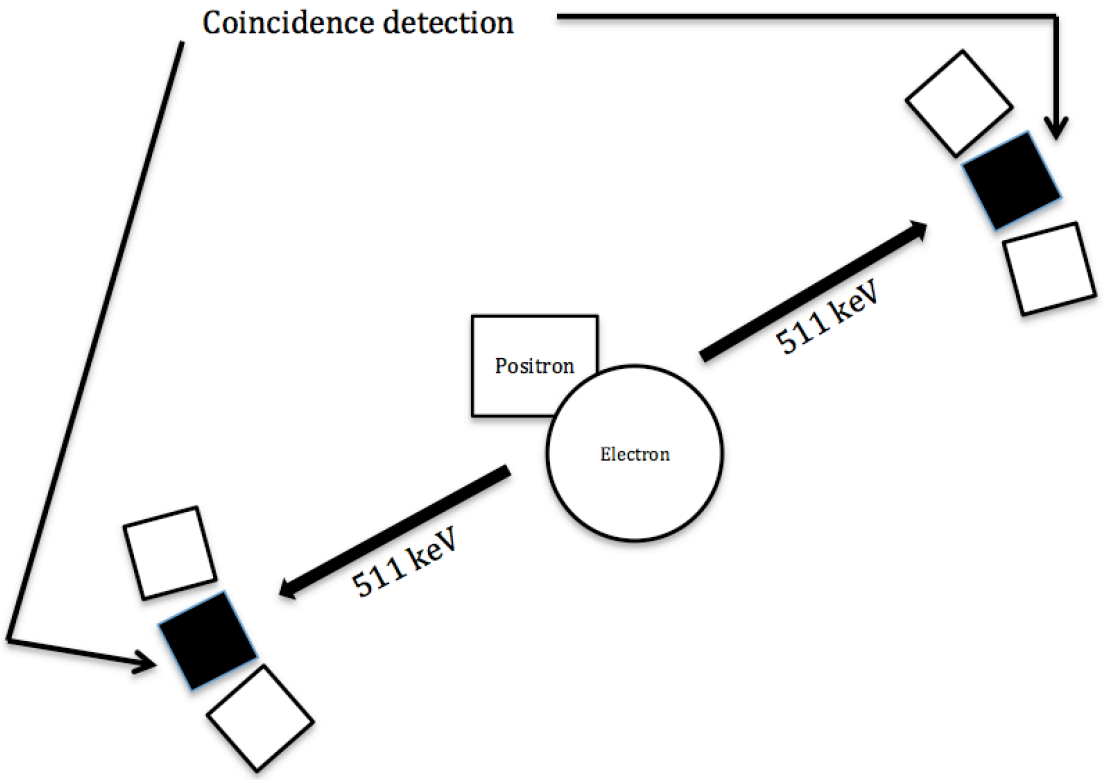

Figure 2.1.2: PET concept of detection of the coincidence annihilation photon that travel back-to-back of 511 keV energy.

The role of PET especially in clinical oncology has increased over the years (Beyer et al, 2000). Introduction of PET-CT later has provided a new dimension of imaging whereby function and anatomy can be assessed together. PET-CT imaging has role in diagnosis, staging, restaging as well as monitoring treatment response in oncology. Furthermore, it helps in the condition whereby the primary lesion is unknown. PET-CT is also able to detect suitable site of biopsy. A study evaluates the role of PET-CT in restaging Hodgkin lymphoma whereby they found that PET-CT has detected bone marrow involvement despite negative bone marrow trephine biopsy report (Moulin-Romsee et al, 2010). The upstaging of the disease is important as the patients had to change to another treatment protocol.

2.2 Pitfalls in PET-CT image interpretation

18F-FDG is distributed based on glucose avidity. Different organs have different glucose requirement. Brain has the highest 18F-FDG avidity due to high glucose consumption by the brain cells. Myocardium will exhibit high 18F-FDG avidity due to high glycolytic metabolism during the non-fasting state. Variable uptake intensities are sometimes seen in the myocardium despite 4-18 hours of fasting (Shreve et al, 1999). Besides physiological metabolism, intense uptake is also seen in the urinary system as a result of 18F-FDG excretion. 18F-FDG activity is high in the collecting system of kidneys as well as urinary bladder. Liver shows less intense of 18F-FDG activity similarly the spleen, bone marrow and renal cortex.

Tonsils in the neck usually showed high 18F-FDG activity as a result of infection/inflammation. Meanwhile, salivary glands uptake is variable (Nakamoto et al, 2005). Skeletal muscle uptake is also variable depending upon the muscles activity and insulin injection prior to 18F-FDG administration. Symmetrical muscle uptake and areas with increased muscle contraction such as vocal cord (excessive speech), extraocular muscles and neck muscles are likely physiological.

In the gastrointestinal tract, there are several conditions attributed to high 18F-FDG uptake such as malignancy and other benign/physiological conditions. Other than smooth muscle activity that is due to peristalsis, other benign condition in the bowel may also take up 18F-FDG. These conditions include inflammatory process such as colitis and duodenitis, infection such as viral and *H.pylori* infection, bleeding and microbial activity. The normal flora in the bowel takes up 18F-FDG that is excreted into

the bowel lumen (Renee et al, 2008). Other than that, drug such as metformin also cause high 18F-FDG uptake in the bowel (Gontier et al, 2008). Metformin is responsible for activation of GLUT-2 on the mucosal surface of the bowel that causes higher avidity of glucose in the bowel (Walker et al, 2005). Patient in hyperglycemic state during 18F-FDG injection will have lower 18F-FDG uptake by the tumor/lesion. Insulin administration to lower down the glucose level can be done provided that the 18F-FDG injection is delayed few hours later to avoid generalised muscle uptake during PET-CT scan (Boellaard et al, 2010)

Normal peristaltic activity of the bowel may cause 18F-FDG uptake in PET-CT. This is termed as physiological uptake. Bowel usually demonstrates variable uptake depending on sites. Diffuse low level of uptake usually observed in the small bowel. Colon demonstrates a more heterogenous uptake especially at the ileo-caecal junction, ascending colon and rectum (Blake et al, 2005). This is attributed to the activity of the sphincter and peristaltic activity. Besides that, the higher 18F-FDG uptake in the caecum and right colon was also attributed to the abundance of lymphocytes in that region (Abouzied et al, 2005). Other study also proposed the high 18F-FDG uptake in ascending colon was also related to the presence of lymphocytes (Lee et al, 2009).

Other conditions that can cause increase bowel activity will also cause higher 18F-FDG uptake. Patients with bowel related illness such as diarrhoea or constipation during the scan time might exhibit high 18F-FDG uptake in the bowel. A case study reported diffuse bowel uptake seen in PET-CT in a patient with fever of unknown origin and diarrhoea (Nihashi et al, 2006). Pre-treating the patient with purging agent such as

senna-glycoside proved that increased bowel motility causes high bowel uptake due to increased in bowel peristaltic activity (Soyka et al, 2010).

Inflammatory reaction attracts and activates inflammatory cells as well as various cytokines and chemical mediators. As a result of this, there is increased in expression of glucose transporter protein on the cell surface, thus causes high affinity of 18F-FDG (Love et al, 2005). PET-CT has been used for evaluation of inflammatory disease such as Crohn's disease and found that it showed better sensitivity and specificity with a promising value as a non-invasive tool of assessment (Louis et al, 2007).

The uptake of 18F-FDG in the bowel appears in variable pattern such as diffuse homogenous uptake, heterogenous uptake, focal intense uptake as well as diffuse low uptake. Diffuse uptake are likely physiological but there were studies found that certain pathology presented as diffuse uptake in PET-CT. Kresnik et al (2002) had reviewed 5 patients that were diagnosed with colitis. Conventional investigation with magnetic resonance colonography, ultrasonography as well as colonoscopy found to be normal but PET-CT showed diffuse bowel uptake. Other studies by Gontier et al, (2008) and Toriihara et al, (2011) also found the similar pattern.

Hideki et al (2009) had conducted a study to look at the effect of oral contrast on bowel uptake in PET-CT scan. This study involved 60 patients underwent PET-CT scan for various indications. Half of the patients were given oral contrast prior to PET-CT scan, while the other half was the control group. The pattern of 18F-FDG distributions

in the bowel was evaluated. The study found that oral contrast caused focal as well as diffuse increased uptake of 18F-FDG in the bowel (Hideki et al, 2009).

Focal intense uptake of 18F-FDG is more suspicious of pathology especially when the corresponding CT image is abnormal. There must be precaution in interpreting this lesion as loop of bowel may present like a bowel mass with high 18F-FDG uptake. Furthermore, certain physiological uptake also presented with focal lesion e.g. in constipation (Kim et al, 1999). The interpretation of the image is usually ambiguous. In patients with known bowel pathology e.g. in colonic carcinoma the image interpretation is really challenging as it may be masked by physiological uptake. Zhuang et al, (2002) had reviewed 197 patients referred for PET-CT to evaluate pulmonary nodules. Out of these patients, 59 of them had incidental diffuse bowel uptake and 17 had focal uptake. Surprisingly, 5 of those with focal bowel uptake turned out to be cancerous by histopathological review. Other study also observed the similar findings (Israel et al, 2005).

However, pattern of uptake alone is not indicative of pathological or physiological process. A study was conducted to evaluate the clinical significance of colonic uptake in patients with known gastric adenocarcinoma involving 239 patients. All of them underwent PET-CT scan and colonoscopy. The study found that although PET-CT showed intense uptake of 18F-FDG in the colon, correlation with colonoscopy and biopsy is still needed to confirm the diagnosis. Semiquantitative evaluation in term of maximum standardised uptake value (SUV_{max}), also showed that there was no specific limit of SUV_{max} to be considered as suspicious of malignancy (Shim et al, 2012).

2.3 Standardised Uptake Value

PET-CT machine measured relative uptake of 18F-FDG in a particular region of interest to quantifiy the uptake. This quantification is called standardised uptake value (SUV).

$$SUV = \frac{\text{Tissue activity (millicurie/millilitre)}}{\text{Injected dose (millicurie)/weight (gram)}}$$

Figure 2.3.1: Calculation formula for standardised uptake value (SUV) (Ziessman et al, 2014)

There are factors that affect SUV value such as patient size/body mass, injection-to-scan time, plasma glucose level, amount of injected dose, region of interest and pixel size (Keyes, 1995). As the SUV is calculated to body weight, changes in body weight may also change the SUV value. Similarly, patient with high plasma glucose level e.g. uncontrolled diabetes mellitus may compete with 18F-FDG to saturate glucose transporter proteins in the body (Ziessman et al, 2014).

The higher SUV value reflects the avidity of the underlying tissues towards 18F-FDG. Besides that, it is used to evaluate the response of certain disease towards therapy (Kinehan & Fletcher, 2010). There are commonly two types of SUV value measured by PET-CT machine, which is maximum SUV (SUV_{max}) and mean SUV (SUV_{mean}). SUV_{max} measures the maximum 18F-FDG uptake in the region of interest corrected to

body weight while SUV_{mean} is the calculated average of 18F-FDG uptake in the region of interest corrected to body weight.

As the measurement of SUV is affected by multiple variables, it is suggested to improve the reproducibility of SUV value by the use of reference tissue and normalization the lesion's SUV to the reference tissue's SUV (Kinehan & Fletcher, 2010). A number of tissues have been used as reference tissue such as mediastinal blood pool, liver, lung and cerebellum. The commonest reference tissue is liver and mediastinal blood pool. The SUV measurement in normal liver and mediastinum is stable over time (Paquet et al, 2004). Therefore, bowel-to-liver ratio is calculated in this study.

The concern over SUV_{max} is that the reported value might be based from a lesion of one pixel. Thus, there is potential bias and noise compared to SUV_{mean}. Therefore, SUV_{mean} was chosen for semiquantitative analysis in this study. A study done in Korea evaluating the effectiveness of Mebeverine in reducing physiological bowel uptake in 18F-FDG PET-CT also used SUV_{mean} and bowel-to-liver ratio in their analyses (Song et al, 2014). Similarly another study done in 2008 looking at the effect of N-butylscopolamine (Buscopan) in reduction of physiological bowel uptake during PET-CT scan also used SUV_{mean} and bowel-to-liver ratio (Emmott et al, 2008).

2.4 Methods utilised to reduce physiological uptake in the bowel

Several studies have been conducted previously to look for appropriate measure to reduce 18F-FDG uptake in the bowel. However, there is no technique found to produce consistent effect till date. The use of purging agent such as senna glycoside has shown an increased in 18F-FDG uptake (Soyka et al, 2010). This is explained by another study that it is related to its function of increasing bowel secretions (Waltenberger et al, 2008). This finding also explained a study by Yamamoto et al (2004) whereby gastric secretory inhibitor (Omeprazole) was used to evaluate its effectiveness in reducing bowel uptake during 18F-FDG PET-CT. They found that introduction of Omeprazole had reduced the physiological bowel uptake (Yamamoto et al, 2004).

However, preparing patient with non-purging agent such as isosmotic fluid does help to clear up bowel uptake. Administration of this fluid orally a day before PET-CT was found to be beneficial. Isosmotic fluid has helped to improve the sensitivity and specificity of the scan (Miraldi et al, 1998). As metformin was found to cause increase in bowel uptake (Walker et al, 2005 and Gontier et al, 2008), witholding metformin for 3 days prior to PET-CT reduced the 18F-FDG uptake in the bowel (Ozulker et al, 2010).

Increased in bowel motility causes spasms in the mucosal layer of the gastrointestinal tract. Antispasmodic agents such as mebeverine and hyoscine have the ability to prevent spasms without interfering the normal gastric peristalsis. In 2014, a study was conducted in Korea to look for the effect of Mebeverine in 18F-FDG PET-

CT scan. Two groups of patients were recruited with total of 161 patients involved. The study found that Mebeverine usage in 18F-FDG PET-CT reduced the bowel uptake (Song et al, 2014). St. Theresa's Hospital in Hong Kong reported that the use of Mebeverine is their routine protocol during 18F-FDG PET-CT to reduce spasms in the gut (Kevin, 2012).

Emmott et al (2008) studied the effect of N-butylscopolamine (Buscopan) in reduction of physiological bowel uptake during PET-CT. The study found that N-butylscopolamine can reduce the bowel uptake and further potentially improves the accuracy of 18F-FDG PET-CT reporting. Earlier than that, a study by Stahl et al (2000) using N-butylscopolamine also found that it causes reduction in bowel uptake during PET scan.

2.5 Pharmacology of Mebeverine and Hyoscine-n-butylbromide

Mebeverine (Duspatalin) is a musculotropic antispasmodic agent that has direct action on the smooth muscle of the gastrointestinal tract. Its spasmolytic effect is due to combination of non-specific depressant and anaesthetic activity together with inhibition of sympathetic effect as it has the ability to block noradrenalin uptake. It is rapidly and completely absorbed after oral ingestion. It is metabolized completely in the body before excretion. It undergoes hydrolysis leading to veratric acid and mebeverine alcohol. Both are excreted in the urine. Furthermore, the mebeverine alcohol is formed partly as carboxylic acid (MAC) and partly as demethylated carboxylic acid (DMAC). The main circulating metabolite in plasma is DMAC with elimination half-life of 2.45 hours. The maximum serum concentration (C_{max}) of this metabolite is 1670 ng/mL, which is achieved at 1-hour time (T_{max}). The usual therapeutic prescription of Mebeverine is 135mg three times per day (maximum 405mg/day). In order to avoid potential side effect, this study administered the therapeutic dose of 135mg 30 minutes before 18F-FDG injection.

Hysocine-n-butylbromide is a spasmolytic agent thas has effect on the smooth muscles of gastrointestinal tract, genitourinary tract as well as biliary tract. It does not cross into the central nervous system as it in the form of quarternary ammonium derivative. Therefore, anticholinergic effects of central nervous system do not occur. However peripherally, it exerts anticholinergic action as a result from ganglionic blocking action within the visceral wall and antimuscarinic effect.

As it formed as a quartenary ammonium compound, it is highly polar and only partially absorbed following oral ingestion (8%). After oral ingestion, the maximum plasma concentration (C_{max}) of this metabolite is around 0.11ng/ml, which approximately achieved at 2-hours time (T_{max}). Following oral ingestion of single dose, the terminal elimination half-life is about 6.2 hours. The main metabolic pathway is hydrolysis of the ester bond that is later excreted in the faeces (approximately 90%) and urine (approximately 2-5%). The therapeutic prescription of oral Hyoscine is 10mg 3-5 times per day with maximum dose of 60mg per day. Similarly, the lowest therapeutic dose of 10mg 30 minutes before 18F-FDG injection was chosen for this study to avoid potential side effects.

Table 2.5.1: The profiles of oral Mebeverine and Hyoscine-n-butylbromide

	Duspatalin	**Buscopan**
Content	Mebeverine hydrochloride	Hyoscine-N-butylbromide
Indication	Symptomatic treatment of abdominal pain and cramps, bowel disturbances and abdominal discomfort related to irritable bowel syndrome. Treatment of gastrointestinal spasm secondary to organic diseases	Gastrointestinal tract spasm and dyskinesia of the biliary system spasm, genitourinary tract spasm.
Overdosage	Theoretically, CNS excitability maybe predicted. No antidote. Gastric lavage and symptomatic treatment is recommended.	Anticholinergic effects maybe observed. Treatment: Parasympathomimetic drugs should be administered.
Contraindication	Hypersensitivitiy	Hypersensitivity Myasthenia gravis, megacolon
Side effect	None known	Anticholinergic effects
Mechanism of action	Antispasmodic agent: Mebeverine is a musculotropic antispasmodic, with a direct action on the smooth muscle of the gastrointestinal tract, relieving spasm without affecting normal gut motility. Since this action is not mediated by the autonomic nervous system, the usual anticholinergic effect maybe absent. Pharmacokinetics: Rapidly and completely absorbed after oral administration. Metabolized completely before excretion. Hydrolysis of mebeverine leading to veratric acid and mebeverine alcohol that will be both excreted in the urine.	Antispasmodic agent: Spasmolytic action against smooth muscle of gastrointestinal tract, genitourinary tract and biliary tract. Does not enter CNS. Peripheral anticholinergic action results from ganglion blocking action within the visceral wall and antimuscarinic activity. Pharmacokinetics: Absorbed as quarternary ammonium compound. Highly polar, therefore only partially absorbed following oral administration (8%). Main metabolic pathway is hydrolytic cleavage of ester bond. Excreted in the feces and the urine.
Administration	Taken 20-30 minutes before meal.	Taken 20-30 minutes before meal.

MIMS Malaysia (2017). Buscopan: Full Prescribing Info. [Online] Available from: http://www.mims.com/malaysia/drug/info/buscopan/?type=full [Accessed 13 August 2017].

MIMS Malaysia (2017). Buscopan: Full Prescribing Info. [Online] Available from: http://www.mims.com/malaysia/drug/info/duspatalin/?type=full [Accessed 13 August 2017].

CHAPTER 3

OBJECTIVES, HYPOTHESES AND RESEARCH FRAMEWORK

CHAPTER 3

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3.1 General objective

To determine the effect of Mebeverine and Hyoscine-n-butylbromide in reducing physiological bowel uptake during 18F-FDG PET-CT.

3.2 Specific objectives

1. To compare SUV_{mean} of bowel and bowel-to-liver ratio among patients receiving Mebeverine, Hyoscine and Control group
2. To compare the degree of bowel uptake and difficulty of image interpretation among patients receiving Mebeverine, Hyoscine and Control group
3. To determine the relationship between the degree of bowel uptake and difficulty of image interpretation

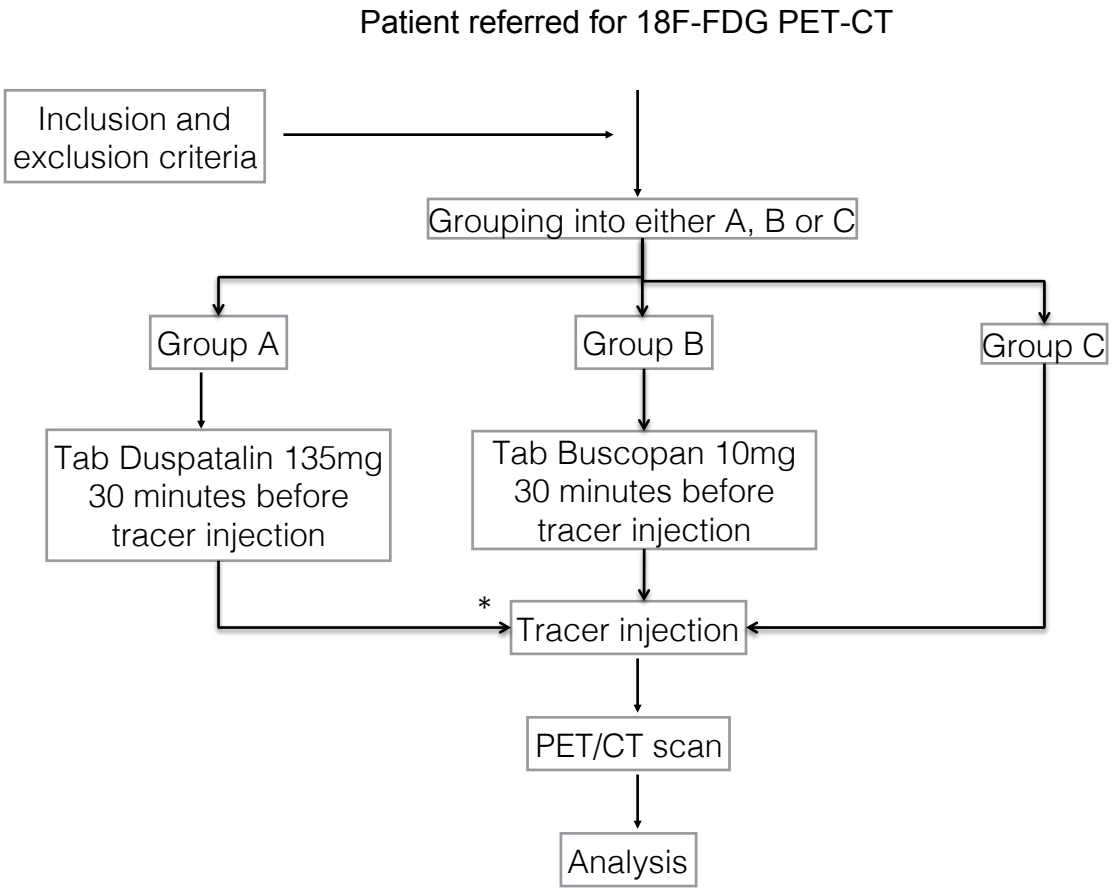
3.3 Null hypothesis

There is no significant effect of Mebeverine and Hyoscine-n-butylbromide to reduce physiological bowel uptake in 18F-FDG PET-CT.

3.4 Alternative hypothesis

There is significant effect of Mebeverine and Hyoscine-n-butylbromide to reduce physiological bowel uptake in 18F-FDG PET-CT.

3.5 Research framework



* Tracer = 18F-FDG

Duspatalin = brand name for Mebeverine

Buscopan = brand name for Hyoscine-n-butylbromide

CHAPTER 4

METHODOLOGY

CHAPTER 4

METHODOLOGY

4.1 Study location

PET-CT Unit, Department of Nuclear Medicine, Penang Hospital.

4.2 Study design and ethical approval

This is a prospective, randomised controlled trial.

This study obtained approval from two ethical boards as follows:

1. Human Research Ethics Committee, Universiti Sains Malaysia (USM): JEPeM Code: USM/JEPeM/16010034.
2. Medical Research and Ethics Committee, Ministry of Health Malaysia: Reference code: NMRR-16-1228-31786 (IIR).

4.3 Study period

Patient recruitment was done in between 1st September 2016 until 28th February 2017.

4.4 Sampling

4.4.1 Source population

All patients referred for PET/CT in Penang Hospital

4.4.2 Study subjects

All patients attending PET/CT in Penang Hospital who consented to take part in this study

4.4.3 Sample size calculation

Alpha: 0.05, Power: 0.8 (80%), Std. Dev.: 0.73, Diff: 0.365 M: 1

Calculated sample size: 64

Addition of 10% drops out rate: 70

Total subject: 210 (where 70 for each group).

Reference: (Song *et al.*, 2014) and (Emmott *et al.*, 2008)

4.4.4 Sampling method

Based on the above calculation, the calculated sample size was 64 patients for each group. After considering 10% drop out rate, the total sample size for each group was 70 patients.

There were 500 patients registered for PET-CT scan during the patient recruitment period. Systematic random sampling was done to get 210 patients to be included in this study. The first patient was numbered as 1 and every other numbers were chosen until 210 patients. Subsequently, simple random sampling was done to nominate the members of groups A (received Duspatalin), B (received Buscopan) and C (control). Random number table available in the book 'Kaedah Penyelidikan Buku 1' was used for this (Piaw, 2011). Therefore, 70 patients were put in every group before further inclusion and exclusion criterias were evaluated.

After considering the exclusion criterias, from the total of 70 patients nominated in each group, 62 patients were recruited in Mebeverine group; 68 patients were recruited in Hyoscine group and 65 patients were in the Control group. The remaining patients who were not selected into this study were

diabetic on metformin therapy and another 5 gave history of diarrhoea a week before the scan.

4.4.5 Inclusion criteria

Patient who went for 18F-FDG PET-CT scan with the age above 18 years old

4.4.6 Exclusion criteria

1. Patient on Metformin, Lactulose, enema or laxatives
2. Patient with history of diarrhoea or abdominal pain for the past 1 week
3. Patient who was known allergy to Mebeverine, Hyoscine, lactose or sucrose
4. Patient who was known of myasthenia gravis, glaucoma and megacolon (determined based on history or previous medical record)

4.5 Research protocol

Patients were fasted for at least 6 hours prior to 18F-FDG injection. Patients' weight and fasting blood glucose were recorded upon arrival. The acceptable glucose level for all patients was 8.0 mmol/L or lower. Mebeverine group patients were given oral Mebeverine 135mg while Hyoscine group patients were given oral Hyoscine-n-butylbromide 10mg 30 minutes before 18F-FDG injection. The patients in Control group were given neither Mebeverine nor Hyoscine-n-butylbromide. They received intravenous 18F-FDG only. The dose of 18F-FDG is based on body weight ranging from 10-20 mCi (370-740 MBq).

PET-CT scanning was done 45 minutes to 1 hour after 18F-FDG injection using a dedicated Discovery ST PET-CT scanner (General Electric Medical Systems, Waukesha, WI, USA). The scanner used Bismuth Germanium Oxide (BGO) crystals, detector field of view (DFOV) of 50 cm with 24 PET ring-detectors. The scan was done covering from the skull to mid-thigh. A contemporaneous low dose non-contrasted CT was also done by the same scanner with 100 mA and 120 kV. CT scan speed at 0.8 s per revolution with 3.75 mm slice thickness. Meanwhile PET acquisition was obtained at 6-8 beds position with overlap of 3.270 mm and 3 minutes emission scan for each bed position. Images were reconstructed using an iterative ordered-subsets expectation maximisation (OSEM) algorithm with CT attenuation correction.

An experienced nuclear medicine physician who was blinded of the clinical data of the patients reviewed the images. The revision was done using GE Advantage Workstation (General Electric Medical Systems, Waukesha, WI, USA). The interpreter used visual analysis to evaluate the degree of bowel uptake and difficulty of image interpretation. The interpreter scored each aspect with number 0 to 2 scale (Table 4.5.1 and Table 4.5.2).

Table 4.5.1: Scoring scale in visual analysis on the degree of bowel uptake

Score	Description
0	No significant bowel uptake compared to background liver uptake
1	Mild bowel uptake compared to background liver uptake
2	Severe bowel uptake compared to background liver uptake

Table 4.5.2: Scoring scale in visual analysis on the difficulty in image interpretation

Score	Description
0	No difficulty to interpret as physiological uptake
1	Slight difficulty to interpret as physiological uptake
2	Most difficult to interpret as physiological uptake

At the same time, the interpreter also semiquantitatively analysed the images by measuring SUV. The interpreter drew a region of interest (ROI) at the bowel area with highest uptake and the computer calculated the SUV_{mean} at this area. The area of bowel with highest SUV_{mean} is taken for statistical analysis later. Similarly in the liver, the same size of ROI was drawn for the computer to calculate the highest SUV_{mean} of liver. All the relevant data collected from the analysis was recorded in a data collection form (Appendix E).

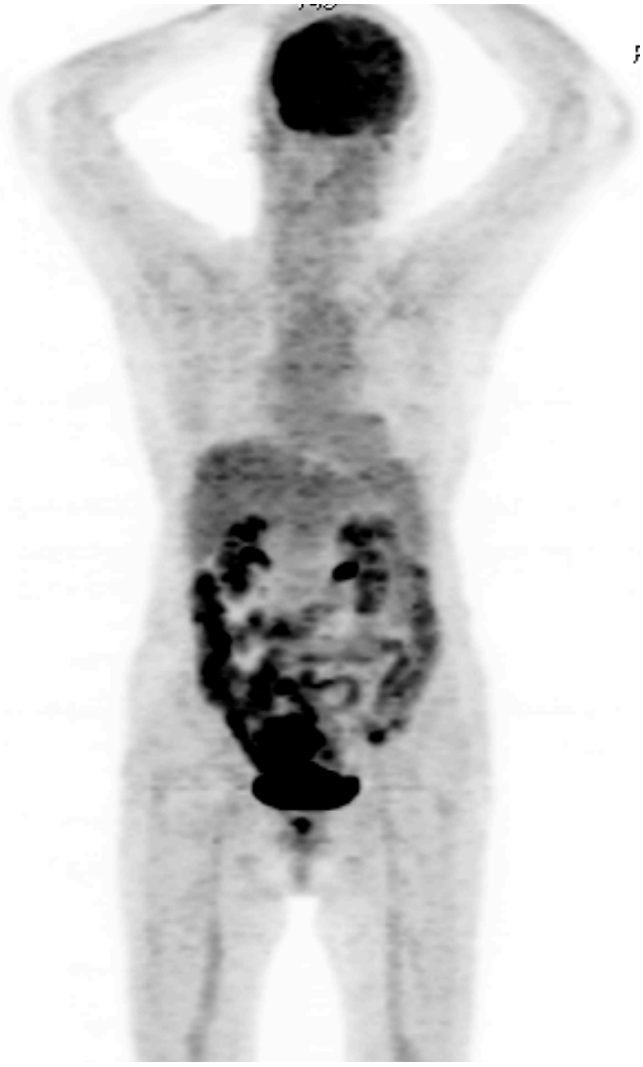


Figure 4.5.1: Example of maximum intensity projection of a patient with diffuse and intense uptake in the bowel with lower uptake in the liver. The interpreter scored 2 for degree of bowel uptake but scored 0 in the difficulty of bowel interpretation. This uptake was more likely physiological rather than pathological. This patient was from the Control group.