COMPARISON OF IMMEDIATE RELEASE ORAL OXYCODONE HYDROCHLORIDE(KAPPA 2 RECEPTOR AGONIST) WITH ORAL PANTOPRAZOLE IN THE TREATMENT OF FUNCTIONAL DYSPEPSIA

BY

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ABBREVIATIONS

ADR	Adverse drug reactions
CNS	Central nervous system
CCK	Cholecystokinin
COX	Cyclo-Oxygenase
FD	Functional Dyspepsia
GAS	Global Assessment Score
GERD	Gastro Esophageal Reflux Disease
GIT	Gastro Intestinal Track
HRQoL	Health Related Quality of Life
H.Pylori	Helicobacter Pylori
HUSM	Hospital Universiti Sains Malaysia
IBS	Irritable Bowel Syndrome
IR	Immediate release
Kg	kilogram
LDQ	Leeds Dyspepsia Questionare
mg	milligram
NA	Nor Adrenaline
NSAID	Non steroidal anti inflammatory drug
NUD	Non Ulcer Dyspepsia
OGDS	Oesophago Gastro Duodenoscopy
PPI	Proton Pump Inhibitor

PS	Pain Score
SERT	Serotonin Reuptake Transporter
SOPD	Surgical Out Patient Department
SPSS	Social Science and Statistical Package
UD	Uninvestigated Dyspepsia
VAS	Visual Analogue Score
5HT	Serotonin

ABSTRAK

Tajuk: Perbandingan Oxycodone Hydrochloride (Agonis Reseptor Kappa 2) dengan Pantoprazole dalam Rawatan Dispepsia Fungsi

Latar belakang: Rawatan bagi Dispepsia Fungsi hingga kini masih lagi belum mencapai tahap memuaskan. Kami menjalankan kajian bagi mengesahkan keberkesanan serta tahap keselamatan Oxycodone Hydrochloride-Agonis bagi reseptor Kappa 2 dalam rawatan Dispepsia Fungsi.

Kaedah: Enam puluh pesakit yang disahkan sebagai Dispepsia Fungsi dikaji secara rawak. Kumpulan Oxycodone Hydrochloride telah menerima 5mg ubat sekiranya perlu sahaja manakala kumpulan asas telah menerima kombinasi Pantoprazole 40mg sekali sehari juga rawatan bagi H.Pylori sekiranya perlu. Setelah lapan minggu, pesakit akan dinilai khasnya tiga penilaian pencapaian utama iaitu perubahan dari sebelum rawatan dengan; penilaian markah keterukan gejala(menggunakan penjumlahan markah LDQ), penilaian umum tahap keberkesanan(dengan membandingkan pesakit yang sembuh dan tidak), serta tahap keterukan kesakitan epigastrik dan kembung menggunakan penilaian LDQ, yang juga digunakan bagi menilai kesan sampingan rawatan yang dikaji.

Keputusan: Setelah lapan minggu, secara keseluruhannya didapati gejala-gejala Dispepsia Fungsi telah mengalami perubahan baik secara ketara pada kumpulan Oxycodone Hydrochloride berbanding pesakit yang menerima Pantoprazole . Analisa penilaian keberkesanan umum(GAS) menunjukkan Oxycodone Hydrochloride lebih berkesan daripada Pantoprazole(26 lwn 1)(Nilai P

<0.001). Jumlah pemarkahan gejala menggunakan LDQ menurun dengan mendadak bagi kumpulan Oxycodone Hydrochloride(13.00±3.29 lwn 20.40±3.07)(Nilai P <0.001) Begitu juga bagi tahap kesakitan epigastrik(2.0±1 lwn 4.0±1) (P<0.001) dan kembung perut(2.0±1 lwn 3.0±1) (P<0.001). Pening adalah kesan sampingan Oxycodone Hydrochloride yang agak ketara berbanding pantoprazole(13 vs 0)(P<0.001). Namun jika dibandingkan kejadiannya dalam kumpulan Oxycodone secara statistiknya adalah tidak signifikan(13 lwn 17)(p=0.465).

Kesimpulan: Penggunaan Oxycodone Hydrochloride jelas membantu merawat Dispepsia Fungsi dengan kesan sampingan yang sederhana.

Kata kunci: Oxycodone Hydrochloride, Pantoprazole, Dispepsia Fungsi

ABSTRACT

TITLE: Comparison of Immediate Release Oral Oxycodone Hydrochloride(Kappa 2 receptor agonist) with Oral Pantoprazole in the treatment of Functional Dyspepsia

BACKGROUND: The treatment of patients with functional dyspepsia remains unsatisfactory. We assessed the efficacy and safety of Oxycodone Hydrochloride-Kappa 2 receptor agonist, in patients with functional dyspepsia.

METHODS: Patients with functional dyspepsia were randomly assigned to receive either Oral Oxycodone Hydrochloride 5mg prn basis and Oral Pantoprazole 40mg od. After eight weeks of treatment, three primary efficacy end points were analyzed: the change from baseline in the severity of symptoms of functional dyspepsia(as assessed by the Leeds Dyspepsia Questionnaire(LDQ)), patients' global assessment of efficacy using Global Assessment Score(GAS) (the proportion of patients poor and good improvement), and the severity of pain and bloatedness as rated by LDQ severity scale. The safety of Oxycodone Hydrochloride assessed by the presence of significant side effect.

RESULTS: We randomly assigned 60 patients for this study. After eight weeks, overall patients in Oxycodone Hydrochloride group had marked improvement of symptoms, as compared with patients receiving Pantoprazole daily. Analysis of patients' global assessment of efficacy(GAS) also revealed that Oxycodone Hydrochloride group was significantly superior to Pantoprazole

with excellent proportion of good(26 vs 1)(P value<0.001). The total LDQ symptom score improved significantly in Oxycodone Hydrochloride groups(13.00±3.29 vs 20.40±3.07)(P value<0.001), with the greatest symptom-score improvement is less than 15(P<0.05). Epigastric pain and bloatedness improvement were greater in Oxycodone Hydrochloride than Pantoprazole; LDQ severity scale for epigastric pain(2.0±1 vs 4.0±1) (P<0.001) and bloatedness(2.0±1 vs 3.0±1) (P<0.001). The side effects of Oxycodone Hydrochloride was giddiness(13 vs 0)(P<0.001). However when comparing it amongst the Oxycodone Hydrochloride group, it was statistically insignificant(13 vs 17)(p=0.465).

CONCLUSIONS: Oxycodone Hydrochloride significantly improves symptoms in patients with functional dyspepsia with tolerable side effects.

Keyword: Oxycodone Hydrochloride, Pantoprazole, Functional dyspepsia

1. INTRODUCTION

Dyspepsia is a common gastrointestinal syndrome in clinical practice and community world wide(Mahadeva S *et al*, 2006). Generally it is refers to a combination of upper gut symptoms such as epigastric pain, burning, discomfort, fullness, early satiety, nausea, vomiting and belching. The causes of dyspepsia are known to include organic like peptic ulcer disease, gastro-esophageal reflux, or non organic cause, which is functional dyspepsia(FD). Functional dyspepsia, also known as non-ulcer dyspepsia(NUD), is the commonest cause of dyspeptic symptoms in the West and increasingly in other parts of the world(Locke GR 3rd, 1998).

The Rome III criteria defined functional dyspepsia as "presence of one or more of the following symptoms : epigastric pain and or epigastric burning sensation, bothersome postprandial fullness, early satiation with no evidence of structural disease (including at upper endoscopy). These symptoms are present in the last 3 months and symptoms onset at least 6 months prior to the diagnosis."

The actual prevalence of this condition is not well known. According to reports, up to 20-30% of the community have recurrent dyspeptic symptoms(Talley NJ *et al*,1992). In some published literature, the reported prevalence is as high as 60%(Dickerson LM *et al*,2004). In Malaysia, one survey found 31.2% of non-ulcer dyspepsia patients were tested positive for Helicobacter pylori(Goh KL *et al*,1997). The epidemiology also varies amongst population.

Functional dyspepsia has various underlying postulated pathophysiologies. The exact pathophysiology is still remains unclear. However, factors including gastrointestinal dysmotility, abnormality in acid secretion, visceral hypersensitivity, Helicobacter pylori infection or stress are thought to be the caused. Within functional dyspepsia, three symptom groups were originally identified: ulcer-like dyspepsia, dysmotility-like dyspepsia, and reflux-like dyspepsia.

FD is not life-threatening medical condition . However, the impact on patients and health care services has been shown to be considerable. In one community survey of several European and North American populations, 20% of people with dyspeptic symptoms had consulted either primary care physicians or hospital specialists, more than 50% of dyspepsia sufferers were on medication most of the time and approximately 30% of dyspeptics reported taking days off work or schooling due to their symptoms(Haycox A *et al*, 1999). Similar report also by other investigators in this field by Moayyedi P *et al*, (2002), including the fact that people with functional dyspepsia have a significantly reduced quality of life when compared to the general population.

Well established medical treatments either non-pharmalogical like diet modification, and pharmalogical include Helicobacter pylori eradication, acid inhibitory agents and prokinetics have been employed. The pharmacologic treatments available to date for the management of functional dyspepsia have been shown to be of limited efficacy. The overall gain still unsatisfactory(Holtmann G *et al*, 2008). However, pharmacotherapy is still considered for many patients in clinical practice.

New emerging treatments include cholecystokinin 1 blockers, Kappa opioid receptor agonists and serotonergic agents 5-Hydroxytryptamine 4 receptors though their application in FD is still in the preliminary stages(Halder SL *et al*, 2005). To date, few studies had discovered the efficacy and the safety of peripheral Kappa opioid agonist such as fedotozine(Read NW *et al*, 1997), and asimadolinein ameliorating the key symptoms associated with FD(Talley NJ *et al*, 2008).

There is a growing evidence that agonists at peripheral kappa receptors can treat certain pain conditions, such as hyperalgesia, an increased sensitivity to stimuli which are not generally noxious(Yaksh, T.L *et al*, 1997). Previous animal experiments have shown that kappa-opioid receptor is up-regulated during visceral inflammatory conditions and hence it may provide a target for pain management(Nozaki C *et al*, 2005).

We would like to expand the study by using Immediate release(IR) Oxycodone Hydrochloride (Kappa 2 receptor agonist)- as another option of treatment in functional dyspepsia. We would like to do a study in order to find the efficacy as well as safety of OxyCodone in the treatment of functional dyspepsia comparing with standard therapy using Proton pump inhibitor- Pantoprazole.

2. LITERATURE REVIEW

2.1. DEFINITION

Dyspepsia is generally defined as chronic or recurrent pain or discomfort centered in the upper abdomen. Basically it refers to combination of upper gut symptoms such as epigastric pain, burning, fullness, discomfort, early satiety, nausea, vomiting and belching.

Discomfort is defined as a subjective negative feeling that is non painful, which can incorporate a variety of symptoms including early satiety or upper abdominal fullness. Patients presenting with predominant or frequent (more than once a week) heartburn or acid regurgitation should be considered to have gastroesophageal reflux disease (GERD) until proven otherwise.

As dyspepsia is a common complaint in clinical practice; therefore, its management should be based on the best evidence. Dyspepsia has often been loosely defined; the most widely applied definition of dyspepsia is the Rome Working Teams formulation, namely chronic or recurrent pain or discomfort centered in the upper abdomen(Drossman DA *et al*, 2000). There are many gastrointestinal tract (GIT). pathologies giving rise to discomfort or pain in the upper abdomen(Table 2.1). However, in up to 60% of patients with upper abdominal discomfort, there is no detectable pathology.

Functional dyspepsia or also known as nonulcer dyspepsia(NUD), describes recurrent or persistent symptoms of discomfort at the upper abdomen, mostly epigastric region, without any identifiable cause or pathology in the upper GIT(Dickerson LN *et al*, 2004).

Table 2.1: Common Organic Causes of Upper GIT Discomfort or Pain

Peptic Ulcer disease
Reflux oesophagitis
Gastric/oesophageal malignancy
Pancreatitis
Biliary track disease
Angina pectoris

2.2. DIAGNOSIS

A useful diagnostic criteria which the physician may use to guide them in the diagnosis is the ROME III criteria for functional dyspepsia which was published in 2006(Table 2.2). Comparing to the older version of the ROME II criteria, the revised Rome III criteria defined functional dyspepsia as "presence of one or more of the following symptoms : bothersome postprandial fullness, early satiation, epigastric pain and or epigastric burning sensation with no evidence of structural disease (including at upper endoscopy). These symptoms are present in the last 3 months and symptoms onset at least 6 months prior to the diagnosis." There are two subcategories of symptom complex,(i). Postprandial distress syndrome and (ii). Epigastric pain syndrome. The postprandial distress syndrome, also known as meal-induced dyspeptic symptoms, includes symptoms of postprandial fullness and early satiation. In clinical practice the symptoms in these 2 categories may be overlapping.

The needs of endoscopic confirmation as NUD or FD is essential, due to many studies done cannot differentiate between Ulcer and non ulcer dyspepsia just based on symptoms. There is convincing evidence that a patients symptoms cannot be used to identify structural disease in uninvestigated dyspepsia(Thompson A *et al*, 2003). Working teams have suggested subdividing dyspepsia into ulcer-like or dysmotility-like dyspepsia based on symptom patterns or predominance; it was postulated that symptom subgroups could identify more homogenous populations that would respond to targeted medical therapy(Drossman DA *et al*, 2000).

However, individual symptoms, subgroup symptoms, and scoring systems have all failed to be useful in identifying underlying peptic ulcer disease, or distinguishing organic from functional dyspepsia. A study from Canada reported that the patient's dominant symptom (including heartburn) failed to predict endoscopic findings in a primary care population(Thompson A *et al*, 2003). It is thus controversial whether subdividing dyspepsia into symptom subgroups aids management in documented functional dyspepsia.

Table 2.2: Rome III Diagnostics Criteria for Functional Dyspepsia

Functional dyspepsia
Diagnostic criteria* Must include:
1. One or more of the following:
a. Bothersome postprandial fullness
b. Early satiation
c. Epigastric pain
d. Epigastric burning
AND
2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.
* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Postprandial Distress Syndrome
Diagnostic criteria Must include one or both of the following:*
1. Bothersome postprandial fullness, occurring after ordinary-sized meals, at least several times per week
2. Early satiation that prevents finishing a regular meal, at least several times per week

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
Supportive criteria
1. Upper abdominal bloating or postprandial nausea or excessive belching can be present.
2. Epigastric pain syndrome may coexist

Epigastric Pain Syndrome
Diagnostic criteria Must include all of the following:*
1. Pain or burning localized to the epigastrium of at least moderate severity, at least once per week
2. The pain is intermittent
3. Not generalized or localized to other abdominal or chest regions
4. Not relieved by defecation or passage of flatus
5. Not fulfilling criteria for gallbladder and sphincter of Oddi disorders

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
Supportive criteria
1. The pain may be of a burning quality, but without a retrosternal component
2. The pain is commonly induced or relieved by ingestion of a meal, but may occur while fasting 3. Postprandial distress syndrome may coexist

Adapted with permission from: Drossman DA, Corazziari E, Delvaux M, Spiller R, Talley NJ, Thompson WG, Whitehead WE. Rome III: The Functional Gastrointestinal Disorders. 3rd Edition Degnon Associates, McLean , VA , 2006.

2.3. FUNCTION DYSPEPSIA SYMPTOMS PATTERN

The dyspepsia symptom complex, which is often aggravated by food ingestion, includes epigastric pain, bloating, early satiety, fullness, epigastric burning, belching, nausea, and vomiting. Overall, surveys suggest that 15% to 20% of the general population experience dyspepsia over the course of a year(Kay L *et al*, 1994). Although often chronic, the symptoms in functional dyspepsia are frequently intermittent, even during a period with marked symptoms(Agrues L *et al* , 2002). Both in the general population and in tertiary care, the most

prevalent symptoms are postprandial fullness, epigastric pain, early satiety, and nausea(Samelli G *et al*, 2003). However, there is considerable heterogeneity in the symptom pattern,both in number and type of symptoms(Tack J *et al* , 2004).

2.4. ETIOLOGY AND PATHOGENESIS

2.4.1. Genetic

Identifying candidate genes associated with functional dyspepsia is still considerable interest. In an interesting report, Holtmann G. *et al*, (2004) observed an association of a specific G protein polymorphism (homozygous 825C genotype of GNbeta3) with functional dyspepsia. These results remain most intriguing because G protein abnormalities could affect many secondary messenger functions. However, the experience in other fields has been that many candidate genes discovered to be linked to common diseases in initial reports fail to be confirmed on subsequent study, thereby tempering all enthusiasm. In addition to G protein abnormalities that could affect many secondary messenger functions, there are a number of other potential neurotransmitters involved in the Pantoprazole of upper gastrointestinal tract motor and sensory function -- polymorphisms of the genes altering these receptors may therefore be very important. Such candidate neurotransmitters include serotonin (5HT), noradrenaline (NA), and cholecystokinin (CCK), among others.

Carlson PJ *et al*, (2005) reported an important new case-Pantoprazole study of potential genotypes in subjects with dyspepsia over healthy Pantoprazoles identified from a US community sample. They looked at polymorphisms of a number of candidate genes, including GNbeta3, the SERT (serotonin reuptake transporter) promoter (SERT-P), 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} , and $alpha_{2A}$ and $alpha_{2C}$. The results seem likely to be important: Those individuals with the 825C alleles as well as subjects with 825T alleles of GNbeta3 were significantly more likely to have meal-unrelated dyspepsia. The other candidate genes that were examined were not associated with dyspepsia. Because GNbeta3 genotypes can result in upregulation or downregulation of cell signaling, it may mean that testing for these polymorphisms could be a useful way of predicting treatment response in functional dyspepsia. This hypothesis requires careful testing in randomized clinical trials. There were limitations to this study. The investigators only acquired data on 41 subjects with dyspepsia and 47 healthy Pantoprazoles; it is important to note that the dyspeptic subjects had not undergone OGDS, and therefore it is unclear how many of these individuals actually suffered from functional dyspepsia. Furthermore, this cohort was a subset of the entire population, and the importance of selectional forces in influencing these results is also somewhat unclear.

2.4.2. Drug Effect

There remains interest in the potential contribution of drug side effects to the development of dyspepsia-particularly FD; indeed, many drugs report dyspepsia as a gastrointestinal side effect associated with their use. However, the most compelling drug association with dyspepsia continues to be the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Economic models

suggest that one of the major determinants of cost-effectiveness of NSAID treatment for arthritis is dyspepsia. Furthermore, there are data suggesting that selective cyclooxygenase (COX)-2 inhibitors (coxibs) induce less dyspepsia than traditional NSAIDs, and that dyspepsia can be reduced by cotreatment with proton-pump inhibitors (PPI) in both of these groups (ie, in patients using traditional NSAIDs or coxibs)(Hawkey C *et al*, 2005). In a meta-analysis that included 37 studies, Spiegel BM *et al*, (2005) evaluated the rates of dyspepsia in patients with arthritis who were at high risk for ulcer complications and who were taking either a coxib alone or a traditional NSAID plus a PPI. In 32 of these studies, the rate of dyspepsia in patients taking a coxib vs a traditional NSAID showed a relative risk reduction of 12% for those taking coxibs.

A further 5 studies that looked at traditional NSAIDs alone vs PPI plus an NSAID showed a 66% relative risk reduction of dyspepsia in the latter group. Therefore, the study authors suggested that a PPI-plus-NSAID combination was likely associated with a greater risk reduction for dyspeptic symptoms than was using coxibs alone. However, the lack of adequate head-to-head data comparing these 2 strategies limits the ability to make any convincing conclusions. This work does, however, add to the growing literature suggesting that using a PPI in combination with an NSAID substantially reduces dyspepsia rates, and that such an approach may be considered in patients with incident dyspeptic symptoms during treatment for arthritis.

2.4.3. Gastric Sensory and Motor Dysfunction

Possible potential mechanism underlying gastric sensory and motor derangements may be peripheral and central nervous system processing abnormalities. Controversy continues as to whether delayed gastric emptying, -- which is detected in up to 40% of patients with functional dyspepsia -- is linked to specific symptoms (dysmotility-like dyspepsia). European studies suggest that this is the case(Sarnelli G *et al*, 2003), but studies from the United States have failed to confirm these results(Talley NJ *et al*, 2001). One external factor that may alter central processing could be abuse in childhood or adulthood, which has been associated with dyspepsia in population-based studies(Talley NJ *et al*, 1994). Geeraerts B *et al*, (2005) studied 162 patients with functional dyspepsia who completed a validated questionnaire on abuse in addition to undergoing gastric emptying and gastric barostat studies. They reported an association between slow solid emptying and a history of childhood sexual abuse. They also found that psychological abuse in adulthood appeared to be associated with gastric hypersensitivity. Changes in gastric accommodation were not associated with abuse. However, these results do not establish a cause-and-effect relationship, and because these were tertiary-referred patients, selection bias also cannot be excluded.

2.5. PATHOPHYSIOLOGY

The pathophysiology of Functional Dyspepsia is still not very well understood. Several pathophysiologic mechanisms have been suggested to play a role in the dyspepsia symptom

complex. These include hypersensitivity to gastric distension, delayed gastric emptying, impaired gastric accommodation to a meal, H. pylori infection, altered duodenal sensitivity to lipids or acid, abnormal duodenojejunal motility, or central nervous system dysfunction. Within functional dyspepsia, three symptom groups were originally identified: ulcer-like dyspepsia, dysmotility-like dyspepsia, and reflux-like dyspepsia.

2.5.1. Hypersensitivity to Gastric Distension

Visceral hypersensitivity has been proposed as a key mechanism that underlies symptom generation in functional gastrointestinal disorders(Camilleri M *et al*, 2001). Several studies have confirmed that, as a group, patients with functional dyspepsia have enhanced sensitivity to balloon distension of the proximal stomach(Merzt H *et al* and 1998, Rhee PL *et al*, 2000). It is now clear that hypersensitivity to distension is present in only a subset of patients(Boeckxstaens GE *et al*, 2002). According to one large study, hypersensitivity of the proximal stomach was associated with symptoms of postprandial pain, belching, and weight loss(Tack J *et al*, 2001), but so far, other, smaller, studies failed to report significant associations of visceral hypersensitivity and the symptom pattern(Rhee PL *et al*, 2000). Another studies indicate that not only the proximal stomach but also, and maybe more intensely, the distal stomach may be involved in symptom generation due to gastric distension(Marzio L *et al*, 2001).

2.5.2. Delayed Gastric Emptying

Several studies have done to address the prevalence and role of gastric emptying in functional dyspepsia. In a meta-analysis of 17 studies involving 868 dyspeptic patients and 397 Pantoprazoles, significant delay of solid gastric emptying was present in almost 40% of patients with functional dyspepsia(Quartero AO *et al*, 1998). However, most of the studies were performed on small numbers of patients and Pantoprazoles. Recent large studies report delayed gastric emptying in 20% to 30% of dyspeptic patients(Samelli G *et al*,2003, Peri F *et al*, 1998, Maes BD *et al*, 1997).

Most small studies have failed to find a convincing relationship between dyspeptic symptoms and presence or severity of delayed emptying(Tack J *et al*, 2004). There were three large-scale, single-center studies showed that patients with delayed gastric emptying for solids are more likely to report postprandial fullness, nausea, and vomiting(Stanghellini V *et al*, 1996, Samelli G *et al*, 2003, Perri F *et al*, 1998), although a large multicenter study failed to find any association(Talley NJ *et al*, 2001).

2.5.3. Impaired Gastric Accommodation

Basically, accommodation of the stomach to a meal consists of a relaxation of the proximal stomach, providing the meal with a reservoir and enabling a volume increase without an increase in pressure. Scintigraphic and ultrasonographic studies have demonstrated an abnormal intragastric distribution of food in patients with functional dyspepsia, with preferential

accumulation in the distal stomach(Gilja OH *et al*, 1996), and gastric barostat studies have confirmed reduced proximal gastric relaxation in response to a meal in patients with functional dyspepsia(Salet GAM *et al*, 1998). A relationship between impaired gastric accommodation and early satiety and weight loss has been reported by some(Tack J *et al*, 2003,Kim DY *et al*, 2001), but has not been confirmed in other studies(Boeckxstaens GE *et al*, 2002). The prevalence of impaired accommodation is particularly high in patients with acute-onset dyspepsia, and this has been attributed to a defect at the level of gastric intrinsic nitrergic neurons(Tack J *et al*, 2003).

2.5.4. Helicobacter pylori Infection

There were many studies have attempted to establish a link between H. pylori infection and functional dyspepsia, but the role of H. pylori in functional dyspepsia remains to be a subject of controversy. Mechanistic studies found no association between H. pylori positivity and the symptom pattern, gastric emptying rate, gastric accommodation, or sensitivity to distension in functional dyspepsia(Rhee PL *et al*, 1999, Sanelli G *et al*, 2003). Most carefully designed studies found no convincing evidence that eradication of H. pylori consistently relieves the symptoms of functional dyspepsia(McColl K *et al*, 1998, Blum AL *et al*, 1998). However there are theories associate Helicobacter pylori infection with FD(Talley NJ et al, 1998; Tytgat TN, 1996). In a local study in Kuala Lumpur, H.pylori was found in 31.2% of the non ulcer dyspepsia patients(Goh KL, 1997). In Singapore, it was found that among the non ulcer dyspepsia patients investigated for H.pylori, the Chinese had the highest prevalence of 48% followed by the Malay, 37%(Kang JY, 1990).

2.5.5. Other Mechanisms

Despite of many possible mechanism mentioned above, there were still a number of other pathophysiologic mechanisms have been implicated in the pathophysiology of functional dyspepsia, based on limited numbers of studies, generally in small groups of patients. These include duodenal hypersensitivity to lipids(Feinle C *et al*, 2001), increased duodenal acid exposure due to impaired duodenal clearance(Lee K *et al*, 2004), lack of postprandial suppression of phasic contractility of the proximal stomach(Simren M *et al*, 2003), and abnormalities of gastric electrical rhythm(Parkman HP *et al*, 1997).

2.6. PREVALENCE

The prevalence of dyspepsia varies considerably between different populations. Such differences might be related to, (1) true difference in frequency of the condition, (2) criteria used to diagnose it and (3) degree of meticulousness to exclude organic causes. Although these may represent genuine epidemiological differences, it is also apparent that the varying definitions used in different population studies may have contributed to this discrepancy.

In studies using "upper abdominal pain" as the definition, the prevalence of uninvestigated dyspepsia (UD) has varied between 7%-34.2%With this definition, the lowest UD prevalence of 7%-8% is seen in Singapore, South East Asia(Ho KY, 1998), slightly higher rates are seen amongst the Scandinavians 14.5%(Agrues L, 2000) and 18.4%(Kay L, 1996), prevalence rates of

23-25.8% are seen in the US(Talley NJ, 1994) with populations in India is 30.4%(Shah SS, 2001) and New Zealand is 34.2%(Haque M, 2000) having the highest rates.

In population studies that have used the Rome I criteria to define uninvestigated dyspepsia, a prevalence between 18%-38% has been observed. The lowest prevalence of 18.4% was recorded in Hong Kong(Hu WH, 2002), whilst higher rates of 26% and 27.8% were noted in US(Drossman DA, 1993) and Taiwan(Lu CL, 2005) respectively, and the highest prevalences of up to 38.2% were observed in populations in Australia(Westbrook JI, 2002).

Then, with use of the Rome II criteria, where symptoms of reflux and IBS are excluded, surveys have reported prevalences around 24%. Population studies in Australia and China reported prevalence rates of 24.4%(Westbrook JI, 2002) and 23.5%(Li Y, 2002) of uninvestigated dyspepsia.

Using the Rome III questionnaires, prevalence of dyspepsia was found 13.4% in community subjects. 47% of these FD patients were classified as postprandial distress syndrome, 26% as epigastric pain syndrome and 27% as overlapping condition. Sensitivity and specificity of Rome III criteria in discriminating FGIDs from organic diseases of the upper GI tract was 60% and 53%, respectively(Uday C Ghoshai *et al*,2011). Frequency of UD and FD varied between 8%-30% and 8%-23%, respectively in Asia (Tables 2.3). and most patients with uninvestigated dyspepsia are found to have FD.

Table 2.3: Summary of Studies on Functional Dyspepsia in Asia

Study	Location	No. of patients	Definition	Age (yr)	Functional dyspepsia (%)
Li et al[42]	China	782	Rome II	>18	69.0
Kwan et al[43]	Hong Kong	1,353	Rome II	Mean 44 (range 18-80)	43.0
Kawamura et al[47]	Japan	2,263	Rome II	Mean 41.1 (range 16-80)	13.0
				<29	13.0
				30-39	14.0
				40-49	14.5
				>50	8.0
Kim et al[44]	Korea	476	Rome II	NA	70.0
Ji et al[77]	Korea	274	Rome II	NA	40.5
Noh et al[78]	Korea	2,388	Rome III	Mean 43.2 (SD ± 8.4)	8.1
Mahadeva et al[45]	Malaysia	210	Leeds Dyspepsia Questionnaire	30 ± 8	62.0
Wai et al[46]	Singapore	5,066	Rome II	20-75 (mean 47.5)	~80.0

2.7. EPIDEMIOLOGY

Population-based studies determining the prevalence of dyspepsia have attempted to identify epidemiological risk factors for UD, and when relavent FD as well(Table 2.4). Below is a brief summary of various parameters that have been studied in association with the prevalence of dyspepsia.

2.7.1 Age

All surveys that have been conducted have examined adults 18 years or older. FD is more common in younger age group. A study from Japan reported that prevalence of FD was 13% and 8% in age groups below and above 50 years, respectively(Kawamura A, 2001). While most surveys have shown that dyspepsia does not appear to be related to any particular age group, several studies have noted some trends. Peak prevalences of UD have been noted between the

ages 45-54 in a Canadian survey(Tougas G,1999), whilst FD appeared to peak in Chinese subjects 41-50 years(Li Y, 2002) and in Japanese adults 50-59 years(Hirakawa K, 1999). In the latter study, dyspepsia sub-types appeared to be associated with different age groups: reflux-like more common in middle-aged adults, dysmotility-like more frequent in those < 59 years and ulcer-like predominant symptoms more frequently in adults < 39 years.

In other populations, the prevalence of UD appeared to decrease with increasing age in British(Jones RH, 1990), Taiwanese(Lu CL, 2005) and Danish(Kay L, 1992) surveys. In the latter survey, there was a significantly lower prevalence of UD in adults > 70 years (10%). compared to those < 60 years (18.4%)(Kay L, 1994). In contrast, a survey in urban Mumbai, India found that UD was more prevalent in adults > 40 years(Shah SS, 2001). Despite these trends, age extremities has not been identified as a predictor of dyspepsia (UD or FD).

2.7.2 Gender

Most population studies have been able to obtain relatively equal ratios of male: female ratios and the majority of them have shown no differences in dyspepsia prevalence between genders, mostly where UD is concerned. Several studies, in different populations, however, have noted consistent female preponderance with dyspepsia(Shaib Y, 2004). Female gender was found to be the only independent risk factor for FD amongst 2018 Taiwanese health check attendees (Lu CL, 2005). In a population-based study in Australia, female adults significantly outnumbered males in most functional GI disorders, including FD(Koloski NA, 2002). As only a few population

studies have examined true FD prevalence, it is likely that the gender effect in surveys of UD have been masked due to the combination of adults with FD and organic dyspepsia.

2.7.3 Ethnicity

The role of ethnicity in dyspepsia has not been examined by most population studies. Most surveys have been done on populations of single/similar ethnic groups, mostly of Caucasian or Oriental background. However, in one of the few studies involving subjects of several ethnic backgrounds from a single institution in the US, African- American race was found to be one of several epidemiological risk factors for UD(Shaib Y, 2004).

In a survey of a multi-racial population in Singapore, South East Asia, the ethnic adjusted prevalence of UD was demonstrated as follows: Chinese 8.1%, Malays 7.3% and Indians 7.5%(Ho KY, 1998). Although the majority ethnic group in Singapore is Chinese, the authors were able to obtain prevalence based on equal representations of the three different ethnic groups.

In a door to door survey on 2,000 subjects of a rural multi- ethnic Malaysian population consisting of Chinese, Indian and Malay, 14.6% had dyspepsia (Rome II criteria). Frequency of dyspepsia was 14.6%, 19.7% and 11.2% in Malay, Chinese and Indian ethnic groups, respectively. Dyspepsia was commoner among Chinese than non-Chinese (19.7% vs 14.2%, $P = 0.062$)(Mahadeva S, 2010). In another study on urban Malaysian population, of 2,039 subjects, 24.3% had dyspepsia (Rome II criteria). Malay ethnicity (prevalence of dyspepsia: 28.3%) was an independent risk factor for dyspepsia (OR, 2.17; 95% CI, 1.57-2.99). At present, little can be

concluded regarding the role of ethnicity and it is clear that more data is required from future studies.

2.7.4. Smoking

Although a common practice world-wide, regular smoking as a risk factor has not been consistent in its association with dyspepsia. In the few population-based studies that have examined FD, smoking has not been shown to be a risk factor. In surveys of patients with UD however, regular smoking has been identifi ed as a risk factor in populations in US(Shaib Y, 2004), Canada(Tougas G, 1999), UK(Moayyedi P, 2000), and India(Shah SS, 2001). This observation may be explained by the proportion of organic disease amongst subjects with UD, as smoking has been identifi ed as clear risk factors for diseases like peptic ulcer disease.

2.7.5. Alcohol

Regular alcohol intake, as a risk factor, has been studied and it has not been shown to be associated with dyspepsia in the vast majority of surveys. However, in the Asia- Pacific region, only population studies in India(Shah SS, 2001) and New Zealand(Haque M, 2000) have showed definite associations between alcohol and UD.

2.5.6. Non-steroidal anti-inflammatory drugs

The effect of non-steroidal anti-inflammatory drugs (NSAIDs). on dyspeptic symptoms have been examined specifically in only two population-based studies. In a survey of American adults from a single institution, regular usage of NSAIDs and Aspirin, bought over the counter, were strongly associated with UD than in Pantoprazoles without dyspepsia(Shaib Y, 2004). In a British study of 4982 adults, NSAID usage was identifi ed as an independent risk factor for UD and thought to be responsible solely for 4% of dyspepsia in the community(Moayyedi P, 2000). Interestingly, data from the African sub-continent may correlate this fact in a study of Nigerian highlanders. "Indulgence in self-medication" amongst the subjects surveyed was found to be a significant risk factor for UD.Although this was not described clearly, and probably included various types of traditional medication, it is probable that analgesics containing NSAIDs may account for a sizeable amount of this "self-medication".

2.7.7. Helicobacter pylori infection

To date, only one population-based study in the UK has investigated the association of *H pylori* infection with UD. Among 8047 subjects who were tested for *H pylori,* those who were infected had more dyspeptic symptoms (44%). than those who were *H pylori* negative (36%)(Moayyedi P, 2000). Subsequent analysis revealed *H pylori* status to be predictive of UD and the authors concluded that *H pylori* infection had a 5% population attributable risk for dyspepsia assuming a causal association. The association of *H pylori* and FD is less clear, but this has only been examined in some detail in non-population-based studies.

2.7.8. Dietary factors

The role of diet in dyspepsia has not been studied by many, probably due to the diversity of dietary habits within individual populations. In the few studies that have attempted to examine dietary factors and their association with dyspepsia, the definitions of food types and categories do not appear to be clear. In the Chinese study examining the prevalence of FD(Li Y, 2002), "bad dietary habits" was shown to be a significant risk factor. However, the authors fail to clarify their definition of this term. In an urban survey in India, Shah et al managed to demonstrate that no differences in dyspeptic symptoms occurred between vegetarians (29.1%) and meat-eaters (31.2%), whilst spicy, fried or food prepared outside the home contributed insignificantly to worsening of symptoms(Shah SS, 2001). In Nigerian adults living in the highlands, the type of staple food consumed was strongly associated with UD, but no specific definitions of food types are given(Ihezue CH, 1996).

The effect of caffeine intake has also been examined in some population studies, particularly from Western studies. Surveys in the US and Europe have reported that excessive coffee or tea intake has not been shown to be related to the presence of dyspepsia/ UD[Bennersen B, 1996). However, in one of the few studies to examine its' role, a Canadian survey showed that heavy intake of cola was associated with markedly increased prevalence of dyspepsia(Tougas g, 1996). An explanation for this observation may be due to the fact that greater quantities of caffeine in cola can be consumed more readily, or it may be a non-caffeine related compound which is responsible for dyspeptic symptoms.

2.7.9. Socio-economic factors

Most population-based studies have examined basic socio-demographic associations in dyspepsia and the majority have not revealed any significant findings, eg between social classes and prevalence of dyspepsia. However studies examining details of socio-economic status were able to elicit associations with dyspepsia. Drossman DA, (1993) in the US noted a strong relationship between lower household income and larger household membership with increased functional GI diseases, including FD. Similarly, a Canadian survey revealed that chronic GI symptoms (UD) were more prevalent in adults with lower household income, those who were unemployed and with lower educational levels(Tougas G, 1999). In a British survey, factors including rented accommodation, no central heating, low educational level and sharing a bed with siblings (surrogate for crowded household) were found to be predictive of UD in adults(Moayyedi P, 2000). Amongst an urban population of dyspeptics in China, "dissatisfaction with financial income" was associated with FD, but this was not as significant as other psychological factors (Li Y, 2002). Finally, in the Nigerian study by Ihezue H, (1996), a larger sized family together with occupational scatter was strongly associated with UD.

2.7.10. Psychological factors

In most population surveys that have studied psychological disturbances as a risk factor, definite risk associations, particularly for FD, have been elicited. In 1994, Talley *et al* had previously reported in an American adult population that sexual, emotional and verbal abuse either in childhood or adulthood were significantly associated with dyspepsia. This, in turn resulted in

more health-care seeking behavior amongst this group of adults. In 1994 Danish survey , Kay and Jorgensen noted that UD was strongly associated with adults who had "experience of problems" and "psychological vulnerability".

In one of the few population-based studies that managed to examine FD in some detail (by excluding structural abnormalities in most of the adults), the authors found that FD patients, as opposed to those with UD alone had a significant association with tranquiliser usage(Bernersen B, 1996), probably a surrogate marker for anxiety or a neurotic behaviour. This observation is similarly observed in an Australian survey where adults with FD scored highly on anxiety and depression scales(Koloski NA, 2002), and in a Chinese study which revealed "pressure from society" and "destructive living habit" as risk factors for FD(Li Y, 2002). Yet another survey in Hong Kong also revealed that subjects with UD had more anxiety, compared to adults with IBS, which appeared to influence health-care seeking habits(.Hu WH, 2002).