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The Introduction should provide a clear statement of the problem, the relevant literature on the subject, and the proposed approach or solution. It should be understandable to colleagues from a broad range of scientific disciplines. The presentation of the case study should include the important information regarding the case. This must include the medical history, demographics, symptoms, tests etc. Kindly note that all information that will lead to the identification of the particular patient(s) must be excluded.

The conclusion should highlight the contribution of the study and its relevance in general medical knowledge.

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The p53 status in patients with common variable immunodeficiency

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Common variable immunodeficiency (CVID) comprises a heterogeneous group of primary antibody deficiencies with complex clinical and immunological phenotypes. A high risk for cancer has been described for some types of cancer among patients with CVID. Mutations in p53, a critical tumor suppressor gene, are one of the most common genetic alterations in human cancers, therefore contributes to the complex network of molecular events leading to tumor formation. This prompted us to investigate the incidence of p53 gene mutations in patients with CVID and evaluated the predictive risk for tumor development. We investigated the presence of p53 mutations in patients with CVID, tumor samples and in the surgical margins of 34 patients with head and neck cancer using single strand conformational polymorphism and sequencing analysis. We investigated the presence of p53 mutations in genomic DNA samples of 20 patients with CVID and 10 healthy controls using polymerase chain reaction and heteroduplex analysis. None of the patients were found to have p53 gene mutations. Only one patient developed non-Hodgkin lymphoma (NHL) during nine years follow-up. P53 mutations was not also detected in tumor biopsy sample. We found no statistically significant association between the presences of p53 mutations in patients with CVID.

Key words: Common variable immunodeficiency, p53 gene, tumor development, apoptosis

INTRODUCTION

Common variable immunodeficiency (CVID) includes a heterogeneous group of conditions characterized by reduced levels of serum immunoglobulins and primary antibody failure (Chapel et al., 2008). Genetic defects in transmembrane activator and calcium modulator and cyclophilin ligand interactor -TACI (TNFRST13B), inducible costimulator (ICOS), B cell-activating factor receptor (BAFF-R) and CD19 account only for a minority (15 to 20%) of cases of CVID; the molecular pathophysiology of the remaining cases remains undefined (Castigli and Geha, 2006). Chronic infections and chronic inflammatory conditions seen in CVID result in a prolonged oxidative and nitrosative stress and an increased cancer risk.

Patients with CVID have an increased risk of malignancy, particularly lymphoma and gastric cancer (Cunningham-Rundles and Bodian, 1999). CVID involves T-lymphocyte abnormalities, which may in part explain the increased incidence of lymphoproliferative and autoimmune diseases seen in patients with CVID. Patients require administration of intravenous immunoglobulins monthly or every three weekly (Chapel and Cunningham-Rundles, 2009).

Apoptosis is a programmed cell death process that plays role in regulation of cell count, organ size and tissue hemostasis throughout the development of the organism. The defects in apoptosis mechanism lead to autoimmunity, immunodeficient state and tumor development. The p53 tumor suppressor gene plays an important role in the regulation of the apoptotic response of cells following exposure to genotoxic stress. The dual role played by p53 in hematopoiesis, inducing proper
cellular maturation as well as maintaining the quiescence of the stem cell population contributes to the homeostasis of the hematopoietic system, ensuring the prevention of malignant transformation. p53 has many mechanisms of anticancer function, and plays a role in genomic stability, and inhibition of angiogenesis. It can initiate apoptosis, the programmed cell death, if DNA damage proves to be irreparable. P53 can activate DNA repair proteins when DNA has sustained damage (Levine et al., 1991). Inactivating mutations at the p53 gene represent the most common genetic lesion of human primary tumors and have etiologically been associated with the onset of neoplasia. Mutant alleles with single missense base substitutions, predominantly within exons 5 to 8, encode for p53 proteins (Molchadsky et al., 2010).

Several alteration in tumour suppressor genes have been reported not only in cancers but also in precancerous processes, suggesting that mutation of the p53 gene is an early event in cancer development. Because malignancy is seen frequent in CVID patients, we planned to study p53 gene mutations in CVID and evaluated the predictive risk for tumor development.

MATERIALS AND METHODS

We analyzed 20 patients with CVID (12 males and 8 females; mean age 7.8 years, range 3.8 to 25 years) and 10 healthy children as a control group (9 males and 1 female, mean age 6.5, range 2.5 to 15 years). In the CVID group there was one patient who also had non-Hodgkin lymphoma (NHL). Genomic DNA was isolated using standard methods from peripheral blood lymphocytes. (Proteinase K incubation and phenol-chloroform extraction). Exons 5 to 8 of p53 gene were amplified by polymerase chain reaction (PCR) and heteroduplex analysis (HDA) with a sensitivity of 80-90% in small DNA fragments was used to investigate the point mutations in the central hydrophobic core of the molecule coded in exons 5 to 8 where most mutations seemed to be clustered (Kiaris et al., 2005). The primary sequences of p53 genes were as below:

E5F 5'-TCA ACT CTG TCT CCT TCC TCT TCC-3'
E5R 5'-CTG GCC AAC CAG CCC TGT CTT-3'
E6F 5'-TTG CTC CTA GTA GGT GCC CC-3'
E6R 5'-CAG ACC TCA GGC GGC TCA TA-3'
E7F 5'-TAG GTT GGC TCT GAC ACC-3'
E7R 5'-TGA CCT GGA AAT CTA CGT GGA CGG-3'
E8F 5'-AGT GGT AAT CTA CTG GGA CGG-3'
E8R 5'-ACC TCG AGT ACT GCT CCC TG-3'

Heteroduplex analysis (HDA) was carried out from the high-quality PCR products (Figure 1). Samples were HDA positive by visual inspection if two bands migrated apart from the wild-type bands.

RESULTS

None of the patients were found to have p53 gene mutations by HDA (Figure 2). No mutation was detected in exons 5 to 8 of p53 gene in any of our patients or control group. The analysis of p53 mutation on tumor tissue of CVID patient who developed NHL was negative. During 9 years follow up, only one patient in 20 developed malignity and chemotherapy does not cure metastatic malignancy. The patient died in a short time of the first chemotherapy regimen.

DISCUSSION

The incidence of malignancy appears overall increased in CVID, occurring in up to 15% of subjects. About 2 to 8% of subjects with CVID are diagnosed with NHL (Chua et al., 2008). Kinlen et al. (1985) reported a 30-fold increase in the risk of lymphoma and a 47-fold increase in the risk for stomach cancers. For 176 subjects in a European study, the observed to expected ratio for lymphoma in CVID was 12.1 and for stomach cancer was 10.3 (Mellermkjaer et al., 2002). In our study group, only one patient developed NHL during 9 years follow-up period.

There is no sufficient number of studies that disclose the predictive risk factors for cancer development among patients with CVID. To our knowledge, p53 mutations on blood sample have not been searched in CVID patients. In this study, we analysed these patients for mutations in p53 which is one of the tumor suppressor genes frequently involved in neoplasia and found no mutation both in patients and controls. There is only one study showed that Bcl-6 mutations, proto-oncogene, have been proposed as a genetic marker for defining the histogenesis of B-cell lymphoproliferation in patients with CVID (Ariatti et al., 2000). Rearrangements of BCL-6 were detected in two thirds of patients with CVID and NHL.

Nearly 50% of gastric cancers show p53 overexpression, and some studies report p53 gene mutations in precancerous lesions, suggesting a role in the early stages of gastric carcinogenesis. The mutated protein has a longer half-life than native p53 (Starzynska et al., 1994; Shiao et al., 1994). Zullo et al. (1999) assessed both histological alterations and p53 overexpression in the gastric mucosa of patients with CVID, and to correlate these findings with Helicobacter pylori infection. In the present study, p53 overexpression was found in 18% of patients, including one with normal gastric mucosa. They hypothesised that both H. pylori and p53 alterations play a role in the gastric carcinogenesis of patients with CVID. We have studied p53 mutations in the tumor tissue obtained from the patient with CVID and NHL. Unfortunately, no mutation was detected.

We conclude that although the number of our patients is not sufficient to make strict comments, p53 gene mutations appears to play no role in the higher incidence of neoplasia in these patients. This study could be done with more extensive patient populations and furthermore investigations of the other apoptosis regulator factors, such as bcl-2, bax and bcl-x, besides p53 mutations are necessary in order to identify the underlying aetiology of malignancy in CVID patients.
Figure 1. The PCR products were controlled on 2% agarose gel stained with ethidium bromide and photographed under UV light with imaging software system (Vilber Laurmat /France) after electrophoresis.

Figure 2. Heteroduplex analysis of exon 7 of p53 gene in lymphocytes from 9 patients.
ACKNOWLEDGEMENTS

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Chapel H, Cunningham-Rundles C (2009). Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br. J. Haematol., 145: 709-727.


A review of the types of presentation among positive angiographic acute coronary syndrome patients in Hospital Universiti Sains Malaysia

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Atypical presentation of myocardial infarction is recognized as an important manifestation of coronary heart disease associated with unfavorable prognosis. Understanding the spectrum of clinical symptoms and presentations are essential to diagnose and deliver appropriate rapid treatment to patients in the emergency department. Hence, this study was carried out to identify the type of presentation of acute coronary syndrome (ACS) and its association with the risk factors related to the atypical presentation in population of study. Out of 260 patients, 25.8% had atypical presentation of ACS with the presentation of right sided chest pain (1.8%), burning chest pain (20.9%) and pricking chest pain (15%). The significant associated diseases were diabetes mellitus and past medical history of ischaemic heart disease (p<0.01) respectively. Other significant associated symptoms were epigastric pain (p<0.001), cough (p<0.01) and giddiness (p<0.01). As a conclusion, ACS with atypical presentations remains an important presentation in the Emergency Department. Despite the availability of advanced medical technology, a thorough history taking remains an important component of diagnosis for a better management and outcome of ACS.

Key words: Atypical myocardial infarction, common presentation, emergency department.

INTRODUCTION

Despite recent major advances, ACS still pose great challenges to emergency physicians from its diagnostic, therapeutic, and prognostic standpoint. This is partly due to its considerable varied clinical manifestations. For example, the silent or atypical presentations such as pleuritic or indigestion-like chest pain are recognized as important manifestations of ACS, as most studies suggest that they are associated with unfavorable prognosis (Sigurdsson et al., 1995; Madias et al., 1995). Such atypical presentations are more common among woman and elderly patients (Jayes et al., 1992). Several studies have concluded that between 2 and 8% of all patients with ACS are discharged home from emergency departments (Chris and William, 2001). Unfortunately, a large proportion of these patients sent home with ACS were younger patients presented with atypical symptoms or those who had non-diagnostic electrocardiography (McCarty et al., 1993). This study was carried out to determine the types of presentation of ACS in our patient
population in emergency department as well as the risk factors associated with such presentations.

**RESULTS**

A total of 362 patients had coronary angiogram done at ICL, HUSM from 1st January to 31st December 2004. Out of these 362 patients, 285 (78.7%) were enrolled into the study, and 25 were excluded. Among the 285 patients enrolled in the study, 193 (74.2%) had typical presentation and 67 (25.8%) had atypical presentation.

The demographic data of patients presented with acute coronary syndrome revealed no significant statistical difference in the type of presentation between gender, race and age. However, there was a higher numbers of atypical presentation in female, Indian and elderly (Table 1).

A retrospective, a one year cross-sectional study which looked into the types of ACS cases presented to Hospital Universiti Sains Malaysia. Patients with age less than 18 years old and those with pre-existing cardiovascular diseases such as congenital heart diseases and those with underlying valvular diseases were excluded from this analysis even if they have positive angiographic findings. Other than that, all patients with positive angiographic findings were included for the analysis.

We obtained the medical records for angiogram findings from the invasive cardiac laboratory (ICL), HUSM. Data entry, interpretation and statistical analysis were done using the Social Science and Statistical Package (SPSS) version 12.0. Statistical analysis using the Chi-Square test, Fisher's exact test and binary logistic regression were employed. Ethical approval for this study was obtained from our institutional ethical review board.

Majority of the atypical presentation of ACS are “no chest pain” (35%), “pricking chest pain” (15%) and “burning type of chest pain” (14%). In terms of associated symptoms, significantly more patients present with coughing (9% versus 1%), giddiness (26.9% versus 9.3%) and epigastric pain (31.3% versus 13.0%) in the atypical presentation group versus the typical presentation group (Table 2).

There is also significantly higher percentage of patients with associated diabetes mellitus in the atypical presentation group compared to the typical presentation group (p=0.01) (Table 3). On the contrary, the percentage of patients with associated past history of ischaemic heart disease was no different between the two groups (p=0.69). (Table 4).

Table 1. Demographic data of patients presented with acute coronary syndrome.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical</th>
<th>Atypical</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Male</td>
<td>155</td>
<td>75.6</td>
<td>50</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>69.1</td>
<td>17</td>
</tr>
<tr>
<td>Racial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>179</td>
<td>73.7</td>
<td>64</td>
</tr>
<tr>
<td>Chinese</td>
<td>11</td>
<td>84.6</td>
<td>2</td>
</tr>
<tr>
<td>Indian</td>
<td>2</td>
<td>66.7</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>17</td>
<td>89.5</td>
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</tr>
<tr>
<td>41-50</td>
<td>44</td>
<td>73.3</td>
<td>16</td>
</tr>
<tr>
<td>51-60</td>
<td>77</td>
<td>75.5</td>
<td>16</td>
</tr>
<tr>
<td>&gt;60</td>
<td>55</td>
<td>70</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 2. Nature of chest pain in typical and atypical ACS.

<table>
<thead>
<tr>
<th>Description</th>
<th>Typical</th>
<th>Atypical</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Yes</td>
<td>193</td>
<td>100</td>
<td>31</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Left sided</td>
<td>192</td>
<td>99.4</td>
<td>28</td>
</tr>
<tr>
<td>Right sided</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Nature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Discomfort</td>
<td>48</td>
<td>24.8</td>
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</tr>
<tr>
<td>Heavy</td>
<td>71</td>
<td>36.7</td>
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</tr>
<tr>
<td>Pressing</td>
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<td>Pricking</td>
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<td>0</td>
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</tr>
<tr>
<td>Tight</td>
<td>15</td>
<td>7.7</td>
<td>1</td>
</tr>
<tr>
<td>Nil</td>
<td>0</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left arm</td>
<td>45</td>
<td>23.3</td>
<td>9</td>
</tr>
<tr>
<td>Back</td>
<td>8</td>
<td>4.1</td>
<td>3</td>
</tr>
<tr>
<td>Jaw</td>
<td>20</td>
<td>10.3</td>
<td>4</td>
</tr>
<tr>
<td>Lower limb</td>
<td>3</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Right arm</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Nil</td>
<td>116</td>
<td>60.1</td>
<td>51</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>47</td>
<td>24.4</td>
<td>14</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>97</td>
<td>50.3</td>
<td>39</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>16.6</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>9.8</td>
<td>9</td>
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<tr>
<td>Sweating</td>
<td>65</td>
<td>33.7</td>
<td>16</td>
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<tr>
<td>Syncope</td>
<td>3</td>
<td>1.6</td>
<td>3</td>
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<tr>
<td>Insomnia</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>1.0</td>
<td>6</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>1.0</td>
<td>2</td>
</tr>
<tr>
<td>Giddiness</td>
<td>18</td>
<td>9.3</td>
<td>18</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>25</td>
<td>13.0</td>
<td>21</td>
</tr>
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</table>
Table 3. Associated risk factors with ACS presentations.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Typical</th>
<th>Atypical</th>
<th>Chi-square test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70</td>
<td>36</td>
<td>0.012</td>
</tr>
<tr>
<td>No</td>
<td>123</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>113</td>
<td>39</td>
<td>0.9</td>
</tr>
<tr>
<td>No</td>
<td>80</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>77</td>
<td>23</td>
<td>0.42</td>
</tr>
<tr>
<td>No</td>
<td>116</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>0</td>
<td>0.305</td>
</tr>
<tr>
<td>No</td>
<td>190</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>6</td>
<td>0.268</td>
</tr>
<tr>
<td>No</td>
<td>183</td>
<td>61</td>
<td></td>
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<tr>
<td>History of IHD</td>
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<tr>
<td>Yes</td>
<td>85</td>
<td>13</td>
<td>0.01</td>
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<td>No</td>
<td>108</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Active smoker</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>117</td>
<td>38</td>
<td>0.575</td>
</tr>
<tr>
<td>No</td>
<td>76</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>85</td>
<td>32</td>
<td>0.598</td>
</tr>
<tr>
<td>No</td>
<td>108</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

disease is significantly higher among the typical presentation group versus atypical presentation group (p=0.01) (Table 3).

DISCUSSION

In our study, atypical presentation of ACS constituted 25.8% (67) of patients, which was almost similar to other finding which found 25 to 30% of patients with myocardial infarction were clinically unrecognized because of the atypical presentation, for which they did not seek treatment (Sigurdsson et al., 1995; Loria et al., 2008). From our study, woman, elderly and Indian had higher atypical presentations, although the result was not statistically significant, as it was limited to the inequality of subjects recruitment. In fact, similar to our findings, other study also found that a woman was more likely to have atypical symptoms compared to men (Roger et al., 2000).

As documented, women with the age of more than 65 years were at higher risk for atypical presentations, which primarily consisted of shortness of breath and epigastric pain (Lusiani et al., 1994). The symptoms of dyspnoea in the setting of myocardial ischaemia may result from the acute loss of myocardial compliance, elevation in left ventricular pressures, and subsequent symptoms of heart failure to present with nausea, vomiting and shortness of breath (Golberg et al., 1998). Those women were more likely to have diabetes mellitus at the time they first experience myocardial infarction compared to men and this might be the reason of why they presented with atypical symptoms (Zucker et al., 1997).

Furthermore, women were more likely to have normal or mild disease and less likely to have left-main and three-vessel disease and were more frequently presented with jaw pain and nausea (Dey et al., 2009). Another possibility was women had difficulty in interpreting the severity of the symptoms. This is further complicated by the confusion that arises when interpreting the perception of the symptoms that they had (Rosenfield, 2001). Women are also less likely to be correctly assesses their symptoms (Healy, 1991). Atypical symptoms in women may also be mistaken as musculoskeletal, gastrointestinal or neurological in origin and inconsistent with the onset of myocardial infarction (Milner et al., 1999). To overcome these problems in primary care setting especially in emergency department, a range of symptoms presentation in women with myocardial infarction and understanding the disease process in women are very useful (Zbierajewski–Eischeid and Loeb, 2009).

Increasing age was associated with higher chances of getting atypical presentation. For elderly, it was estimated that only 38% of patients older than 60 years with autopsy proved myocardial infarction, had the correct diagnosis before death (Bayer et al., 1986; Cocchi et al., 1988). Varying factors were thought to contribute to these findings, including decline in mental functions, alteration or absence of pain perception secondary to sensory neuropathies or an altered pain threshold. Impaired communication, difficulty in expressing symptoms and delay in the perception of angina pain also further contributed to the atypical presentation (Ambeditable et al., 1994). Other than that, the cardiac pain was frequently confused by many co-morbid conditions present in elderly (Gregoratos, 2001). Since the most common atypical presentation of myocardial infarction in elderly was shortness of breath instead of chest pain, this caused difficulty in making a diagnosis (Woon and Lim, 2003; Everts et al., 1996). The presentation of acute myocardial infarction is modified by age-related changes in endothelial function, smooth muscle cell activity, diastolic function and response to circulating catecholamine and these explained why the elderly has...
higher atypical presentation of myocardial infarction (Maheshwari et al., 2000).

Pain perception among racial and ethnic disparities are differently perceived and tolerated. The inter-individual differences in pain sensitivity are reported to be heritable as the result of polymorphisms of pain-relevant genes (Kim et al., 2004; Uhl et al., 1999). Nepalese and Indian found to have more tolerated to pain compared to Caucasian and Hispanic (Carmen et al., 2003). The different pain perception might be related to the interaction between endorphin and the important primary targeting receptor that is, μ-receptor (Ikedo et al., 2005). The μ-receptor1 is known to be polymorphic especially at the locus of A118G (Lotsch and Geisslinger, 2005). The variants of A118G might confer the different effect of pain perception which will be under-interpreted in A118G variants group as atypical myocardial infarction. For those who presented with chest pain, the nature of the pain was described as pricking and burning. Kontos and colleagues also identified that burning sensation as in classic chest pain may be suggestive of myocardial ischaemia (Bardy, 1997; Kantos et al., 1997; Selke et al., 1995). Besides the above mentioned presentations, cough, giddiness and epigastric pain were significantly present in the atypical ACS presentation. These non specific associated symptoms may be related to the neuronal stimulation in response to ischaemia and may be also related to the non-independent underlying medical illness such as diabetes mellitus and hypertension or stress related mechanism (Terkelsen et al., 2005).

In our study, 41% (106) patients suffered from DM. Of this number, 27% of diabetic patients who had coronary artery disease presented with atypical chest pain as compared to atypical chest pain (13.8%). There was a significant difference in clinical presentation between typical and atypical presentation of ACS among diabetic patients. Our findings again re-emphasize the importance of DM as an important independent predictor of a probability of ACS or CAD in our population. High blood sugar and duration of diabetes in uncontrolled diabetes will damage the nerve cells (Angelika et al., 2004). Subsequently, peripheral neuropathy, autonomic neuropathy and focal neuropathy may affect the pain perception (AOL Health, 2007). Loss of autonomic function will affect the nerve conduction to the heart subsequently affect the sweating mechanism, pain perception and the heart rate control that occurs unpredictably. Hence, patients with diabetic might perceive pain differently as atypical in nature.

Interestingly, past history of IHD was associated with typical presentation of myocardial infarction. The possible explanation is the brain learns from its past experience. Well established medical history and experienced of having previous angina pain may alert the patients regarding their illness and make them aware about the consequence of acute coronary disease (Amtz et al., 2004; Katja et al., 2008). Consequence, any chest discomfort or abnormal feelings directly will make them concern about risk of having a new episode of acute myocardial infarction.

In conclusion, atypical presentation of ACS is common and consisted of a quarter of our local population. A greater awareness of atypical presentation may improve awareness among medical personals working in emergency care setting. High index of suspicion with very skillful history clerking and examination may reduce the missed diagnose of acute myocardial infarction.

REFERENCES


In vitro and in vivo evaluation of acetylsalicylic acid in Khat (Qat) chewing healthy volunteers

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Department of Pharmaceutics, Faculty of Pharmacy, Sana’a University, Yemen.

Accepted 20 January, 2012

Aspirin is being extensively used in Yemen as analgesic, antipyretic, anti-inflammatory and anti-platelets aggregation for prophylaxis of thrombotic heart diseases. The objective of this study was to evaluate 2 common brands of aspirin present in the market, weight variation, disintegration and dissolution, hardness and drug content and the effect of Khat chewing on their bioavailability. 28 healthy male volunteers (14 Khat chewing and 14 Khat non-chewing) were enrolled in the study; each received a single dose (600 mg) of aspirin. Urine samples were collected for 24 h. The urine concentrations of salicylic acid were then determined using UV-Visible Spectrophotometer.

Results obtained revealed that as weight variation, hardness, friability, dissolution, disintegration and drug content for both brands (a, b) were closely related to each other and within the acceptable pharmacopeial limits. For in vivo study, the results obtained showed that higher cumulative percentage excreted after 24 h, higher peak height (mg/h), higher percentage of bioavailability and the higher extent of absorption in Khat non-chewing volunteers than Khat chewing volunteers. While longer time of elimination was observed in Khat chewing volunteers than Khat non-chewing volunteers. In conclusion, we suggest that Khat chewing had a worse effect on the bioavailability and pharmacokinetic properties of the studied drug.

Keywords: In vitro, in vivo, aspirin, Khat chewing.

INTRODUCTION

Aspirin is one of the most commonly used drugs due to its usefulness as an analgesic, anti-inflammatory, anti-thrombotic and anti-platelet agent, and its ready commercial availability (Gordon et al., 1994). It was introduced in the late 1890's and has been to treat a variety of inflammatory conditions (Thun et al., 2002). However, the anti-platelet activity of this agent was not recognized until almost 70 years later (Awtry and Loscalzo, 2000). The ingestion of 325 mg of aspirin every other day reduced the incidence of myocardial infarction by over 40% in male physicians (Jimenz et al., 1992).

It has poor water solubility; hence its dissolution rate is the rate limiting step, thereby affecting its bioavailability (Bamigbola et al., 2009).

The pharmacological activity of acetylsalicylic acid is mainly due to salicylic acid, a metabolite formed after hydrolysis. The increase in the urinary pH produced an increase in the renal clearance of salicylate and thus produces reduced plasma level of the salicylate level (Awtry and Loscalzo, 2000; Clissold, 1986; Patrono et al., 1998).

After oral administration, 80 to 100% absorbed in the stomach and in the small intestine. However, bioavailability is lower because partial hydrolysis occurs during absorption and there is a "first-pass" effect in the liver (Borga et al., 1976).

Elimination half life: 4.7 to 9 h (average 6 h) and the half-life dose-related. Acetylsalicylic acid when administered to normal volunteers is reported to have a half-life of only 13 to 20 min after which it is immediately hydrolyzed to Salicylic acid (Done, 1960).

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Aspirin has various side effects on the gastro-intestinal tract, and primarily causes gastric lesions, ulcerations and erosions (Sung et al., 2000).

No report on effect of khat chewing on the availability of aspirin tablets since most of the Yemeni peoples are khat chewer, where supporters of Khat chewing claim that it is useful in diabetic patients because it lowers blood glucose, it acts as a remedy for asthma, it eases symptoms of intestinal tract disorders (Al-Meshal et al., 1985) and maintains social contact as a socializing herb (Kalix, 1984).

The objective of this study to evaluate 2 common brands of aspirin present in the market such as weight variation, disintegration and dissolution, hardness and drug content and the effect of Khat chewing on their bioavailability.

MATERIALS AND EQUIPMENTS

Aspirin®, 300 mg acetylsalicylic acid, uncoated tablet, brand A (Shapacho -Yemen, Batch No 1140), brand B (Bayer-Germany, Batch No 00110928), aspirin standard (Porte-Pharma, Germany), hydrochloric acid, ethanol and sodium hydroxide (BDH ,England). Ferric chloride (Himedia Lab, India), sodium acetate trihydrate and phenol red (Brixworth-N.UK).

UV-Visible Spectrophotometer (UV-1601(PC) S220V, CAT NO. 20-67501-93, Shimadzu Corporation, assembled in Australia), dissolution tester, disintegration tester, hardness tester, friability tester (Pharma test: Germany) and electronic balance(Sartorius: USA).

Methodology

Weight variation, friability, hardness and disintegration were carried according to USPXXX methodology. Dissolution test was carried for the two brands using USPXXX (2007) methodology in which 500ml of 0.05M acetate buffer maintain at 50 rpm at 37±0.5°C at 265±2 nm. Drug contents was also carried out according to USP, in which a number of aspirin tablets was grinded and accurately weighed amount equivalent to 0.5 g of aspirin placed in flask with 50 ml of 0.5 N NaOH, boiled gently for 10 min. Phenol red was used as indicator and the excess of NaOH was titrated by 0.5 N hydrochloric acid till the solution became colourless. Blank determination was performed, using 0.5 N NaOH and 0.5 N hydrochloric acid. The amount of 0.5 N NaOH which actually reacted with aspirin was determined.

In vivo study in biological fluids

28 healthy male volunteers with no history of GI, liver or kidney diseases were shared in this study. Each volunteer was instructed to abstain from all medications or foods that might interfere with the drug such as (ethanol, caffeine, chocolate, and tea) for at least 24 h before getting aspirin dose. They also asked to abstain from taking any prescription drugs for 2 weeks before the study or any other drug including vitamins, for at least 1 week before until the end of study. Following an overnight fast, each volunteer was instructed to void his bladder and ingest 250 ml of water. In 1 h before and the 0 h. Urine samples were taken as control and 600 mg of aspirin was ingested with 250 ml of water. No foods or liquids other than water permitted for 4 h following ingestion of dose. Cumulative urine samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h. The volume of collected urine samples measured at each collection time and samples were refrigerated immediately. Each volunteer was instructed to drink 250 ml of water after each urine collection for the first 3 h and simple uniform meal was served after the 4 h sample (Emmanuel et al., 2009). 2 ml of urine sample was taken in a test tube and added 10 ml of analytical reagent (ferric chloride 1 g/100 ml distilled water). Spectrophotometer was maintained at 540 nm. And the pharmacokinetic parameters determined in this study were overall elimination rate constant, the biological half-life of elimination, the absorption rate constant and the biological half-life of absorption. The overall elimination rate constant was determined by the amount of drug remaining to be excreted method. The last few (terminal) points of cumulative amount excreted were subtracted from the total amount excreted and plotted versus time. The slope of the curve gave the overall elimination rate constant (Kₑ/2.303).

RESULT AND DISCUSSIONS

The data obtained for in vitro studies of the two brands (A) and (B), (weight variation, hardness friability and disintegration) within the acceptable limits. Dissolution test passed USP value which is 80% at 30 min and drug contents confirm the USP limit which is 80% at 30 min and drug content) within the acceptable limits. Dissolution test passed USP value which is 80% at 30 min and drug content (Ritschel, 1976).

As shown in Table 2, the cumulative mg of salicylate excreted after 24 h, the urinary peak height (mg/h), the time to reach that peak (h) and the percent bioavailability were used as the bioavailability parameters to evaluate and compare Khat chewing and none chewing volunteers. It is well known that the cumulative urinary excretion data describe the extent of bioavailability of the drug (Ritschel, 1976).

As shown in Table 3 and Figure 1; the cumulative salicylate excreted after 24 h for Khat none chewing volunteers ranged from 433.94 to 521.39 mg with an average value of 477.67 mg, the results are in good accordance with that mentioned (Gadalla et al., 1989), but for all the Khat chewing volunteers ranged from 372.40 to 416.18 mg with an average value of...
Table 1. Physicochemical parameters of the two brands of aspirin (A) and (B).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Brand A</th>
<th>Brand B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight variation (mg)</td>
<td>360.70 ± 0.15</td>
<td>358.1 ± 0.26</td>
</tr>
<tr>
<td>Hardness (kg)</td>
<td>4.21 ± 0.07</td>
<td>7.12 ± 0.05</td>
</tr>
<tr>
<td>Friability %</td>
<td>0.94 ± 0.01</td>
<td>0.31 ± 0.01</td>
</tr>
<tr>
<td>Disintegration (min.)</td>
<td>1.10 ± 0.12</td>
<td>2.42 ± 0.19</td>
</tr>
<tr>
<td>Dissolution % (30 min.)</td>
<td>93.91 ± 0.31</td>
<td>88.92 ± 0.24</td>
</tr>
<tr>
<td>Drug Content %</td>
<td>102.43 ± 0.21</td>
<td>97.53 ± 0.34</td>
</tr>
</tbody>
</table>

Table 2. Average bioavailability and pharmacokinetic parameters obtained from the Khat non-chewing and Khat chewing volunteers.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Khat non chewing</th>
<th>Khat chewing</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative% excreted after 24 h</td>
<td>91.122</td>
<td>75.212</td>
<td>0.000</td>
</tr>
<tr>
<td>Peak height (mg/h)</td>
<td>67.834</td>
<td>55.381</td>
<td>0.013</td>
</tr>
<tr>
<td>Time of peaking (h)</td>
<td>2.501</td>
<td>2.433</td>
<td>0.874</td>
</tr>
<tr>
<td>Percent Bioavailability</td>
<td>91.082</td>
<td>75.211</td>
<td>0.000</td>
</tr>
<tr>
<td>Absorption rate constant (1/h)</td>
<td>0.764 ± 0.03</td>
<td>0.736 ± 0.05</td>
<td>0.934</td>
</tr>
<tr>
<td>Half-life of absorption (h)</td>
<td>0.915 ± 0.04</td>
<td>0.960 ± 0.08</td>
<td>0.753</td>
</tr>
<tr>
<td>Elimination rate constant (1/h)</td>
<td>0.209 ± 0.03</td>
<td>0.159 ± 0.02</td>
<td>0.023</td>
</tr>
<tr>
<td>Half-life of elimination (h)</td>
<td>3.302 ± 0.22</td>
<td>4.361 ± 0.30</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Table 3. The cumulative and average Cumulative mg salicylate excreted after 24 hr following oral administration of aspirin and the average urinary excretion rates of aspirin in Khat non-chewing and chewing volunteers.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Average cumulative of salicylate excreted after 24 h Mean ± SE</th>
<th>The average urinary excretion rates of aspirin Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Khat none chewing volunteers</td>
<td>Khat chewing volunteers</td>
</tr>
<tr>
<td>1.0</td>
<td>8.96 ± 0.82</td>
<td>8.46 ± 1.08</td>
</tr>
<tr>
<td>1.5</td>
<td>26.33 ± 0.69</td>
<td>23.26 ± 0.93</td>
</tr>
<tr>
<td>2.0</td>
<td>51.36 ± 0.64</td>
<td>42.39 ± 0.18</td>
</tr>
<tr>
<td>3.0</td>
<td>94.36 ± 1.39</td>
<td>64.61 ± 0.23</td>
</tr>
<tr>
<td>4.0</td>
<td>137.56 ± 0.68</td>
<td>110.04 ± 0.77</td>
</tr>
<tr>
<td>6.0</td>
<td>190.62 ± 0.23</td>
<td>151.78 ± 0.46</td>
</tr>
<tr>
<td>8.0</td>
<td>275.09 ± 0.52</td>
<td>212.09 ± 1.36</td>
</tr>
<tr>
<td>10.0</td>
<td>347.35 ± 1.37</td>
<td>262.22 ± 0.90</td>
</tr>
<tr>
<td>12.0</td>
<td>402.72 ± 0.73</td>
<td>309.74 ± 0.33</td>
</tr>
<tr>
<td>24.0</td>
<td>447.70 ± 0.94</td>
<td>344.69 ± 1.08</td>
</tr>
<tr>
<td>1.0</td>
<td>477.67 ± 1.26</td>
<td>394.29 ± 1.10</td>
</tr>
</tbody>
</table>

394.29 mg. The Khat none chewing and Khat chewing’s volunteers gave a different cumulative amounts excreted, it is of higher value for the Khat none chewing volunteers of 83.38 mg, Khat none chewing volunteers showed the greater extent of bioavailability, while Khat chewing volunteers showed the lower extent of bioavailability. The peak height of the urinary excretion rate curve as well as the time to reach the peak could be used as suitable parameters to describe the rate and extent of aspirin absorption.
The results indicated that the urinary peak height for the Khat non chewing volunteers ranged from 61.18 to 74.44 mg/h with an average of 67.81 mg/h. For the Khat chewing volunteers ranged from 40.29 to 61.05 mg/h with an average of 50.67 mg/h as shown in Figure 2. So Khat non-chewing volunteers showed the higher peak height while Khat chewing volunteers showed the lower peak height.

As shown in Figure 2, the results indicated that time taken to reach peak urinary concentration for the Khat none chewing volunteers ranged from 1.5 to 4.0 h with an average of 2.5 h while for the Khat chewing volunteers ranged from 2.0 to 4.0 h with an average of 2.43 h. From the average values of the time to reach the peak, Khat none chewing volunteers showed the longer while Khat chewing volunteers showed the shorter time of peaking.

As illustrated in Table 1; the bioavailability of the oral dose aspirin shown that for the Khat non-chewing volunteers ranged from 82.74 to 100% with an average of 91.08%. But for Khat chewing volunteers ranged from 68.29 to 78.59% with an average of 75.21%.

The results indicated that physiological availability decreased significantly, at which Khat none chewing volunteers again showed higher bioavailability while Khat chewing volunteers again showed lower bioavailability.

Generally, on the basis of the calculated bioavailability parameters for commercial aspirin product brand (A) in Khat none chewing and Khat chewing volunteers. The Khat none chewing volunteers showed the best results while Khat chewing volunteers showed the worst results. That means, Khat none chewing had the higher values of the cumulative mg salicylate excreted after 24 h, peak height, percent of bioavailability as compare to the results obtained from Khat chewing volunteers.

The extent of absorption of aspirin in Khat chewing volunteers is lower than that of Khat none chewing volunteers and that may be attributed to the gastrointestinal tract disturbances which mostly described in chronic Khat chewers.

The stringent characteristic of tannins appears to be account for reports of periodontal diseases, stomatitis, esophagitis and gastritis.

Tannin is also believed to delay intestinal absorption (Report of WHO, 1980). Moreover, the ingredients of Khat leaves are numerous, but the major and most abundant ingredients include 6 major alkaloids, tannins (7
to 14%) and flavonoids (Luqman and Danowski, 1976). In order to make this in vivo evaluation of aspirin product of more biological significance, some pharmacokinetic parameters were computed and these parameters were computed for a product and both Khat none chewing and Khat chewing volunteers, assuming first order elimination from single compartment (Fitzgerald, 1991; Lopez-Farre et al., 1995).

As shown in Table 1; the values of elimination rate constant $K_e$, elimination half life $t_{1/2}$ with standard errors in Khat none chewing and Khat chewing volunteers were shown to be $(0.2096 \pm 0.03)$, $(3.30 \pm 0.22)$ and $(0.1590 \pm 0.02)$, $(4.36 \pm 0.30)$ respectively.

Also the half life of elimination for a product in Khat none chewing volunteers was found to be ranged from 2.55 to 4.45 h with an average value of 3.30 h, which corresponded to an elimination rate constant of $0.2096 \text{ h}^{-1}$. While in Khat chewing volunteers it was found to be ranged from 5.53 to 3.71 h with an average value of 4.36 h, which corresponded to an elimination rate constant of $0.1590 \text{ h}^{-1}$. The results were in good accordance with that reported (Katzung, 1998).

The results show longer time of elimination in Khat chewing volunteer and this may attributed to that, Khat affects the urinary system by relaxation of bladder wall and closure of internal sphincter and urine retention may

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**Figure 2.** The average excretion rate mg/h of aspirin in Khat none chewing and Khat chewing volunteers.
also occur and maximum urine flow rate is reduced (Nasher et al., 1995).

The values of absorption rate constant $K_a$, absorption half-life $t_{1/2}$ with standard errors in Khat non-chewing and Khat chewing volunteers were shown to be $(0.7635 \pm 0.03)$, $(0.919 \pm 0.04)$ and $(0.7356 \pm 0.05)$, $(0.96 \pm 0.08)$ respectively.

The half life of absorption for brand (a) in Khat none chewing volunteers was found to be ranged from 0.79 to 1.04 h with an average value of 0.915 h, which corresponded to an absorption rate constant of 0.7635(1/h). While in Khat chewing volunteers was found to be ranged from 0.71 to 1.21 h with an average value of 0.96 h, which corresponded to absorption rate constant of 0.7356 ($h^{-1}$).

In general, results in Table 2: indicated that closely related absorption rate constant in both Khat none chewing and Khat chewing volunteers. Khat none chewing volunteers had the higher extent of absorption, percent bioavailability than that of Khat chewing volunteers.

Comparison of the data obtained for the pharmacokinetic parameters (percent cumulative, percent bioavailability, high peak concentration, elimination rate constant ($h^{-1}$)) and half-life of elimination (h) between Khat chewing and Khat none chewing volunteers revealed that the differences were statistically significant ($P < 0.05$). But the difference in the absorption rate constant ($h^{-1}$) and half life of absorption (h) was not statistically significant ($P > 0.05$) were shown in Table 2.

<table>
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UPCOMING CONFERENCES

**XXXI World Congress of Internal Medicine**  
Santiago, Chile, 11-15 November, 2012

**European Society of Intensive Care Medicine - LIVES 2012**  
Lisbon, Portugal, 13-17 October, 2012.

**SoCRA 21st Annual Conference**  
Las Vegas, Nevada - September 21, 22, and 23, 2012  
Preconference Workshops- September 20, 2012
Conferences and Advert

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12th World Congress on Environmental Health, Vilnius, Lithuania, 21 May 2012

International Congress of Environmental Science and Technology (Argentina Ambiental 2012), Mar del Plata, Argentina, 28 May 2012

August 2012
4th EuCheMS Chemistry Congress (ECC), Prague, Czech Republic, 26 Aug 2012

September 2012
8th Congress of Toxicology in Developing Countries (CTDC8), Bangkok, Thailand, 10 Sep 2012

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March 2013
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