Unexpected Life-Threatening Drug Interaction: Hypoglycaemia secondary to Anti-Helicobacter pylori Therapy

Dear Editor,

Ulcer syndrome and diabetes are both common in elderly people in Hong Kong. Detection of the causative agent Helicobacter pylori (Hp) is essential for better cure of peptic ulcer. Unfortunately, we faced a patient suffering from dangerous hypoglycaemia secondary to oral hypoglycaemic agents and Helicobacter Pylori eradication combination.

A 78-year-old gentleman was admitted to hospital for diabetic control, he was maintained on glibenclamide 10mg om, 5mg noon and metformin 1g tds, as his sugar control improved after admission by better dietary restriction, with fasting/2hr haemoglucostix 8.1 and 11.5 mmol/l respectively. As he was found to be anaemic with haemoglobin of 9.8g/dl and iron saturation of 9% only, upper endoscopy was performed which showed multiple duodenal ulcers with positive rapid urease test. So one week course of amoxycillin 1g bd, omeprazole 20 mg bd, and clarithromycin 500mg bd was started. In subsequent two days, his haemoglucostix was progressively lower requiring reduction in dosage of glibenclamide until on day 3 post-endoscopy, his haemoglucostix was 0.9-1 mmol/l which persisted for one day despite all diabetic drugs were stopped, with confirmed blood glucose value as low as 1.6 mmol/l only. On direct questioning, he was found to have omitted meals because of poor appetite, which was attributed to the triple therapy. His diabetic drugs were slowly re-introduced and the original dosage resumed five days after the triple therapy.

Ulcer syndrome is common worldwide and has been related to Helicobacter pylori infection. As a result its detection indicates the need for eradication therapy. At present, the commonly prescribed drugs are triple therapy of omeprazole, amoxycillin and clarithromycin for one week, which is generally well tolerated except causing some nausea.

Diabetes mellitus is also common in our ageing and affluent society, most of them being non-insulin-dependent diabetes on dietary restriction and oral hypoglycaemic agents. As most of our patients are relatively old, their control is generally loose to prevent hypoglycaemic complications.

Often, the classic side-effects of appetite suppression, nausea and vomiting due to the high dosage of antibiotics were neglected, with most physicians stressed on compliance for successful eradication to prevent recurrence. Unfortunately, the combination of hypoglycaemic agents with markedly reduced calorie intake can result in dangerous hypoglycaemia. As most of upper endoscopy was done as out patients in Hong Kong, some of the hypoglycaemia complications may be missed. Elderly people living alone will be particularly vulnerable to such complications.

Although glibenclamide should be avoided in elderly diabetic patients due to its long half life, it is still one of the most commonly prescribed sulphonylureas, especially in the government general out patient clinics. We hope that our experience will alert our colleagues to avoid glibenclamide in elderly diabetics, particularly the prescription of two times daily dosage.

To conclude, all diabetic patients offered Hp eradication therapy should be warned of the potential side effects, with similar information dispatched to the relatives. Physicians should be prepared to reduce the dose of hypoglycaemic drugs at least temporarily when prescribing drugs that may suppress the appetite of patients.

Yours sincerely,

Dr. Yu-Tak Hung, MBChB, FHKCP
Senior Medical Officer

Dr. Kin Wong, LMCHK
Medical Officer

Dr. Edmund Chow, MBBS, FRACP
Consultant Physician

Department of Medicine, Our Lady of Maryknoll Hospital.
Shatin Pass Road, Wong Tai Sin, Kowloon, Hong Kong.
Address Correspondence to: Dr. Y.T. Hung

Dear Editor,

This is a reasonably well written paper which makes a valid point. The main thrust of the paper is that anorexia is caused by triple therapy given to treat Hp and that in the presence of diabetes, this anorexia leads on to hypoglycaemia. The main conclusion is that hypoglycaemic agents should be reviewed prior to commencing anti-Hp therapy.

The main problem with the paper is that the aetiology of hypoglycaemia is not specific to anti-Hp therapy and in fact could be caused by any medication given to an elderly sick diabetic patient. This in fact is well known and is a matter of good clinical practice.

Also in the discussion some time should have been given to discussing whether anti-Hp therapy should have been given at all. Some authors believe that elderly frail patients should only be given H2 antagonists, mainly due to the risk of pseudomembranous colitis from antibiotics but diabetes mellitus may represent another group where this approach may be appropriate.

Prolonged Activated Partial Thromboplastin Time (APTT) in an 86-year-old Patient

Dear Editor,

An 86-year-old female smoker was admitted to a medical ward in December 1996 because of acute exacerbation of chronic obstructive pulmonary disease. She was afebrile and her shortness of breath improved with bronchodilators and oral antibiotics. Blood tests including blood gases were normal. However, clotting profile was ordered by a new intern and showed a prothrombin time (PT) of 10 seconds (control 10 to 12 seconds) and an activated partial thromboplastin time (APTT) of 53.6 seconds (control 27 to 37 seconds). The clotting profile was rechecked twice and revealed similar results (PT 10.1 and 10.2 seconds; APTT 54.6 and 57 seconds). The patientís APTT was completely correctable by addition of normal plasma incubated for 2 hours at 37 degree Celsius. The plasma concentrations of relevant clotting factors were determined and the results were: factor XII 18%, factor XI 89%, factor IX 230%, and factor VIII:C 31.8% of normal. Factor XII deficiency was established. No circulatory inhibitors were identified. She had no evidence or history of abnormal bleeding. The patientís family consisted of a son, 2 daughters and a granddaughter. They were all invited to come to our hospital for factor XII screening. One of her daughters refused to come, while the blood tests of other family members did not show evidence of factor XII deficiency (Table 1).

Table 1. Results of family member screening

<table>
<thead>
<tr>
<th></th>
<th>Son (M/45)</th>
<th>Daughter (F/65)</th>
<th>Granddaughter (F/13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTT (sec)</td>
<td>29.8</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>Factor XII</td>
<td>49</td>
<td>158</td>
<td>93</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>10.2</td>
<td>9.3</td>
<td>10.5</td>
</tr>
</tbody>
</table>

(PT control 10 to 12 seconds; APTT control 27 to 37 seconds)

The APTT and PT measure the plasma intrinsic and extrinsic coagulation activity respectively. However, prolongation of APTT does not always indicate increased bleeding tendency. Factor VIII, IX, XI and von Willebrand factor (vWF) deficiencies were associated with prolonged APTT and bleeding complications. Similar consequences were also reported in patients with factor VIII, IX and von Willebrand factor inhibitors. Subjects with prekallikrein and HMW kininogen deficiency had neither bleeding nor thrombotic tendency. On the contrary, patients with lupus anti-coagulant syndrome had higher risks of thromboembolism despite their prolonged APTT. The above elderly lady was deficient in factor XII which is a zymogen of a serine protease that initiates the contact phase of intrinsic pathway of coagulation in vitro. It was first discovered by Ratnoff and Colopy in 1955 during a routine pre-operative screening of John Hageman who had this plasma defect. Factor XII deficiency is inherited as an autosomal recessive trait. Bennett, et al. reported a kindred probably inherited as an autosomal dominant characteristic. Since neither homozygous or heterozygous is symptomatic, the true prevalence of the deficiency is not known. Some authors believe that factor XII deficiency is the most common cause of isolated prolonged APTT in a non-bleeding subject. Heterozygotes had factor XII levels between 20-60% were reported with an average of about 50%. Homozygous subjects had virtually undetected factor XII activity (less than 1% of normal pooled plasma). It has been shown that Asians have lower level of factor XII. Diagnosis of factor XII deficiency is usually made by noting a prolonged APTT and normal PT in an asymptomatic patient. Definitive diagnosis needs specific quantitative factor XII assay by functional assay.

The absence of haemorrhagic consequence in either heterozygous and homozygous factor XII deficient subjects suggested this factor is not necessary for normal haemostasis to occur in vivo.