Palliative Medicine Grand Round

Drug Interactions in Palliative Care

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ABSTRACT
Advanced cancer patients are at risk of potential drug interactions because they are often on many medications. Drug-drug interactions can be kinetic, dynamic and pharmaceutical. Pharmacokinetic interactions mainly involved Cytochrome P450 enzymes system. Currently, more emphasis is placed on the newer information about its genetic polymorphism. It is important to recognize the potential drug interactions of commonly used medications, such as phenytoin, warfarin, anti-depressants and opioids to avoid possible side effect or toxicity.

HKSPM Newsletter 2010 Apr Issue No. 1 p12-16.

Introduction
Cancer patients often receive numerous medications for treating the cancer, co-morbid conditions or the associated symptoms. In the palliative care setting, drug-drug interactions are common. It can result in potential risks to patients.

Case 1
Madam C, a 52-year-old lady, was a known hepatitis B carrier. She was diagnosed to have adenocarcinoma of recto-sigmoid colon with laparoscopic anterior resection done in November 2006. The staging was T3N0 Duke’s B. In April 2009, she was found to have tumour recurrence with metastasis over the brain, scalp, manubrium, lung and lymph nodes. She received whole brain radiotherapy (RT) in June 2009. Later, she was found to have bone metastasis in the skull, manubrium, distal left femur and cervical spine. Palliative RT was given to the distal left femur.

Madam C was regularly followed up in oncology department and she was planned for palliative chemotherapy in July 2009. However, she was admitted to medical department for generalized tonic-clonic convulsion in July 2009. The staging was T3N0 Duke’s B. In April 2009, she was found to have tumour recurrence with metastasis over the brain, scalp, manubrium, lung and lymph nodes. She received whole brain radiotherapy (RT) in June 2009. Later, she was found to have bone metastasis in the skull, manubrium, distal left femur and cervical spine. Palliative RT was given to the distal left femur.

Computed tomography (CT) of brain showed a 2 cm heterogenous lesion with peri-focal edema in left frontal lobe and mass effect. The dose of dexamethasone was increased and phenytoin was started. She was clinically unfit for further chemotherapy.

She was then transferred to our palliative care unit. Her medications included diclofenac, phenytoin, dexamethasone, pantoprazole, lamivudine and senna. She developed convulsion in ward. Her phenytoin level was 29umol/L (reference range: 40-79umol/L). Phenytoin was increased from 300mg to 330 mg per day. There was no further convulsion and she was discharged.

In summary, this was a case of carcinoma of colon with brain metastasis. The drug level of phenytoin was suboptimal, suggesting the possibility of drug-drug interaction between phenytoin and dexamethasone.

Case 2
Mr. T, a 58-year-old gentleman, was a chronic smoker. He had history of paroxysmal atrial fibrillation, ischaemic heart disease and chronic rheumatic heart disease with mitral stenosis. Mitral valve replacement (MVR) and coronary artery bypass graft surgery were done in Jan 2009. His medications included digoxin, warfarin, isosorbide dinitrate and rabeprazole.

He presented with haemoptysis in May 2009. CT Thorax found right lower lobe carcinoma of lung with multiple lymph nodes metastasis. Emergency bronchoscopy with stenting was performed. He refused palliative radiotherapy and preferred Chinese medicine.

He was later admitted to the acute medical ward for fast atrial fibrillation. Amiodarone infusion was given for control of heart rate and oral amiodarone was given for maintenance. International normalized ratio (INR) was elevated to 3.14. In view of persistent haemoptysis and the interaction between warfarin and amiodarone, amiodarone was switched to sotalol. Serial INR was monitored and the level was around 1.6 while on sotalol. He was then discharged with stabilisation of the INR.
In summary, this was a case of carcinoma of lung with history of MVR on regular warfarin; subsequently complicated by haemoptysis. There was drug-drug interaction between warfarin and amiodarone. The potentiated effect of warfarin was dangerous by increasing the risk of haemoptysis.

**Discussion**

Drug interactions are defined as ‘the possibility that one drug may alter the intensity of pharmacological effects of another drug given concurrently’. It can involve interactions between drugs and disease, drugs and chemicals in the environment, drugs and drugs, and drugs and nutrients.

Drug-drug interactions can be classified into (1) pharmacokinetic, (2) pharmacodynamic and (3) pharmaceutical. Pharmacokinetic interactions refer to that in which one drug affects the disposition of another. The interaction can alter absorption, binding, distribution, transportation to the site of action, biotransformation, metabolism and excretion. Pharmacodynamic interaction arises when there is an interaction at the site of action – a receptor or physiologic system. The effect can be synergistic, additive, or antagonistic. Pharmaceutical interactions occur when there are physical incompatibilities between drugs.

**Pharmacokinetic interactions**

Cytochrome P450 (CYP) hepatic enzymes are major sites of drug metabolism. It can be found in hepatocytes and other parts of body, such as the intestinal mucosa, brain, and kidney. The P450 system of enzymes consists of more than 20 families of enzymes. These families are defined by cDNA techniques. Several of these enzymes show genetic polymorphism.

The most extensively studied enzyme is isozyme CYP2D6. This enzyme is inherited in autosomal recessive pattern. Newer studies, using molecular techniques such as polymerase chain reaction and restriction fragment length polymorphism, have characterized more than 90% of the genetic defects in the CYP2D6. Defects that give rise to loss of activity include complete gene deletion, splice site mutation, single base pair deletion and gene rearrangements. Three groups of individuals are identified: ultra-rapid, extensive and poor metabolizers. Most individuals are extensive metabolizers, but there is variation among different ethnic groups. For example, the percentage of poor metabolizers in the White is around 5-10%. In Asian and African Americans, the incidence of poor metabolizers is much lower, around 1-2%. For the West African, the poor metabolizers are up to 18%.

The implication of recognition of different metabolizers is important in daily practice. Eichellbaum et al. suggested that if the standard dose of medications is used, extensive metabolizers may be under-treated. On the other hand, the poor metabolizers may be over-treated. In poor metabolizers, activation of the drug may be ineffective. There can be decreased elimination, prolonged half-life, and potential for drug accumulation that may cause toxicity.

**Prevalence of drug interaction in palliative care**

In general medical wards, the rate of potential drug interaction was approximately 60%. Studies conducted in emergency departments showed that the rate ranged from 16% to 47%. Davidson et al. concluded that almost 70% of ambulatory patients with variable clinical conditions were exposed to potential drug interactions.

For cancer patients, drug interactions are also very common. In a retrospective study of 100 hospitalized cancer patients, 63% were exposed to at least one drug combination with the potential to interact. Another recent study of 405 ambulatory cancer patients receiving cancer-directed therapy found that one-third were at risk of drug interactions.

Riechelmann et al. conducted another study to describe the epidemiology of potential drug interactions in cancer patients receiving supportive care exclusively. Among 372 eligible patients, 250 potential drug interactions were identified in 115 patients (31%, 95% confidence interval 26%-36%). The most commonly involved drugs are warfarin and phenytoin. Most interactions were classified as being of moderate severity (59%) and 42% of them were supported by levels 1-3 of evidence. In multivariate analysis, increasing age (P < 0.001), presence of co-morbidity (P < 0.001), cancer type (brain tumors, P < 0.001), and increasing number of drugs (P < 0.001) were associated with greater risk of drug interactions.
Drug interactions in common individual drug groups in palliative care

**Anticonvulsants**

Phenytoin causes induction of CYP3A4. It is commonly used with dexamathasone in palliative setting for treating brain metastasis. Phenytoin increases the rate of metabolism of dexamethasone through induction of hepatic microsomal enzyme, thus decreasing its drug level. Dexamethasone can both increase and decrease the phenytoin level. However, the exact mechanisms are still not well known. Phenytoin should be stepped up to 600-1000 mg/day if dexamethasone is used concurrently.\(^2^2\) It is impossible to predict the levels of phenytoin in an individual patient who is also on dexamethasone. Therefore, careful monitoring of phenytoin levels is highly recommended. After successful control of the tumor-associated brain edema, both dexamethasone and phenytoin should be tailed down simultaneously according to close drug level monitoring.\(^2^2\)

**Anticoagulants**

Warfarin is well known to interact with different medications, diet or herbs. It is mainly metabolized by CYP2C9. Drugs, such as amiodarone, anti-fungal agents and anti-depressants, that inhibit the isozymes will potentiate the effect of warfarin.\(^2^3\) Another mechanism is related to the interruption of the vitamin K cycle. Acetaminophen inhibits vitamin K-dependent carboxylase, a key enzyme in the vitamin K cycle. Hence, it may have possibility of potentiating the effect of warfarin.\(^2^3\)

**Tricyclic anti-depressants (TCAs)**

Amitriptyline and clomipramine are metabolized by multiple isozymes of P450 cytochrome. Consequently, there is a significant risk of unfavourable pharmacokinetic interaction. Amitriptyline is metabolized by 2D6, 3A4, 1A2, 2C9 and 2C19 isozymes, while clomipramine by 3A4, 1A2, 2C19 isozymes. Drugs suppressing the activity of the above-mentioned isozymes will increase the risk of undesirable effects of TCAs. TCAs may increase the potency of sympathomimetics, causing an increase in blood pressure. Impaired absorption of oral drugs may occur because of the strong cholinolytic effect of TCAs that inhibits peristalsis of the digestive tract.\(^2^4\)

**Selective Serotonin reuptake inhibitors (SSRIs)**

Paroxetine and fluoxetine show the greatest inhibition of CYP2D6. Fluvoxamine has its greatest inhibitory effect on CYP1A2. Other drugs in this class have less effect on the enzymes. Clinically significant interactions of SSRIs can occur when it is used with agents that have a narrow therapeutic index e.g. TCAs. Poor metabolizers may also reduce its clearance and produce adverse drug effects.

**Analgesics**

Codeine is metabolized to morphine by CYP2D6. It is ineffective for pain control in patients lacking CYP2D6 or if CYP2D6 is inhibited by other drugs. Phenotyping for CYP2D6 should be considered, so that codeine can be avoided in those CYP2D6 inhibitors. Caraco et al.\(^2^5\) evaluated the effect of codeine phosphate in individuals who were known to be poor or extensive metabolizers in the CYP2D6 system. Clearance by the extensive metabolizers was 200-fold greater than poor metabolizers.\(^2^5\)

There are many drugs that can suppress the CYP2D6 and affect the metabolism of codeine. These include SSRIs e.g. fluoxetine; TCA, e.g. amitriptyline; metoclopramide; haloperidol; methadone and valproic acid.\(^2^4\) Caution should be taken when co-administering these groups of drugs.

Tramadol is another opioid that is metabolized by CYP2D6. Therefore, similar to codeine, the simultaneous administration of tramadol with drugs that inhibit the activity of CYP2D6 is not recommended. Apart from its influence on opioid receptors, tramadol also inhibits serotonin reuptake in the descending antinociceptive system. Combination of SSRIs and tramadol has an increased risk of serotonin syndrome.\(^2^4\)

Methadone is cleared by the CYP3A4 and it strongly inhibits CYP2D6. It also auto- induces its metabolism. Methadone toxicity may cause bradycardia, mood swings, depression of the respiratory centre and an increased risk of potentially lethal arrhythmia, due to QT prolongation on ECG.

Common drugs that suppress CYP3A4 include: SSRIs; antibiotics such as ciprofloxacin, clarithromycin; anti-fungal agents, such as ketoconazole; diltiazem; methadone and valproic acid.\(^2^4\) Methadone should be cautiously combined with benzodiazepeine derivatives due to the significant toxicity of this combination. When
methadone is used with TCAs, methadone disturbs their metabolism, by inhibiting the activity of the CYP2D6 isozyme. Barbiturates, carbamazepine, rifampicin, risperidone and glucocorticosteroids suppress the analgesic action of methadone, probably because of interactions with CYP3A4.  

Table 1. Common drugs suppressing the selected CYP P450 isozymes

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate</th>
<th>Drugs suppressing the isozyme activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Codeine</td>
<td>Tramadol, SSRIs (e.g. fluoxetine), TCAs (Amitriptyline)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metoclopramide, Haloperidol, Methadone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valproic acid</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Methadone</td>
<td>SSRIs (e.g. ciprofloxacin, clarithromycin)</td>
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<tr>
<td></td>
<td></td>
<td>Anti-fungal agents (e.g. ketoconazole)</td>
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<tr>
<td></td>
<td></td>
<td>Diltiazem, Methadone, Valproic acid</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Warfarin</td>
<td>Amiodarone</td>
</tr>
<tr>
<td></td>
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<td>Anti-fungal agents, SSRIs</td>
</tr>
</tbody>
</table>

Figure 1

A summary flow chart of the common drug interactions

**Conclusion**

Poly-pharmacy in palliative care increases the potential risk of drug-drug interactions. Pharmacokinetic interactions involving the CYP enzymes and its genetic polymorphism play an important role in drug interactions. The common drug interactions occur with phenytoin, warfarin and common opioids (Fig. 1, Table 1). We should take great caution during co-administration of different groups of drugs.

References