Seminar on Research & Development of Chinese Medicines 2015

Measures to Ensure the Quality and Safety of Chinese Medicines in Hospital Authority

Teresa Ngan
Senior Pharmacist, Chief Pharmacist’s Office
Hospital Authority
10 Sept 2015
Background

2003
- Toxicology Reference Laboratory
- 3 CM Clinics in operation
  (Tripartite approach: NGO-HA-U)

2014
- 18 CM clinics
- No. of attendance: ~1M
- 50% Yin pian (YP 飲片) : 50% CM granules
- Decoction service (14%)
# Measures to Ensure the Quality and Safety of CM in HA

## Quality Assurance
- Procurement Requirements of CM Products
- In-house Sample Testing
- In-house Quality Monitoring Mechanism

## Pharmaco-vigilance
- CM Toxicology & Safety Media Monitoring
- Herbal Adverse Events / Poisoning Sentinel System
- Drug Information Service on CM

## Clinical Application
- Use of CM in HA hospitals
- Research Focus in Meeting Clinical Needs

## Knowledge Sharing and Application
- Knowledge database
- Conferences, seminars, continuing education sessions

## Way Forward
Procurement Requirements of CM Products

**CM Ordinance**
- Wholesale licence in CHM
- Wholesale licence in pCM
- Manufacture licence in pCM

**Protection of Endangered Species of Animals and Plants Ordinance**
- Convention certificates

**Import and Export Ordinance**
- Import licences
  - 31 CHM in Sch 1
  - 5 CHM in Sch 2
  - pCM

**Food Safety Ordinance**
- Notice of Registration as Food Importer / Food Distributer

**HA Requirements**
- CM Clinics
- CM specification
- Engage experts in CM samples verification

**GMP**
- Yin pian (Jan 2008)
- pCM (Jul 2004)

**Certificates of Analysis**
- Heavy metal
- Pesticide residues
- Aflatoxins
- Toxic ingredients
- 7 volumes, since 2005
In-house Sample Testing

Factors for Risk Stratification
1. Toxicity e.g. Sch 1 CM in CM Ordinance
2. Specific CM in Chinese Pharmacopeia (CP) with safety concern e.g. herbal markers for authentication
3. Local surveillance data e.g. reported poisonings / ADRs in HK
4. Volume of use

Specific Tests
1. Authentication and quality
2. Safety
   a) Heavy metals, pesticide, microbial limits
   b) Aflatoxins
   c) Intrinsic toxic ingredient(s) in CM
   d) Others requirements by HA, e.g.
      - Toxic contaminants: aconitine, atropine, aristolochic acid…
      - Dyes and foreign matters (e.g. auramine O)
Standards and Methods

<table>
<thead>
<tr>
<th>Laboratories involved:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Laboratory accredited through HOKLAS</td>
</tr>
<tr>
<td>2. Institutions involved in the establishment of the HKCMMS</td>
</tr>
</tbody>
</table>

### Standards
- HKCMMS / CP
- HOKLAS

### Methods
- HKCMMS / CP
- In-house methods

### Tests
1. Authentication and quality
2. Safety
   - a) Heavy metals, pesticide, microbial limits
   - b) Aflatoxins
   - c) Intrinsic toxic ingredient in CM
   - d) Others requirements by HA, e.g.
     - Toxic contaminants: aconitine, atropine, aristolochic acid...
     - Dyes and foreign matters (e.g. auramine O)

---

* HOKLAS: Hong Kong Laboratory Accreditation Scheme
* CP: Chinese Pharmacopeia
* HKCMMS: Hong Kong Chinese Herbal Medicine standards
In-House Quality Monitoring Mechanism

CM Pharmacy
- CM clinics - Pharmacy as gatekeeper
- Communicate to Chief Pharmacist’s Office (CPO), HA

CPO, HA
- Evaluation and assessment of the situation
- Assigning of action index (e.g. keep in view, batch suspension)
- Sourcing of alternatives
- Risk communication and logistics arrangements with suppliers & frontline

All stakeholders
- Stakeholders: CM clinics, HA (e.g. CM department, HA Toxicology Services, HA hospitals with AED)
- Risk communication / risk alert
CM Toxicology and Safety Media Monitoring

- Daily monitoring via global & local news / websites

- Risk communication with stakeholders, e.g.
  - CM Toxicology & Safety Media Monitoring (中藥毒理及安全媒體監聽)
  - 香港中藥中毒及不良反應資料匯總

- Early signal detection for local hazard identification & risk assessment
  - HA Toxicology Services (HA Toxico-intelligence Team)
Herbal Adverse Events / Poisoning Sentinel System

- Established in Aug 2004
- CM-related adverse events / poisoning notification in HA
- Work closely with the HK Department of Health on important public issues (Hong Kong Poison Control Network - HKPCN)
- Adverse events reported provide valuable information and signal clinical significance areas
- Identify herbs with potential toxicity for literature review, database development and research
Drug Information Service on CM

- Enquires from western and Chinese medicines professionals in HA, mainly clinicians
- Enquiries mainly involve:
  - Adverse reactions and toxicities of CM
  - Interpretation of CM prescriptions
  - Identification of processed herbs
  - Herb-drug interactions
  - Legislations and regulations on CM
Well-defined Risk Stratification Matrix

Local Experience & Clinical Management

Novel Approach for Risk Assessments on Use of CM in HA Hospitals

**Expert Panel**

- Toxicologist,
- Clinicians from various specialties (e.g. oncologist cardiovascular, liver, renal)
- Clinical pharmacologist
- Pharmacists
- CM experts (e.g. practitioners)
- Academia

**Risk Rating:**

High, Moderate, Low, No Reported Risk

**Recommendations:**

- Impact on clinical effects
- Use in at-risk patient group(s)
- Concurrent use with certain drug(s) or specific monitoring (e.g. TDM, INR)
Objectives

- Create a registry of carefully documented HILI cases in patients under HA
- Identify risk factors and clinical outcomes of HILI

Process

1. Pilot study in 08/09 -- identified culprit hepatotoxic herbs by ruling out underlying causes and through literature review
2. Herb-induced Liver Injury Network (HILIN) formed in 2009 -- to conduct a prospective study (paper published in 2011*)

Consists of:-

- Hepatologist
- Toxicology expertise (clinicians from Poison Centre and Toxicology Reference Lab)
- Pharmacist (western medicines & Chinese medicine)

3. Use of scientific soring system in clinical setting

- RUCAM - Roussel Uclaf Causality Assessment Method

• **Objectives of the Study**
  - To identify any clinical and theoretical interactions of commonly used herbal medicines with drug groups of paramount concern in the HA
  - To determine the interactions identified in terms of the mechanisms of action, degrees of severity and levels of evidence

• **Evidence-based Process**
  - Blind parallel evaluation by University group and HA group
  - Refer to expert panel if consensus cannot be reached

  ![Diagram](image.png)

  - Drug groups: anti-cancer drugs, drugs for CVS, metabolic syndromes, CNS etc.
Background

The HA Drug-herb Interactions Database is developed through joint collaboration by the Hospital Authority and academic institution(s) with a strong background in western medicines and Chinese medicines (CM) education and research.

The HA Drug-herb Interactions Database is aimed to provide information on adverse drug-herb interactions (DHI) to healthcare professionals on specific drug groups, based on the latest published information from both English and Chinese databases at the time of data extraction and with a level of significance (LOS) rating assigned (Refer to Table 1. Level of Significance). The rating 1, 2, or 3 denotes the LOS from highest to lowest, whereas an asterisk would be indicated for which adverse drug-herb interaction was not known or studied (e.g., toxicity of the drug-herb combination was not studied despite a beneficial effect on its efficacy might have been demonstrated).

With the information retrieved, only primary data was assessed; therefore, reviews that describe an interaction but cited the original sources were excluded; however, the original source referred to was included. Jadad scores would be assigned to randomized controlled trials (RCT) as a determinant of the quality of RCT. While a set of criteria was developed for the evaluation of the relevant drug-herb interaction information and its level of significance, critical appraisal examining the articles was not performed. As the focus of the database is primarily on Chinese medicines that are commonly used by the people in Hong Kong, information relating to health food or supplements may not be found in this database.

DHI reports

Reviewed information would be reported as a unique pair of drug(s) and herb(s) with a LOS rating assigned on the potential interaction, brief summary, and the reference(s) used.
### Sample of HDI report

#### Interaction of CM / Herbal Medicine(s) with Anticancer Drug(s)

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>CM / Herbal Medicine(s) / (Compound)</th>
<th>Severity of Adverse HDI</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td>Hypericum perforatum, St. John's wort</td>
<td>High</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not known</td>
<td>E</td>
</tr>
</tbody>
</table>

#### Effects:
The combination of St. John's wort and irinotecan may decrease the drug efficacy of irinotecan in various cells and animal models as well as cancer patients.

#### Mechanism:
The combination of St. John's wort and irinotecan may affect the pharmacokinetics of irinotecan.

#### Management:
Concomitant administration of irinotecan and St. John's wort should be avoided.

#### Discussion:

#### References:

#### Level of Significance

<table>
<thead>
<tr>
<th>Severity of Adverse HDI</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>A, B, C, D, E</td>
</tr>
<tr>
<td>Moderate</td>
<td>A</td>
</tr>
<tr>
<td>Mild</td>
<td>B</td>
</tr>
<tr>
<td>Insignificant / Uncertain</td>
<td>C</td>
</tr>
<tr>
<td>Not known</td>
<td>*</td>
</tr>
</tbody>
</table>

Herbal Toxicology Database

Handbook Published in Jan 2002

Database Established in Aug 2004

HA Herbal Toxicology Database

- Home
- About This Database
- Task Force
- Links

- Monograph Search
  - By Names
  - By Ingredients
  - By Products

- Table Search
  - System
  - Action/Symptoms
  - Ingredient
  - CM
  - Reference

- Management
  - General Treatment
  - GI Decontamination
  - Antibodies

- Traditional Use
- Traditional Use

- Help
- Glossary

596 monographs on herb
- Pharmacology
- Toxicology
- Herb-drug interaction
- Photos

Task Force on Clinical Toxicology (HA)
[Members: clinicians, pathologists, toxicologists and pharmacists]
### Search Tips

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phrases</td>
<td>“當歸”, “dang gui”, “blood pressure”</td>
<td>(with no space in between the words)</td>
</tr>
<tr>
<td>Keywords (AND)</td>
<td>scalp acupuncture, scalp AND acupuncture, scalp acupuncture</td>
<td>(with a space in between the words)</td>
</tr>
<tr>
<td>Keywords (OR)</td>
<td>胆 OR 胃, spleen OR stomach</td>
<td></td>
</tr>
<tr>
<td>Keywords (NOT)</td>
<td>胆 NOT 胃, cholesterol NOT high, cholesterol - high</td>
<td></td>
</tr>
</tbody>
</table>
# Synonyms Table of CMs

<table>
<thead>
<tr>
<th>Chinese name</th>
<th>Latin name</th>
<th>Chinese plant name</th>
<th>Latin plant name</th>
<th>Pinyin</th>
</tr>
</thead>
<tbody>
<tr>
<td>人參</td>
<td>RADIX ET RHIZOMA GINSENG</td>
<td>人參</td>
<td>Panax ginseng C. A. Mey.</td>
<td>Renshen</td>
</tr>
<tr>
<td>人參葉</td>
<td>FOLIUM GINSENG</td>
<td>人參</td>
<td>Panax ginseng C. A. Mey.</td>
<td>Renshenye</td>
</tr>
<tr>
<td>兒茶</td>
<td>CATECHU</td>
<td>兒茶</td>
<td>Acacia catechu (L. f.) Wild.</td>
<td>ErCha</td>
</tr>
<tr>
<td>九里香</td>
<td>FOLIUM ET CACUMEN MURRAYAE</td>
<td>九里香 千里香</td>
<td>Murraya exotica L. Murraya paniculata (L .) Jack</td>
<td>JiuliXiang</td>
</tr>
<tr>
<td>九香蟲</td>
<td>ASPONGOPUS</td>
<td>九香蟲</td>
<td>Aspongopus chinensis Dallas</td>
<td>Jiuxiangchong</td>
</tr>
<tr>
<td>刀豆</td>
<td>SEMEN CANAVALIAE</td>
<td>刀豆</td>
<td>Canavalia gladiata (Jacq.) DC.</td>
<td>Daodou</td>
</tr>
<tr>
<td>三七</td>
<td>RADIX ET RHIZOMA NOTOGINSENG</td>
<td>三七</td>
<td>Panax notoginseng (Burk.) F. H. Chen</td>
<td>Sanqi</td>
</tr>
<tr>
<td>三白草</td>
<td>HERBA SAURURI</td>
<td>三白草</td>
<td>Saururus chinensis (Lour .) Baill.</td>
<td>Sanbaicao</td>
</tr>
</tbody>
</table>
Way Forward

Policy Address 2014

Electronic Health Record
To be launched in 2016

Chinese Medicine Hospital

Hong Kong Certified Materia Medica
2014
END