SAFETY MONITORING OF HERBALS
THE MOROCCAN EXPERIENCE

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INTRODUCTION

- Herbal medicines are widely used around the world

- The case in Morocco where HM, as with all medicines, have been shown to have adverse effects, which are related to a variety of causes, essentially in relation to:
  - Self-medication
  - Quality of HM (contamination, adulteration)
  - Unlicensed products
  - Incorrect dosing
  - Other particular conditions of use
Other particular conditions of use

- Different parts of plant
- Different methods of preparation
- Inadequate knowledge by HP and consumers
- Socioeconomic level
- Sociocultural level (spiritual interpretation of ARs as a process of healing)
- Inadequate label
- Concurrent use of HM & conventional drugs
SAFETY MONITORING OF HERBALS IN MOROCCO

Setting up

- The safety of Herbals is monitored through the Centre Anti Poison et de Pharmacovigilance du Maroc
- Pharmacovigilance Department
- Pharmacovigilance of HM or Phytovigilance Unit
- Implemented in September 2000
- Two full time persons
SAFETY MONITORING OF HERBALS IN MOROCCO

Role

- Assessment of risks and benefits of HM
- Ultimate aim is to protect patients from herb induced harms
Functioning

- Globally, the same monitoring as conventional drugs both at national and international levels
- Some adaptation to herbals
A single reporting form covering all HP

Facilitate reporting with an adaptation for HM raw material: part of the herb used, type of extraction and dose

(Quality of reports)

Attract the attention of HP (Quantity of reports)
DATA MANAGEMENT

Data Storage

- Database that collates all case reports of suspected AEs in relation with HM was developed.
- Database includes case reports submitted through the spontaneous reporting system and intensive monitoring programmes (surveys, prevalence studies).
DATA MANAGEMENT

Data Quality

- An additional requirement identifying at least:
  - part of the herb used
  - type of extraction
  - indication
  - dose

- Data elements of reports are complete as possible
RECORDING AND CODING
THE IDENTITY OF HERBALS

Unlike Drugs …

- HATC classification is not used
- The binomial nomenclature (part used if specified)
- HM contain multiple ingredients and it is not always possible to identify them all
- HATC classification for the whole plant but not for a given part (or else several places in the HATC classification)
- Mixture of several HM
- HM from other countries
To analyze the causes of AEs, many causality assessment methods are available.

- They have been developed for conventional drugs.
- These can be applied with difficulty to HM.

Many Challenges!!
CAUSALITY ASSESSMENT

CHALLENGES

Data Analysis

- HM identification
- A lack or quality of information, example dose/quantity: handle, pinch, tablespoon, herbal infusion
- Incompatible time criteria: regularly, quite a few times, frequently
- Limited literature data (knowledge of some HM and their medicinal use has not been documented)
Analysis of the Global WHO database

- Since 2004, Moroccan AEs of HM reports are sent to UMC via VigiFlow (irregular activity)
- Daily routine
- First quarter 2013, HM data analysis was made from WHO database
As for now UMC don’t perform any specific herbal signal detection, but the herbal reports are included in the **general signal detection work**.

The challenge in detecting such signals is not due to the technical process, but due to the **underreporting** of such reactions and the fact that HM have their own **specificities not found for drugs**.
**HERBALS SIGNAL DETECTION**

**EXAMPLE: CADE OIL**

A positive IC value indicates that a particular *Juniperus oxycedrus* oil-ADR pair is reported more often than expected, based on all the reports in the database.

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### Dataset Details

- **Dataset date:** 2013-05-05
- **Number of combinations in result:** 4
- **Total number of reports:** 8,073,388

### Signal Detection Table

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<th>preferred base</th>
<th>preferred term</th>
<th>critical</th>
<th>N_comb</th>
<th>IC</th>
<th>ICn25</th>
<th>N_drug</th>
<th>N_adr</th>
<th>N_country</th>
<th>N_dechal</th>
<th>N_rechal</th>
<th>N_fatal</th>
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<tr>
<td><strong>details</strong></td>
<td>reports</td>
<td>Juniperus</td>
<td>Dyspnoea</td>
<td>6</td>
<td>2.08</td>
<td>0.71</td>
<td>33</td>
<td>253,219</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td><strong>details</strong></td>
<td>reports</td>
<td>Juniperus</td>
<td>Renal failure chronic</td>
<td>Yes</td>
<td>3</td>
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<td>0.39</td>
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<td>35,604</td>
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<td>reports</td>
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<td>Hypoaesthesia</td>
<td></td>
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<td>2.24</td>
<td>0.19</td>
<td>33</td>
<td>58,825</td>
<td>1</td>
<td>0</td>
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<tr>
<td><strong>details</strong></td>
<td>reports</td>
<td>Juniperus</td>
<td>Coma</td>
<td>Yes</td>
<td>3</td>
<td>2.15</td>
<td>0.10</td>
<td>33</td>
<td>70,082</td>
<td>1</td>
<td>0</td>
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</table>
MOROCCAN HERBAL DATABASE REPORT

September 2000 to December 2012

“Some data”
NUMBER OF HERBALs AEs REPORTED

- 2105 reports until December 2012
- A continued increase in reported cases
- 7 to 10% of all notifications
GRADING OF THE SEVERENESS OF ADVERSE EVENTS

<table>
<thead>
<tr>
<th>GRADING OF THE SEVERITY</th>
<th>NO. (%) [n = 1116]</th>
</tr>
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<tbody>
<tr>
<td>Grade 0*</td>
<td>11 (1.0)</td>
</tr>
<tr>
<td>Grade 1**</td>
<td>258 (23.1)</td>
</tr>
<tr>
<td>Grade 2***</td>
<td>665 (59.6)</td>
</tr>
<tr>
<td>Grade 3****</td>
<td>108 (9.7)</td>
</tr>
<tr>
<td>Grade 4*****</td>
<td>74 (6.6)</td>
</tr>
</tbody>
</table>

*: no symptoms or symptoms not in relation with AEs of HM  
**: symptoms spontaneously regressive  
***: pronounced symptoms  
****: severe with life-threatening  
*****: death (which coincide with taking HM)
ESSENTIAL TOOLS FOR PHARMACOVIGILANCE OF HERBALS

- Books (Center Library)
- Scientific Articles (personal collection)
- Websites and Databases (PubMed, Toxinz, Micromedex, ...)
- National pharmacovigilance Centers Bulletins
- All kind of documents via all types of information sources
ESSENTIAL TOOLS FOR THE PHARMACOVIGILANCE OF HERBALS

The WHO offers many guidelines and other documents

Help to identify the challenges in monitoring the safety of HM

Propose approaches for overcoming them
MOROCCAN TRADITIONAL PHARmacOPOEIA
COUNTRIES MAY DEVELOP TOOLS FOR THE MONITORING THE SAFETY OF HERBALS

**BOTANICUS**, summarizes more than 279 standard botanical names and their 2294 vernacular ones
**PHYTOTOX**, concerns relevant toxic data of 120 plants available in Mediterranean region (Example: *nutmeg*)
PHYTOTOX

Myristica fragrans Houtt.

- Tachycardie, hypotension artérielle, parasthésie, hypothenmie et/ou hypothermie et délire (STEIN et al., 2001). Cette intoxication peut conduire au décès en cas d'ingestion d'une quantité importante de graines. Le décès a pu être observé au cours d'un collapsus avec état de choc et acidose (JOUGLARD, 1977).

Les manifestations cliniques sont proches de celles de l'intoxication atropinique à l'exception du myosis (myosis pour la toxine atropinique) (BRUNETON, 1999).

- Traitements : décontamination (charbon activé), détoxification symptomatique. Traitement sodifiant et anticholinestérasique pour les distorsions psychiques en plus de l'équilibre hydroélectrolytique et de l'hématose essentiellement (JOUGLARD, 1977 ; SANGALI et al., 2010).

Bibliographie

- JANSEN N, et LACKMANN G M (1990). Nutmeg oil: Identification and quantification of its most...
TO MAKE US KNOWN

More HM ARs Reporting

- BIP & Revue Toxicologie Maroc

- Dedicated page with general information on safety of HM on the web site (www.capm.ma)

- Reporting form can be downloaded

- Meetings dedicated to HM

- TV & radio programmes (local language mainly)
OPPORTUNITIES

- A PhD Scientist specialized in Aromatic and Medicinal Plants was recruited to the center, who initiated the pharmacovigilance of HM activity

- The same two persons: acquisition of specific technical expertise over the years
OPPORTUNITIES

- Work in tandem with the Poison Control Center, with whom we share the same building

  The proximity is important for better quality and quantity of reporting

- We use the Poison Control Center database as an important source for HM adverse effects

  Indeed
## POISON CONTROL CENTER DATABASE

### REPORTING SYSTEM

<table>
<thead>
<tr>
<th>SPONTANEOUS</th>
<th>No. (%) [n = 1157]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone</td>
<td>20 (1.73)</td>
</tr>
<tr>
<td>Internet</td>
<td>18 (1.56)</td>
</tr>
<tr>
<td>On-site consultation to the center</td>
<td>78 (6.74)</td>
</tr>
<tr>
<td>Post</td>
<td>29 (2.51)</td>
</tr>
<tr>
<td>Toxicovigilance (Poison Control Center)</td>
<td>80 (6.91)</td>
</tr>
<tr>
<td>Total</td>
<td>860 (74.33)</td>
</tr>
</tbody>
</table>

### INTENSIVE MONITORING PROGRAMMES

(Surveys and prevalence studies)

|                                                      | 252 (21.78) |

### LITERATURE

(Published national case reports)

|                                                      | 45 (3.89)  |
CHALLENGES

Regulation & Quality Assurance and Control

Main challenge !!!

- National regulation for HM doesn’t exist
- Registration of some HM products (about 10%)
- No quality assurance and control
- Other sources of poor quality of HM: counterfeiting, open borders and uncontrolled distribution channels
CHALLENGES

Many others ….

- *Underreporting*
- Causality assessment *special HM*
- Herbal practitioners
  - A useful source of information (prescribers and dispensers)
  - *Excluded from reporting system*
  - *No effective regulation of HM practitioners*
    - Identifiable in law, governed by professional codes of practice and have agreed standards of training and competency ??
CONCLUSIONS

There is way to go …

- Moroccan pharmacovigilance of HM database is an important source of information that can be used as part of the surveillance system of HM

- The regulatory issues constitutes the main challenge for HM safety monitoring

- Pharmacovigilance of HM situation is different from that of conventional drugs
THANK YOU FOR YOUR ATTENTION