Consideration: which is the most important in new drug development?


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Outline

• **Background**
  – **Neck pain** is a common symptom.
  – Many patients use **complementary and alternative medicine**, including **traditional Chinese medicine**, to address their symptoms.

• **Current studies on the new herb medicine, ‘Qishe Pill’**
  – To establish the **preparation processes** of a TCM theory-based **Formula**
  – To investigate the **potential mechanism** in **vivo** and in **vitro**
  – To assess the **safety and effectiveness** in Phase II, III, IV clinical trials

• **Challenges and ideas**
  – **Individualized medicine** is a trend.
  – TCM theory-based **constitutional types** may work.
Cervical radiculopathy

- A significant public health problem worldwide
  - Bad posture, everyday wear and tear, overuse or injury
- Related symptoms
  - Neck pain
  - Neck and arm discomfort.
  - Pain radiates to the upper or lower arm
  - Sensory distribution of the nerve root
**Stage I Formula Design**

- To design the formula as TCM principal
  - To tonify *Qi* (vitality)
  - To activate *Blood* (circulation)
- To establish the preparation processes
- To provide some pre-trial parameters

<table>
<thead>
<tr>
<th>Table 1 Standard formula (Capsule ingredients)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chinese name</strong></td>
</tr>
<tr>
<td>Huang Qi</td>
</tr>
<tr>
<td>She Xiang</td>
</tr>
<tr>
<td>Chuan Xiong</td>
</tr>
<tr>
<td>Fang Ji</td>
</tr>
<tr>
<td>Qing Feng Teng</td>
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<td>Niu Huang</td>
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*Pharmaceutical Terminology from Hsu [7].
Contents of the 19 active compounds in Qishe Pill
Contents of the 19 active compounds in Qishe Pill
## Contents of the 19 active compounds in Qishe Pill

<table>
<thead>
<tr>
<th>Compound</th>
<th>Sample1 (mg/g)</th>
<th>Sample2 (mg/g)</th>
<th>Sample3 (mg/g)</th>
<th>Sample4 (mg/g)</th>
<th>Sample5 (mg/g)</th>
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<tr>
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<td>SN</td>
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<td>ON</td>
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<td>DZ</td>
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<td>FNT</td>
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<td>AG-IV</td>
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<td>0.5720</td>
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<td>CA</td>
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<td>2.8714</td>
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<td>AG-III</td>
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<td>0.0992</td>
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<td>BR</td>
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<td>0.0023</td>
<td>0.0023</td>
<td>0.0019</td>
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### Contents of the 19 active compounds in Qishe Pill Compound
Stage II
Mechanism investigation

A. To inhibit **Inflammatory**
B. To decrease **apoptosis**
C. To prevent **angiogenesis** and degradation

- **In vivo**
  - Overuse
  - Animal model
  - Cold
  - Mechanical loading
  - **Inflammatory**
  - **Spine and disc**
  - **Disc degeneration**
  - **In vitro**
  - **Molecular mechanism**
  - 6-K-PGF1α
  - iNOS
  - COX-2
  - PGE2
  - **Collagen**
  - MMPs
  - **apoptosis**
  - TNF-α
  - Fas
  - Bcl-2

**Animal model**
- Mechanical loading
- Overuse
- Cold
To establish rat model

1. Normal
2. Nerve root compressed
3. Adrenaline & cortisol
4. Fatigue
5. Disease & ‘Zheng’ Model

Common Cervical radiculopathy
Blood-stasis ‘Zheng’
Qi-deficiency ‘Zheng’
A. To inhibit Inflammatory

- Decrease the contents of PGE2 and 6-K-PGF1α
- Equal effect with Fenbid
- Prior to other former herbal formula
A. To inhibit Inflammatory

- Decrease the contents of IL-1α, IL-6, TNFα
- Inhibit mRNA expression of iNOS, COX-2
B. To decrease apoptosis

- To decrease apoptosis of *nucleus pulposus* cell in disc and chondrocytes
- To improve the structure of disc
C. To prevent angiogenesis and degradation

- To promote chondrocytes to synthesize extracellular matrix
- To decrease activity of matrix metalloproteinases (MMP)
Stage III Clinical Trials

A. Phase II —— Safety & effectiveness
B. Phase III —— Safety & efficacy
C. Phase IV —— Post-marketing surveillance

Challenges and ideas
Placebo

Experiment

Positive

Outcome

Follow-up

Phase II Clinical Trials

Phase III Clinical Trials

Safety & Effectiveness

Safety & Efficacy

Further development

WHY

Clinical Practice

Y/N
Challenge 1

How to utilize the information of subjects efficiently?
Phase II

Phase III

Phase IV

Neck pain

Neck disability

ROM of neck

Zheng assess

Safety & Efficacy

Post-marketing Surveillance

Subject — Information — Subgroup — Efficacy classification
Challenge 2

How to individualize the treatment from clinical trials
Aged 18～35岁
BMI 19～24
laboratory indexes
Medical history
Compliance
Drug & alcohol abuse
The difference in reaction of medicine shows individual difference in constitutional type.
Challenge 3

How to demonstrate the relationship of formula (Monarch, minister, assistant and guide in TCM prescription)
Idea 3

PK of western medicine
Single Ingredient, Multi-dosage

PK of herbal medicine
Multi-ingredient, Multi-dosage

Will clinical pharmacokinetics research data provide some evidence on *individual difference* or *herbal interaction*?
Population Pharmacokinetics (PPK)

A bridge of formula and constitutional type
Population

1. How to set?
2. How to use?
The nine constitutional types

- Type A: Gentleness
- Type B: Qi-deficiency
- Type C: Yang-deficiency
- Type D: Yin-deficiency
- Type E: Phlegm-wetness
- Type F: Wet-heat
- Type G: Blood-stasis
- Type H: Qi depression
- Type I: Special

Differ from

- General
- Physical
- Psychological

Sign

- Health
- Illness
<table>
<thead>
<tr>
<th>Condition</th>
<th>General characteristics</th>
<th>Physical characteristics</th>
<th>Psychological characteristics</th>
<th>Sign of health</th>
<th>Sign of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentleness</td>
<td>Yin-Yang balanced</td>
<td>Full of vitality and well-proportioned</td>
<td>Mild character</td>
<td>Good cold and hot tolerance, sleep well, good appetite and no fatigue</td>
<td>Less disease</td>
</tr>
<tr>
<td>Type A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qi-deficiency*</td>
<td>Insufficiency of primordial Qi</td>
<td>Weakened muscle*</td>
<td>No desire to speak</td>
<td>Short of breath, listless and low voice and easy to sweat and fatigue</td>
<td>Palpitations and influenza</td>
</tr>
<tr>
<td>Type B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang-deficiency</td>
<td>More insufficiency of primordial Qi</td>
<td>Slightly muscle atrophy</td>
<td>More quiet and introverted</td>
<td>Intolerance of cold, loose stool, clear abundant urine and easy to catch a cold</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Type C</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Yin-deficiency*</td>
<td>Yin-fluid deficiency</td>
<td>Slim body</td>
<td>Quick-tempered</td>
<td>Feverish palms and soles, dry mouth and throat, dry eyes, flushing cheek, and dry skin is usual</td>
<td>Fatigue syndrome, muscle fatigue and insomnia</td>
</tr>
<tr>
<td>Type D</td>
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<td></td>
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<tr>
<td>Phlegm-wetness</td>
<td>Body fluid stasis and phlegm-wetness aggregation</td>
<td>Obese body with accumulate fat around abdomen</td>
<td>Prudent</td>
<td>Feeling body heaviness, chest distress and excessive phlegm, sticky mouth, and sticky sweating in usual</td>
<td>Stroke and Diabetes</td>
</tr>
<tr>
<td>Type E</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet-heat</td>
<td>Internal accumulation of damp-heat</td>
<td>Slim body</td>
<td>Tend to be irritable</td>
<td>Likely to suffer from acne, thirsty, bad breath, bitter taste in the mouth in usual</td>
<td>Constipation, scabies and jaundice</td>
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<tr>
<td>Type F</td>
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</tr>
<tr>
<td>Blood-stasis*</td>
<td>Poor blood circulation</td>
<td>All body types</td>
<td>Tend to be annoying and forgetful</td>
<td>Frequent pain* and ecchymosis and g loomy complexion</td>
<td>Chronic pain*</td>
</tr>
<tr>
<td>Type G</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Qi-depression</td>
<td>Depression and stagnation of Qi</td>
<td>Slim body</td>
<td>Depressive, sensitive and suspicious</td>
<td>Frequently sigh, distention and pain in chest</td>
<td>hypochondria</td>
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<tr>
<td>Type H</td>
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<tr>
<td>Special diathesis</td>
<td>Special diathesis</td>
<td>All body types</td>
<td>All types</td>
<td>Hypersensitiveness</td>
<td>Asthma and urticaria</td>
</tr>
<tr>
<td>Type I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
To utilize information

Outcome including Disease & Zheng
To target population

The wider distribution &
The more effective
Pharmacokinetics

1. Population PK vs classical PK?
2. Clinical PK of herbal medicine?
Face it or Avoid it?

PPK VS PK
Demographics
- Sex、age、BMI

Primary screening

Secondary screening
- Physical examination
  - 血压、心率、心电图、呼吸状况、肝肾功能和血象无异常或异常无临床意义；

Healthy subjects
- Constitutional Types decision
  - 由两名有一定资历的中医师单独评定
  - 中医四诊仪评估取达成共识的判断

4 sub-group
4 constitutional types (n=144)

Type A
n=12*3

Type B
n=12*3

Type C
n=12*3

Type D
n=12*3
• 16 time windows for blood collection (5ml) in 3 days
  • 2304 samples for PK analysis of each ingredient
• 6 time windows for urine collection in 3 days
黄芪甲苷、5-0-甲基维斯阿木醇苷、毛蕊异黄酮、
毛蕊异黄酮葡萄糖苷、芒柄花素、芒柄花素苷、
黄芪皂苷Ⅲ、黄芪皂苷Ⅰ、洋川芎内酯A、
洋川芎内酯I、粉防己碱、防己诺林碱、木兰花碱、
盐酸巴马汀、四氢巴马汀、盐酸小檗碱、
四氢表小檗碱、青藤碱、蛇床籽素、大豆素、
异补骨脂素 ......

\[ C_{\text{max}}, T_{\text{max}} \]

\[ AUC_{0-t} = \frac{(t_{i+1} - t_i)(C_i + C_{i+1})}{2} \]

\[ t_{1/2} = \frac{\ln(2)}{k_e} \]

\[ AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{k_e} \]

CYP1A1、CYP1A2、CYP2D6、
CYP2C9、CYP2C19、CYP2E1、
CYP3A4和CYP3A5

试验前后生命体征监测
一般体格检查，血尿常规，血生化及心电图检查。
试验前后体质分型判定

SNP on pharmaco-metabonomics

PK parament

Constitutional type and vital sign
芪麝丸临床药代动力学前期预试验结果

Stephaniae Tetrandrae
- 粉防己碱
- 防己诺林碱
- 5-O-甲基维斯阿米醇苷

Ovientvine
- 芒柄花苷
- 芒柄花素

Ovientvine & Stephaniae Tetrandrae
- 盐酸巴马汀
- 木兰花碱
- 四氢小檗碱
- 盐酸药根碱
- 盐酸小檗碱
- 四氢巴马汀

Radix Astragali
- 黄芪甲苷
- 毛蕊异黄酮
- 毛蕊异黄酮葡萄糖苷
Qishe Pill PPK modeling

Fixed effect factors
- Age
- Sex
- BMI
- Constituional types

Individual plasma-time curve

Individual modeling

Model Verification

Qishe Pill PPK modeling

SNP on pharmacometabonomics

Gene-level individualization

Herbal interaction
Founded in 1960, one of earliest National TCM Clinical Research Bases
National demonstration hospital of TCM
National model establishment, Regarded as spiritual civilization unit in Shanghai for 12 years
Ranked 1st in the national re-evaluation of A hospital of TCM
 Ranked 2st in the national hospital competitiveness of TCM(2014)
Thank you for your attention!