R & D of Artemisinin and its derivatives

by

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1. Background of their R & D

Time: 1960’s during Vietnam War
Characters: Vietnam, China
Event: more casualties than weapon killing
Story: Viet Nam asked China to do R & D of antimalarials;
Mao’s call: many Chinese scientists in medical circle (WM or TCM) were involved in R & D of antimalarials
2. Where artimisinin comes?

It is isolated from medicinal plant, Artemisia annua, which has been used as a TCM drug in China for more than 2000 years.

It was first recorded as an antimalarial in “Handbook of Prescriptions for Emergency Diseases”, written by Ge Hong, famous TCM physician of Eastern Jin Dynasty in 340 A.D.

It also is described as an antimalarial in “Compendium of Materia Medica” by Li Shi Zhen in 1596, during Ming Dynasty: It says: Chill and fever caused by malaria can be relieved by Qinghao preparations.
“Handbook of Prescriptions for Emergency Diseases”

written by Ge Hong, famous TCM physician of Eastern Jin Dynasty in 340 A.D.
Artemisia annua
Artemisia annua
3. Its discovery

(1) Water extract has no antimalarial activity.
(2) Alcohol extract is effective.
(3) Ether-extract’s efficacy much better.
   At an oral dosage of 1g/kg x 3 against P. berghei, and 1.3g/kg twice a day for 8 days against P. cynomolgi, the extract completely cleared the blood parasites.
(4) In 1972, first clinical trial with Ether-extract was carried out with 30 cases, and confirmed the lab work.
(5) Finally, artemisinin was isolated from the extract in 1972.
4. Chemical structure

- A new compound
- Sesquiterpene lacton with a peroxygroup
- Molecular formula: $C_{15}H_{22}O_5$
- Molecular weight: 282
- Water-insoluble or oil-insoluble
In order to find out more potent or water-soluble or oil-soluble derivatives:

1. Dehydroartemisinin (DHA):
   4 times more potent

2. Artemether (ARM):
   oil-soluble - intramuscular im

3. Artesunate (ARS):
   Artesunate sodium - water-soluble - iv
Basic structure

R₁ = C=O  

R₂ = CH₃OCH₃  

R₃ = COOH  

R₄ = CH₃OH
dehydroartemisinin

artemether

artesunate
6. New drugs made from artemisinin or its derivatives

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose form</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>artemisinin</td>
<td>Tablet, suppository</td>
<td>artemisinin</td>
</tr>
<tr>
<td>Dehydroartemisinin</td>
<td>Tablet</td>
<td>dehydroartemisinin</td>
</tr>
<tr>
<td>artesunate</td>
<td>Tablet</td>
<td>50mg ; 100mg</td>
</tr>
<tr>
<td>artesunate</td>
<td>Injection (iv)</td>
<td>60mg</td>
</tr>
<tr>
<td>artemether</td>
<td>Tablet, capsule</td>
<td>40mg ; 50mg ; 25mg</td>
</tr>
<tr>
<td>artemether</td>
<td>injection (im)</td>
<td>1ml:80mg ; 0.5ml:40mg</td>
</tr>
</tbody>
</table>
7. Pharmacological characteristics

A lot of lab work and clinical trials were undertaken with artemisinin from 1973 to 1980. Its pharmacological features:

1. asexual forms of the erythrocytic stage
2. effective against CO-resistant malaria
3. inhibits gamocyte to infect mosquito
4. quickly clears parasitemia and fever
5. higher recrudescence
8. Toxicological tests

- Artemisinin and its derivatives were found to be embryo-toxic.
- When 1/200 of LD50 Artemisinin was orally given to pregnant rats on the 6-15th day of gestation, all the fetuses were absorbed.
9. Pharmacokinetics profile

1. Quick absorption
2. Short half life: only 1 hours
3. Peroxy group to be broken
4. Widely distribution in body
5. Penatrate Blood-Brain Barrier into brain
10. Overcome its recrudescence

the treatment duration was prolonged to 5-7Ds

- **Combination with another antimalarial**
  
2) **DDS**(drug delivery system)
3) **Chemical modification**
4) **Others**
## 11. Drug combinations

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose form</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether combination</td>
<td>Tablet</td>
<td>Artemether(20mg), Lumefantrine(120mg)</td>
</tr>
<tr>
<td>Dehydro-artemisinin combination</td>
<td>Tablet</td>
<td>Dehydroartemisinin(32mg), Piperaquine phosphate(320mg) and TMP(90mg)</td>
</tr>
<tr>
<td>Dehydro-artemisinin combination</td>
<td>Tablet</td>
<td>Dehydroartemisinin(40mg), Piperaquine phosphate(320mg)</td>
</tr>
</tbody>
</table>
12. Research in my lab--DDS

DDS---Prolong its half life and overcome recrudescence

- Transdermal patch of artemether

In order to overcome its weakness, an artemether transdermal preparation is developed, whose half life in the blood is significantly prolonged.
(1) Pharmacokinetics of Patch

Its P.K studies were carried out in mice, with orally-taken artemether as a reference.
Fig. 1  Plasma concentration-time curves of artemether and its metabolite in mice after a 4 day’s oral administration of ARM 75 mg.kg⁻¹
Fig. 2 Plasma concentration-time curves of ARM in mice after the transdermal administration of ARM.
Fig. 3 Plasma concentration-time curves of ARM in mice after the transdermal administration of ARM 75 mg.kg⁻¹.
Fig. 4 Plasma concentration-time curves of ARM’s metabolite DHA, in mice after the transdermal administration of ARM 75 mg.kg-1
<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Total dose</th>
<th>Administrative route</th>
<th>Clearing (%) of parasitemia</th>
<th>Recurrence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 x 4ds</td>
<td>400</td>
<td>Oral(i.g)</td>
<td>100 (10/10)</td>
<td>80 (8/10)</td>
</tr>
<tr>
<td>200 x 4ds</td>
<td>800</td>
<td>Oral(i.g)</td>
<td>100 (10/10)</td>
<td>0 (0/10)</td>
</tr>
<tr>
<td>37.5</td>
<td>37.5</td>
<td>Transdermal</td>
<td>100 (10/10)</td>
<td>10 (1/10)</td>
</tr>
<tr>
<td>75</td>
<td>75</td>
<td>Transdermal</td>
<td>100 (10/10)</td>
<td>0 (0/10)</td>
</tr>
<tr>
<td>150</td>
<td>150</td>
<td>Transdermal</td>
<td>100 (10/10)</td>
<td>0 (0/10)</td>
</tr>
</tbody>
</table>
(2) Antimalarial activity of Artemether Patch

Single patch is used during 4 days:

① At a dose of 37.5 mg / kg,
   Clear up the parasitemia, but recurrence occurs within 30 days.

② At a dose of 75 mg / kg,
   Completely clear up the parasitemia without any recurrence within 30 days.

The results showed that the dose of artemether transdermal patch is 1/8-1/10 of the oral dose of artemether.
2) Other transdermal preparation

Artesunate patch has the same efficacy as artemether.

In addition, ointment of artmesinin and its derivatives are under R & D.
3) DHA-PEG injection

• Use of PEG (Polyethylene Glycol)
  ① To synthesize water-soluble DHA is investigated.
  ② PEG-DHA is successfully synthesized and displays a potent antimalarial effect on the mice infected with P. berghei.

• Also, an action-lasting (7 days) s.c injection is under development.
### Tab. 2 antimalarial acitivity of DHA-PEG iv. injection compared with orally-taken DHA in the mice infected with P. berghei

<table>
<thead>
<tr>
<th>Groups</th>
<th>Dose /D x 4Ds</th>
<th>Inhibition(%)</th>
<th>Recurrence ( % )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>none</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>DHA ( Oral )</td>
<td>100mg/kg</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>DHA ( Oral )</td>
<td>50mg/kg</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>DHA-PEG ( iv )</td>
<td>50mg/kg</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>DHA-PEG ( iv )</td>
<td>25mg/kg</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>DHA-PEG ( iv )</td>
<td>12.25mg/kg</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
We are willing to cooperate with you to make the R & D of the new preparations successful.
Thank you!