

New Drug (Chemical Drug) Application Materials (13th)

Zhongzhou Ointment

Experiment & Literature Materials of General Pharmacology Research

Application Unit: Developer Zhao Zhongzhou
Yunnan Zhongzhou Pharmaceutical Co., Ltd.

Zhongzhou Ointment

New Drug Application Materials (13th)

Experiment & Literature Materials of General Pharmacology Research:

In recent years, based on the medical research, it has been demonstrated that rosacea is a kind of human facial skin lesion and inflammation, which is caused by a high degree of demodex infection.

The skin lesion areas are prone to be attacked by bacteria, which leads to the recurrence of inflammation in the defected skin areas, and then results in the changes of proliferation, scar and capillary expansion in the local skin areas. As for the study ointment for external use, the inventor selected some drugs that have the pharmacological functions of killing parasites and bacteria, resisting fungus, dissolving horn, promoting local blood circulation, relieving swelling, pain, and itching, astringing, dispersing inflammation and moistening skin, whose pharmacological conclusions all have been well-recorded.

Various kinds of drugs are combined together as a compound preparation — ointment for external use.

Targeting at the skin lesion and inflammation, each drug in the compound recipe not only has the function of killing bacteria and demodex to eliminate pathogens, but also has the efficacy of promoting the physiological blood circulation of the local skin to astringe the skin lesion, relieve inflammation and promote healing. In this ointment, each drug in the compound recipe not only has the individual functions of its own pharmacological effects, but also could exert the cooperative therapeutic effects on the basis of its characterized complementary functions.

Due to rational and moderate formulation, proportion and selection of drugs, as well as appropriate manufacturing technique, the therapeutic effects and stability of this ointment have been maintained.

In this way, it has overcome all the defects of the unsatisfactory efficacy of various so-called “rosacea ointment” compound preparations, which have been reported and introduced in current dermatology journals and newspapers. Therefore, this ointment has become a unique new product with a high recovery rate.

As for the in-vitro anti-demodex experiment, Mr. Li Zongduo, principal researcher of the Pharmacology & Toxicology Experiment Center of Henan College of Traditional Chinese Medicine, who is responsible for the animal experiments of pharmacology, toxicology and pharmacodynamics of this new drug, has visited and consulted Director Li, Teaching and Research Sector of Parasitology of Beijing Medical College, Director Zhu, Teaching and Research Sector of Parasitology of Tianjing College of Traditional Chinese Medicine, and Director Liu, Teaching and Research Sector of Parasitology of Nanjing Railway Medical College, all of whom have ever done some research related to human demodex. According to the current research situation at home and abroad, passage and reproduction of human demodex remains unavailable by in-vitro cultivation, thus in-vitro anti-demodex experiment could not be carried out yet, and the researcher only evaluate the anti-demodex effects of the new drug by comparing pre-treatment and post-treatment conditions of patients.

Anti-inflammation Effects of Zhongzhou Ointment

Experimental Materials:

- I. Drugs: Zhongzhou Ointment, pale yellow ointment, contains 30g drug in 100g ointment, provided by the inventor Zhao Zhongzhou.
- II. Animals: rats of Kunming species, provided by the Animal Sector of Henan College of Traditional Chinese Medicine.
- 140 rats, with the Anti-inflammation Effects of Zhongzhou Ointment weight of 20g \pm g, 70 males and 70 females, were randomized into 7 groups, 20 in each group. 24h before the experiment starts, cut off 2cm (approx.) of back fur of each rat, and then

1.	Apply	Zhongzhou Ointment	25 mg/kg
2.	Apply	Zhongzhou Ointment	50 mg/kg
3.	Apply	Zhongzhou Ointment	75 mg/kg
4.	Apply	“Fu Man Ling (demodexicidin)” Ointment	25 mg/kg
5.	Apply	“Fu Man Ling (demodexicidin)” Ointment	50 mg/kg
6.	Apply	“Fu Man Ling (demodexicidin)” Ointment	75 mg/kg
7.	Apply	Vaseline	75 mg/kg

for consecutive 7 days, and after the last administration, drip 0.05 ml xylene on the left aural area of each rat to induce inflammation, respectively. 15 min later, kill all the rats and cut off both ears of each rat, then use a punching device (diameter 8mm) to get a round ear slice and weigh each slice with a scale, results are as follows:

Table 1. Effects of Zhongzhou Ointment on Ear Edema of Rats

Group	Number of Animals (N)	Dosage (mg/kg)	Mean Differences of Weight (left ear - right ear) ($\bar{X} \pm SD$) mg
Vaseline	20	75	9.71 \pm 1.30
Fu Man Ling	20	25	2.81 \pm 0.87***
Fu Man Ling	20	50	2.64 \pm 0.93***
Fu Man Ling	20	75	2.62 \pm 0.93***
Zhongzhou Ointment	20	25	2.61 \pm 0.98***
Zhongzhou Ointment	20	50	2.24 \pm 0.79***
Zhongzhou Ointment	20	75	2.21 \pm 0.81***

Conclusion:

Compared with vaseline, Zhongzhou Ointment has more significant anti-inflammatory effects on the ear edema of rats that was induced by xylene ($P < 0.01$); and this anti-inflammatory effects are stronger than that of Fu Man Ling.

Anti-demodex Effects of Zhongzhou Ointment on Demodex Rosacea

Patient No.	Before treatment	After treatment								
			1 month X ₁	X ₁ ²		2 month X ₂	X ₂ ²		3 month X ₃	X ₃ ²
1	86	36	-50	2500	15	-71	5041	10	-76	5776
2	42	20	-22	484	1	-41	1681	1	-41	1681
3	45	14	-31	961	4	-41	1981	3	-42	1764
4	54	25	-29	841	10	-44	1936	10	-44	1936
5	58	12	-46	2116	5	-53	2809	0	-58	3364

$$\sum X_1 = -148 \quad \sum X_1^2 = 6902 \quad \sum X_2 = -250 \quad \sum X_2^2 = 13148 \quad \sum X_3 = -261 \quad \sum X_3^2 = 14521$$

Conclusion:

t₁=6.607 P₁<0.05

t₂=8.784 P₂<0.01

t₃=7.796 P₃<0.05

Significant anti-demodex effects after 1 month of treatment

Highly significant anti-demodex effects after 2 months of treatment

Significant anti-demodex effects after 3 months of treatment

Treatment Observation Unit: 153 Hospital of China Ministry of Machinery & Electronics

Treatment Observation Period: from Mar. 1986 to Feb. 1988

Principal Physician: Zhao Zhongzhou

Original Data Stored at: 153 Hospital of China Ministry of Machinery & Electronics, Liaoyang

Table 3:

Patient's Name	Demodex De- tection Degree at 1st Visit	Demodex De- tection Degree after 1 month	Demodex De- tection Degree after 2 months	Demodex De- tection Degree after 3 months	History of Present Illness	Diagnosis and Therapeutic Outcomes
Yuan Zhengxian	86	36	15	10		Symbiosis of both Demodex folliculoron and Demodex brevis, Deep Proliferative Demodex Rosacea, Clinical Recovery
Chen Zhenfu	42	20	1	1		Symbiosis of both Demodex folliculoron and Demodex brevis, Deep Proliferative Demodex Rosacea, Clinical Recovery
Zhu Jierong	45	14	4	3		Symbiosis of both Demodex folliculoron and Demodex brevis, Superficial Demodex Rosacea, Clinical Remission
Wei Xuegao	54	25	10	10		Symbiosis of both Demodex folliculoron and Demodex brevis, Deep Proliferative Demodex Rosacea, Clinical Recovery
Zhuang Fubin	58	12	5	0		Symbiosis of both Demodex folliculoron and Demodex brevis, Deep Proliferative Demodex Rosacea, Clinical Remission
Total	285	107	35	24		
Remarks	<p>1: Counting method of demodex detection degree: prepare a quantitative demodex detection device, i.e. a 0.5mm³ groove, squeeze out some sebum from the skin lesion and fill it into the groove, then remove it to a piece of glass slice with some plant oil on it. After dilution, counting could be carried out under a microscope (1-400 magnification), including adult demodex, residual body, eggs and larva.</p> <p>2: The relationship between demodex degree and clinical symptoms. During treatment, as the clinical symptoms were relieved and remitted, and the demodex degree also decreased or became negative.</p> <p>3: Conclusion: P1<0.05, with significance; P2<0.01 with highly significance; P3<0.05 with significance.</p>					

Treatment Observation Unit: 153 Hospital of China Ministry of Machinery & Electronics

Treatment Observation Period: from Mar. 1986 to Feb. 1988

Principal Physician: Zhao Zhongzhou

Original Data Stored at: 153 Hospital of China Ministry of Machinery& Electronics, Liaoyang

References (refer to New Drug Application Materials 3rd Prescription Drugs)

1. Chinese Pharmacopoeia, 53rd edition, 1963;
2. New Pharmacology, Chen Xinqian, People's Medical Publishing House 1951;
3. Pharmacology, People's Medical Publishing House;
4. Pharmacy, Xi Nianzhu, Gu Xueqiu, People's Medical Publishing House;
5. Dermatology, Zhu Desheng, People's Medical Publishing House;
6. Observation on the Efficacy of "Fu Mei Ling" on 756 Cases of Demodex Rosacea – Qu Kuizun, Themes Compilation of Academic Symposium on Demodicidosis, Qingdao, China, Jul. 1988
7. Observation on the Anti-demodex Efficacy of Zhongzhou Ointment on Demodex Rosacea Patients, NDA material 5th, material of pharmacodynamics experiment 3rd.

References:

1. Procedures and methods of safety evaluation for cosmetics. National Standard of the People's Republic of China.
UDC 668.58.001.4 C51 GB 7919-87
Procedures and methods of safety evaluation for cosmetics.
2. OECD toxicity test guidelines for chemicals.
Drug Management Bureau, Ministry of Health; Institute for the Control of Pharmaceutical and Biological Products [NICPBP], Ministry of Health; Pharmacopoeia Commission of the Ministry of Health. Apr. 1984.
3. Measures for new drug approval.
Ministry of Health, People's Republic of China. Jul. 1985
4. Experiment Unit: Pharmacology & Toxicology Experiment Center of Henan College of Traditional Chinese Medicine.
Experiment Period: from Jul. 1990 to Jul. 1991
Principal Researcher: Li Zongduo
Original Data Stored at: Pharmacology & Toxicology Experiment Center of Henan College of Traditional Chinese Medicine.