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Compilation of Documents on the Findings of the Ongoing

Re-evaluation of the Safety and Efficacy of the Anti-Drug Medication HEA(N)TOS

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Contents

Introduction

The anti-drug medication HEANTOS which is based on the traditional herbal medicine of Vietnam was initially authorized for tests in patients on 8 February 1991 by the Ministry of Health. Since then it is claimed to have cured over 7,000 Vietnamese drug users of their addiction. Such initial indications of efficacy as well as interest by both Vietnamese and international scientists in the medication led the Vietnamese government to request the United Nations to provide assistance in the further development of HEANTOS in December 1995. An agreement on the "International Scientific Development of the Anti-Drug Medication HEANTOS" was signed in May 1997 between the UN Development Programme and the Vietnamese government.

Although HEANTOS had been provisionally approved for further testing and use in 1991 by the Health authorities, new regulations on safety in the use of herbal medicine were introduced by the Ministry of Health on 12 March 1996 (Decision No. 371/BYT-QD) . As HEANTOS is based on traditional herbal medicine it would have to be subject to a re-evaluation according to the new regulations. Furthermore, cooperation between inventor Tran Khuong Dan and scientists at the Institute of Chemistry led to a standardization of HEANTOS from syrup to capsule form, at the same time improving the short and long term efficacy of HEANTOS. And finally, the re-evaluation according to higher protocol standards is both part of the ongoing international scientific cooperation as well as a pre-condition for the nation-wide use of HEANTOS in the treatment of drug addicts.

In October 1997, the Ministry of Health called for the formation of a scientific advisory committee, to be chaired by the Vice Minister of Health Mr. Le Ngoc Trong, that would be responsible for the final evaluation and appraisal of HEANTOS (Decision No. 2306/BYT-QD). At the same time Vice Minister Le Ngoc Trong instructed the Central Psychiatric Hospital to implement the "Testing and Evaluation of the Safety and Efficacy of the Anti-drug Medication HEANTOS".

HEANTOS is currently available in three categories:

- *HEANTOS 1*: 0.500 g, used for detoxification, 3-5 days
- *HEANTOS 2*: 0.250 g, used to promote sleep during detoxification
- *HEANTOS 3*: 0.250 g, used to prevent recidivism, 1-6 months

All three HEANTOS categories were subject to tests under the re-evaluation. According to guidelines agreed upon with the scientific advisory committee in March 1998 tests would be carried out to determine:

1. The pharmaceutical standard and stability of the HEANTOS capsules, carried out by the Institute for Materia Medica, Ministry of Health, in April 1998
2. The safety of HEANTOS through pharmacological experiments, carried out by the Institute for Drug Quality Control, Ministry of Health, in September 1998, January 1999 and May 1999
3. The efficacy of HEANTOS in humans, carried out by the Central Psychiatric Hospital, Ministry of Health, Phase I carried out in 30 patients in July 1999

The results of these tests have been translated into English and put together in this report, followed by the original official Vietnamese versions for reference.

Summary of findings

Pharmaceutical standard of HEANTOS

Capsules of HEANTOS 1, 2 & 3 "achieved good standards in both dissolvent degree and weight equality." (IMM, 24 April 1998)

Safety of HEANTOS

"In the three samples (Heantos -1; Heantos -2 and Heantos -3), series No.1, manufactured on 20 April 1998, produced at the Central Psychiatric Hospital on 11 May 1998, no toxins or addictive substances could be found." (IDQC, 15 September 1998)

"Heantos-2... was tested in mice and rabbits... with co-administration of morphine and heroin. The animals did not show any signs of convulsion, such as tetanism or spastic paralysis during observations. The animals showed signs of exhaustion, reduced activity and lethargy (in mice) up to 5-8 hours after administration. After 24 hours, most of the animals were in normal condition again." (IDQC, 30 January 1999)

"Heantos-2... was tested for pharmacological activity in white mice at a dose... 15 times higher than the normal dose per day for humans. Heantos-2 was tested alone or in combination with morphine or heroin. Mice showed signs of tiredness, slowed motion and sleepiness. In mice receiving Heantos -2 or Heantos-2 in cobination with morphine or heroin, possibilities for recovery from myo-injury was observed after 24 hours." (IDQC, 14 May 1999)

Short-term efficacy of HEANTOS

HEANTOS "supports the alleviation of withdrawal from drug addiction. The medicine has effects that reduce cravings, reduce paresthesia, reduce symptoms of digestive disorder, recover the patients' sleep habits and that help the patients recover their health rapidly as well as clear their minds." (CPH, August 1999)

HEANTOS "basically help[s] the patients avoid or overcome withdrawal symptoms and to recover their health rapidly." (comments on short-term efficacy tests by Prof. MD. Hoang Bao Chau, Former Head of Institute of Medicine, August 1999)

LIST OF THE SCIENTIFIC COMMITTEE FOR THE RE-EVALUATION OF HEANTOS

1. Prof. Dr. Le Ngoc Trong
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2. Prof. Dr. Tran Manh Tuan
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4. Prof. Dr. Hoang Tich Huyen
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2.	Prof. Dr. Phuong Dinh Thu	Experimental Pharmacology
3.	Prof. Dr. Phuong Dinh Thu	Clinical Pharmacology
4.	Pharm. Nguyen Huu Lam	Deputy Inspector General, Ministry of Health
5.	Prof. Dr. Trinh Van Quy	Drug Quality Control
6.	Prof. Dr. Tran Viet Nghi	Health and Psychiatry
7.	Dr. Tran Van Cuong	Clinical Anti-drug Treatment
8.	Physi. Nguyen Huu Hung	Inspector, Ministry of Health

Ministry of Health
Institute of Materia Medica
***
Standards Analysis Department

Socialist Republic of Vietnam
Independence - Freedom - Happiness

ANALYSIS AND EXPERIMENT FROM No. 04/1.98

Analysis sample:	Capsules of Heantos 1 (Capsule No. 0, with yellow-brown color)
Requirements:	Examination of Capsule Standards
Place of submission:	Department of Pharmacy
Date:	23 April 1998
Method of analysis:	Subject to DDU W II, part III (Appendix 1.8)

ANALYSIS RESULTS

No.	Requirements	Results
1	Dissolvent degree: less than 30 minutes	8 minutes
2	Weight equality: ± 7.5% (compared to the average weight of a capsule of 0.5191 grams)	Good

CONCLUSION

Capsules of Heantos 1 achieved good standards in both dissolvent degree and weight equality.

Hanoi, 24 April 1998
Head of the Pharmaceutics Institute
(Signed and Sealed)
Associate Doctor Nguyen Thuong Dong

Ministry of Health
Institute of Materia Medica
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Standards Analysis Department

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ANALYSIS AND EXPERIMENT FROM No. 04/2.98

Analysis sample:	Capsules of Heantos 2 (Capsule No. 1, with white-red color)
Requirements:	Examination of Capsule Standards
Place of submission:	Department of Pharmacy
Date:	23 April 1998
Method of analysis:	Subject to DDU W II, part III (Appendix 1.8)

ANALYSIS RESULTS

No.	Requirements	Results
1	Dissolvent degree: less than 30 minutes	7 minutes
2	Weight equality: ± 10% (compared to the average weight of a capsule of 0.2440 grams)	Good

CONCLUSION

Capsules of Heantos 1 achieved good standards in both dissolvent degree and weight equality.

Hanoi, 24 April 1998
Head of the Pharmaceutics Institute
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ANALYSIS AND EXPERIMENT FROM No. 04/3.98

Analysis sample:	Capsules of Heantos 3 (Capsule No. 1, with white-red color)
Requirements:	Examination of Capsule Standards
Place of submission:	Department of Pharmacy
Date:	23 April 1998
Method of analysis:	Subject to DDU W II, part III (Appendix 1.8)

ANALYSIS RESULTS

No.	**Requirements**	**Results**
1	Dissolvent degree: less than 30 minutes	7 minutes
2	Weight equality: ± 10% (compared to the average weight of a capsule of 0.2440 grams)	Good

CONCLUSION

Capsules of Heantos 1 achieved good standards in both dissolvent degree and weight equality.

Hanoi, 24 April 1998
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Associate Doctor Nguyen Thuong Dong

Ministry of Health
Institute of Drug Quality Control

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No. 215 VKN/KH

REPORT ON THE EXPERIMENTAL RESULTS FROM HEANTOS SAMPLES

In compliance with the contract signed between the Institute of Chemistry, National Center for Natural Science & Technology and the Institute of Drug Quality Control, Ministry of Health on the 12 June 1998 concerning toxicity experiments on Heantos samples, the Institute of Drug Quality Control would hereby like to provide the following results:

1. Experimental samples

The samples have been tested at the Pharmaceutical Department of the Central Psychiatric Hospital according to the report on sample experiments dated 11 May 1998.

1.1 Heantos 1

The samples are in hard capsules with orange bodies and red caps. There are no chemical symbols on the capsules which come in plastic bottles of 100 capsules per bottle. The label reads:
Heantos- 1
0.50g/capsule
Series:1
Date of Manufacture: 20 April 1998

The powder in the capsules is rough and dark brown with a sweet and spicy taste, smelling of cinammon volatile oil.
Average weight of powder in one capsule is 0.522g/capsule.
Enclosed documentation includes the sample component formula which includes 13 different pharmaceutical materials. The prescription reads as follows:
First three days: 10 capsules, 2-3 times per day, average dose of 20 and maximum 40.

1.2 Heantos 2

The samples are in hard capsules with white bodies and red caps. There are no chemical symbols on the capsules which come in plastic bottles of 40 capsules/bottle. The label reads:
Heantos 2: 0.25g/capsule
Used for sleeping during detoxification

Series: 1
Date of Manufacture: 20 April 1998

The powder in the capsules is white and slightly agglomerated.
Average weight of powder in capsules is 0.256g/capsule.

The prescription reads:
To be taken continuously for 4 weeks, with an initial dose of 5 capsules per day, reduced weekly by one capsule per week. If normal physiological sleep fails to be achieved, this dose can be used for up to 6 months.

2. Experimental Results

2.1 Chemical analysis to find common toxins and addictive substances

+ Method
For each experimental sample, powder quantities taken as follows:
Heantos -1: 40 capsules
Heantos -2: 20 capsules
Heantos -3: 20 capsules

To each powder sample, 150-200ml of distilled water is added, followed by H_2SO_4 of 10% to a PH of 3-4. After this the mixture is steamed for 30 minutes. The residue is filtered and cleaned in acidified distilled water (50ml) after which the liquid is purified according to processes for finding toxins and addictive substances in two environments of acid and alkaline.

Experimental results of the three types of Heantos

Experiment	Results
To find tranquilizers, e.g. gacdenal, meprobamat	negative
To find excess insecticides: Wofatox, pArathion, Diazinon, Bassa, Padan, Monitor	negative
To find addictive narcotic substances: morphine, heroin, seduxen, pethidin, methadone	negative
To find alcaloids of toxic pharmaceutical materials, e.g. Ngon leaves, O dau, Nux Vomica, Stramonium	negative
To find common alcaloids: reaction against Dragendorff	positive Experimental samples have traces with the same color and Rf as standard Rotundin

2.2 Toxicity experiments

2.2.1 Test animals

Experimental standard, dominant white mice of both genders, with a weight of 20g, ± 2g.

Experimental standard, dominant rabbits of both genders, with a weight of 2.0kg, ± 0.5kg

2.2.2 Experimental methods

- Methods for defining toxin of medicine - Health Publishing House 1996

- Guidelines provided in conjunction with Decision No. 371/BYT-QD of the Ministry of Health dated 12 March 1996 concerning determination of the safety and efficacy of traditional medicines.

- Experiments were carried out according to the principles and methods of toxin research as described in "Principles and Methods of Toxicology", A. Wallace Hayes, 1994

2.2.3 Experiments and results

2.2.3.1 Determination of toxins
+ Experiments

Grind powder from the capsules in porcelain mortars, add a little distilled water and continue until powder becomes pasty and smooth. Gradually add water to obtain a consistent liquid.

The mice were fasted 16 hours before being tested on, although they could drink water freely. The mice were able to drink water with assistance from researchers who gave them water using a curved needle with an obtuse head.

Tests are carried out to determine the lethal dose for mice. Each experimental sample is to be tested on 36 mice, randomly divided into 6 groups: one control group drinking distilled water and 5 groups drinking experimental samples with different doses. The mice will be evaluated after 5 days of drinking experimental samples.

+ Results

Heantos - 1

Groups	No. of Mice	Experimental Dose	Number of dead mice	Condition of the mice
1	6	0	0	The mice in the control group ate, drank and acted normally. 30 minutes to 1 hour after having taken the medicine, the mice in the testing groups acted slowly, then fell asleep. After 2 or 3 hours, the mice in groups taking small doses began waking up and moving. After 22 hours most of the mice ate and drank, though the mice in group 5 and 6 still acted slowly. One mouse in group 6 died. After 48 hours all mice ate, drank and acted normally.
2	6	2.5	0	
3	6	5.0	0	
4	6	7.5	0	
5	6	10.0	0	
6	6	12.5	1	

Heantos -2:
- 5 to 10 minutes after drinking the medicine, mice in all groups looked tired, acted slowly, then slept soundly. After 3 hours, some mice in the groups taking large doses died.
- After 24 hours, some mice in the groups taking smaller doses began to act, eat and drink.
- Mice in groups taking large doses died in two days, the rest of them still looking very tired and acting slowly. After 4 days, the mice began to behave, eat and drink normally, but they seemed to lose more weight compared to the control group.
- Number of dead mice and the LD_{50} value calculated according to Behrens methods are recorded in the following table. The rate of dead mice with Heantos -2 samples are to be calculated according to Behrens methods:

Groups	Testing dose	Actual no. of dead/live mice	Accumulated frequency	
			No. of dead/live mice	% of dead mice
1	0.74	0/6	0/18	0
2	1.48	2/4	2/12	14.3
3	2.22	3/3	5/8	38.5
4	2.96	2/4	7/5	58.3
5	3.70	5/1	12/1	92.3
6	0	0/6	Control	

LD_{50} = (2.65 ± 0.29)g/kg
Reliable limit calculation with P = 0.05
LD_{50} = (2.65 ± 0.57) g/kg

Heantos -3

Groups	No. of Mice	Experimental Dose	Number of dead mice	Condition of the mice
1	6	0	0	The control group mice, ate and behaved normally. After 12 to 10 minutes of taking drugs, testing groups mice began acting slowly adter which they slept. After 3-4 hours, mice in groups taking taking large doses looked very tired, they lay quiet and sweat. One mouse in Group 6 died after 6 hours. After 24 hours, mice in groups taking small doses began acting, while some mice in Groups 4 and 6 died. After 72 hours, most of the mice ate and drank, while mice in Groups 5 and 6 nstill acted slowly, and seemed to lose weight and eat less.
2	6	2.5	0	
3	6	5.0	0	
4	6	7.5	1	
5	6	10.0	1	
6	6	12.5	3	

Determination of toxins
+Experiment

Grind powder from the capsules in porcelain mortars, add a little distilled water and continue until powder becomes pasty and smooth. Gradually add water to obtain consistent liquids with different concentrations:

- Heantos -1: equivalent of 4/5 powder quantity in a capsule /5.0 ml
- Heantos -2: equivalent of 1/5 powdẻr quantity in a capsule /5.0 ml
- Heantos -3: equivalent to 1/2 powder quantity in a capsule /5.0 ml

Experimental samples are prepared everyday before administering them in the animals. The liquid samples are to be stirred each time before giving it to the rabbits.

- The experiment is conducted on 13 rabbits, divided into two groups - 7 rabbits in the test group and 6 in the control group.

Test Group: are given a dose of 5.0 ml/kg/day of the prepared smaples
Control Group: are given 5.0 ml/kg/day of distilled water.

- Everyday the rabbits are given experimental samples once in the morning, administered by rubber hose directly into the rabbit's stomach. Rabbits will drink experimental samples for one month.

-Rabbits in all groups are fed under the same conditions and according to the same nutritional systems.

- Monitoring and evaluation: Rabbits will be monitored everyday in terms of food consumption, operating abilities, excretion, urine, color of hair and eyes, etc.

- Before experimenting, the rabbits'normal indications of weight, body signs, blood, liver and kidney functioms are determined. At the conclusion of the experiment, the rabbits will be evaluated based on these indications and will be dissected to survey inner organs.

- Results will be compared for all test and control group rabbits before and after the experiments and between the control and test groups according to the guidelines of traditional medicine.

+ Results

Heantos -2

Condition of rabbits
During the experiment, rabbits in the control group acted normally, ate and drank a lot, had dry excretions and smooth hair - theri hair wasn't matted or dry. Rabbits in the test group taking Heantos -2 looked tired, acted slowly, ate and drank normally, did defecate but their hair wasn't as smooth as that of the rabbits in the control group.

Weight

Groups		Weight (kg)		P
	n	Before testing	After testing	before - after
Control	6	2.30 ± 0.26	2.36 ± 0.22	> 0.05
Test	6	2.04 ± 0.14	2.06 ± 0.23	> 0.05
P		> 0.05	> 0.05	

Quantity of Globules

Groups		Quantity of globules (x 10^6)		P
	n	Before testing	After testing	before - after
Control	6	4.46 ± 0.15	4.52 ± 0.29	> 0.05
Test	6	4.19 ± 0.49	4.33 ± 0.19	> 0.05
P		> 0.05	> 0.05	

Quantity of Leucocytes

Groups		Quantity of leucocytes (x 10^3)		P
	n	Before testing	After testing	before - after
Control	6	7.06 ± 3.22	6.62 ± 1.76	> 0.05
Test	6	7.6 ± 1.5	7.0 ± 2.7	> 0.05
P		> 0.05	> 0.05	

Leucocyte formula

Types of Leucocytes (%)	Groups	n	Before testing	After testing	P
Neuter	-Control -Test	6 6	20.8 ± 10.1 19.0 ± 9.0	39.3 ± 6.4 33.8 ± 6.0	< 0.05 < 0.05
P			> 0.05	> 0.05	
Mono	-Control -Test	6 6	1.2	 0.85	
Acid	-Control -Test	6 6	1.3 1.0	0.2 0	
Lymph	Control -Test	6 6	76.2 ± 12.1 79.16 ± 9.0	60.0 ± 6.4 63.8 ± 12.4	< 0.05 > 0.05
P			> 0.05	> 0.05	

There is a change of leucocyte formula in both the test and control groups. There are no significant differences between the test and control groups at the conclusion of the experiment.

Blood pigment

Groups	n	Blood pigment (g/l)		P before - after
		Before testing	After testing	
Control	6	116.0 ± 10.1	98.3 ± 2.3	< 0.05
Test	6	120.2 ± 17.2	102.3 ± 5.2	> 0.05
P		> 0.05	> 0.05	

There was a reduction of blood pigment in the control group but no significant differences compared to the test group.

Hematocrit

Groups	n	Hematocrit (l/l)		P before - after
		Before testing	After testing	
Control	6	0.4 ± 00.4	0.4 ± 0.03	> 0.05
Test	6	0.32 ± 0.06	0.38 ± 0.06	> 0.05
P		> 0.05	> 0.05	

Total Protein

Groups	n	Total Protein (g/l)		P before - after
		Before testing	After testing	
Control	6	46.0 ± 0.7	53.2 ± 5.2	> 0.05
Test	6	47.8 ± 6.4	54.0 ± 10.5	> 0.05
P		> 0.05	> 0.05	

Bilirubin serum

Groups	n	Bilirubin (µmol/l)		P before - after
		Before testing	After testing	
Control	6	5.00 ± 1.00	3.63 ± 0.68	< 0.05
Test	6	4.67 ± 0.69	3.80 ± 0.37	> 0.05
P		> 0.05	> 0.05	

There was a reduction of Bilirubin serum in both groups, the reduction in the control group had a significance of P = 0.05. There was no significant difference between the control and test groups.

GOT serum

Groups	n	GOT (Ul/l)		P before - after
		Before testing	After testing	
Control	6	128.5 ± 15.7	114.2 ± 16.9	> 0.05
Test	6	127.2 ± 15.0	119.0 ± 9.0	> 0.05
P		> 0.05	> 0.05	

GPT serum

Groups	n	GPT (Ul/l)		P before - after
		Before testing	After testing	
Control	6	83.2 ± 9.8	76.7 ± 18.4	> 0.05
Test	6	87.5 ± 0.60	75.2 ± 3.4	< 0.05
P		> 0.05	> 0.05	

Concentrations of GPT serum fell after the experiment in both groups, the reduction in the test group had a significance of P = 0.01. However, there was no siginificant difference between the test and control gorups both before and after the experiment.

Creatinin serum

Groups	n	Creatinin (µmol/l)		P before - after
		Before testing	After testing	
Control	6	120.8 ± 16.5	102.8 ± 18.4	< 0.05
Test	6	120.5 ± 21.4	98.5 ± 19.9	> 0.05
P		> 0.05	> 0.05	

Ure serum

Groups	n	Ure (mmol/l)		P
		Before testing	After testing	before - after
Control	6	6.63 ± 0.3	4.57 ± 0.82	< 0.05
Test	6	6.9 ± 0.7	4.8 ± 0.9	> 0.05
P		> 0.05	> 0.05	

General observations: there were no differences in the arrangement and condition of inner organs between the control and test groups after the experiment.

Heantos -1 and Heantos -3

Condition of rabbits
During the experiment, rabbits in all groups behaved, ate and drank normally, they had dry excretions and smooth hair - not matted or dry.

Weight

Groups	n	Weight (kg)		P
		Before testing	After testing	before - after
Control	6	2.18 ± 0.11	2.23 ± 0.17	> 0.05
Heantos -1	7	2.27 ± 0.11	2.39 ± 0.16	> 0.05
Heantos -3	7	2.33 ± 0.18	2.40 ± 0.14	> 0.05
P (C - H_1) P (C - H_3)		> 0.05 > 0.05	> 0.05 > 0.05	

Quantity of globules

Groups	n	Quantity of globules (x 10^6)		P
		Before testing	After testing	before - after
Control	6	4.11 ± 0.08	5.15 ± 0.64	< 0.05
Heantos -1	7	4.09 ± 0.28	5.46 ± 0.67	< 0.05
Heantos -3	7	4.03 ± 0.26	5.67 ± 0.60	< 0.05
P (C - H_1) P (C - H_3)		> 0.05 > 0.05	> 0.05 > 0.05	

The increased quantity of globules is significant within the three groups, but there were no significant differences between the control and test gorups.

Quantity of Leucocytes

Groups	n	Quantity of leucocytes (x 10^3)		P
		Before testing	After testing	before - after
Control	6	8.20 ± 1.99	8.13 ± 2.10	> 0.05
Heantos -1	7	7.75 ± 1.39	6.32 ± 1.73	> 0.05
Heantos -3	7	7.95 ± 0.71	6.57 ± 2.14	> 0.05
P (C - H_1) P (C - H_3)		> 0.05 > 0.05	> 0.05 > 0.05	

Leucocyte formula

Types of Leucocytes (%)	Groups	n	Before testing	After testing	P
Neuter	-Control	6	39.40 ± 7.6	39.3 ± 6.4	> 0.05
	-H1	7	36.28 ± 9.58	33.8 ± 6.0	> 0.05
	-H3	7	39.28 ± 15.26	39.86 ± 12.42	> 0.05
P			> 0.05	> 0.05	
Mono	-Control	6	0.5	1.83 ± 0.75	
	-H1	7	2.57 ± 2.43	0.86 ± 0.71	
	-H3	7	1.43 ± 0.35	0.28	
Acid	-Control	6	1.20	0	
	-H1	7	0.71	0	
	-H3	7	0.42	0	
Lymph	Control	6	62.83 ± 14.25	60.17 ± 14.62	> 0.05
	-H1	7	61.40 ± 9.94	57.43 ± 15.70	> 0.05
	-H3	7	59.28 ± 15.62	59.43 ± 13.49	> 0.05
P			> 0.05	> 0.05	

Blood pigment

Groups	n	Blood pigment (g/l)		P
		Before testing	After testing	before - after
Control	6	125.33 ± 9.75	125.83 ± 16.88	> 0.05
Heantos -1	7	132.71 ± 16.69	117.43 ± 11.72	> 0.05
Heantos -3	7	124.71 ± 24.85	123.14 ± 11.72	> 0.05
P (C - H_1) P (C - H_3)		> 0.05 > 0.05	> 0.05 > 0.05	

Hematocrit

Groups		Hematocrit (l/l)		P
	n	Before testing	After testing	before - after
Control	6	0.39 ± 0.01	0.43 ± 0.02	> 0.05
Heantos -1	7	0.38 ± 0.05	0.45 ± 0.05	< 0.05
Heantos -3	7	0.39 ± 0.04	0.44 ± 0.03	> 0.05
P (C - H_1)		> 0.05	> 0.05	
P (C - H_3)		> 0.05	> 0.05	

The reduction in blood pigment in the group taking Heantos -1 after the experiment had a significance of P = 0.01, but there was no significant difference between this group and the control group.

Total Protein

Groups		Total Protein (g/l)		P
	n	Before testing	After testing	before - after
Control	6	50.83 ± 6.75	58.83 ± 2.63	< 0.05
Heantos -1	7	48.00 ± 4.26	53.57 ± 6.39	> 0.05
Heantos -3	7	53.29 ± 4.26	56.29 ± 6.04	> 0.05
P (C - H_1)		> 0.05	> 0.05	
P (C - H_3)		> 0.05	> 0.05	

Bilirubin serum

Groups		Bilirubin (µmol/l)		P
	n	Before testing	After testing	before - after
Control	6	4.72 ± 0.45	5.75 ± 0.94	< 0.05
Heantos -1	7	4.47 ± 0.36	5.41 ± 0.50	< 0.05
Heantos -3	7	4.74 ± 0.67	5.36 ± 1.00	> 0.05
P (C - H_1)		> 0.05	> 0.05	
P (C - H_3)		> 0.05	> 0.05	

Bilirubin increased in the three groups, the increase in the test group taking Heantos -1 and the control group had a significance of P= 0.05. There was no significant difference between the control and test groups.

GOT Serum

Groups		GOT serum (Ul/l)		P
	n	Before testing	After testing	before - after
Control	6	131.67 ± 13.88	127.17 ± 11.25	> 0.05
Heantos -1	7	128.29 ± 14.56	128.57 ± 12.78	> 0.05
Heantos -3	7	134.86 ± 15.98	147.57 ± 11.72	> 0.05
P (C - H_1)		> 0.05	> 0.05	
P (C - H_3)		> 0.05	> 0.05	

GPT serum

Groups		GPT serum (UI/l)		P
	n	Before testing	After testing	before - after
Control	6	95.83 ± 7.81	80.50 ± 11.25	< 0.05
Heantos -1	7	91.86 ± 8.87	82.43 ± 3.90	> 0.05
Heantos -3	7	93.43 ± 9.58	88.14 ± 8.87	< 0.05
P (C - H_1)		> 0.05	> 0.05	
P (C - H_3)		> 0.05	> 0.05	

Creatinin serum

Groups		Creatinin (µmol/l)		P
	n	Before testing	After testing	before - after
Control	6	141.33 ± 5.32	129.17 ± 7.45	> 0.05
Heantos -1	7	133.57 ± 8.87	129.71 ± 15.97	> 0.05
Heantos -3	7	130.14 ± 5.68	121.85 ± 6.39	> 0.05
P (C - H_1)		> 0.05	> 0.05	
P (C - H_3)		> 0.05	> 0.05	

Ure serum

Groups		Ure serum (mmol/l)		P
	n	Before testing	After testing	before - after
Control	6	6.52 ± 0.71	5.78 ± 0.41	> 0.05
Heantos -1	7	5.70 ± 0.60	5.58 ± 0.25	> 0.05
Heantos -3	7	5.68 ± 0.50	5.58 ± 0.18	> 0.05
P (C - H_1)		> 0.05	> 0.05	
P (C - H_3)		> 0.05	> 0.05	

General observation: There were no differences between the inner organs of the control and test groups after the experiments were concluded.

3. Conclusion

In the three samples (Heantos -1; Heantos -2 and Heantos -3), series No.1, manufactured on 20 April 1998, produced at the Central Psychiatric Hospital on 11 May 1998, no toxins or addictive substances could be found.

- Toxins:
+ Results of testing for toxins on white mice:

Heantos -1: Small lethal dose: 10.00 g/kg
Minimum lethal dose: 12.50 g/kg
Heantos -2: Small lethal dose: 0.740 g/kg
Lethal dose of 50% (LD_{50}): 2.65 ± 0.57 g/kg (with P = 0.05)
Heantos -3: Small lethal dose: 5.00 g/kg

Minimum lethal dose: 7.50 g/kg

+ Results of testing for toxins in rabbits that took the medicine for one month

Heantos -1: With a dose of 4/5 powder quantity of one capsule/kg/day (equivalent to the maximum dose of a person/day), there were no significant differences between the test and control groups based on the bio-chemical and hematological indicators of the rabbits used.

Heantos -2: With a dose of 1/5 powder quantity in one capsule/kg/day (twice the dose of a person/day), there were no significant differences between the test an control groups based on the bio-chemical and hematological indicators of the rabbits used. The rabbits tested looked more tired and acted more slowly than the control group rabbits.

Heantos -3: With a dose of 1/2 powder quantity in one capsule/kg/day (5 times the dose of a person/day), there were no significant differences between the test an control groups based on the bio-chemical and hematological indicators of the rabbits used.

Hanoi, 15 September 1998
HEAD OF THE INSTITUTE
(Signed and Sealed)
Associate Professor and Doctor Trinh Van Dong

Ministry of Health
Institute of Drug Quality Control

Socialist Republic of Vietnam
Independence - Freedom - Happiness

No.: 02/ NCKH

REPORT ON THE EXPERIMENTAL PHARMACOLOGY OF HEANTOS-2

According to the contract on experimental studies of Heantos-2 with the Institute of Chemistry (National Center for Natural Sciences and Technology), the Institute of Drug Quality Control hereby presents the results:

1. Materials and method

1.1 Materials:
Heantos-2, batch No. 01, manufacturing date 20/04/1998, collected from the Central Psychiatric Hospital and stored at the Institute for Drug Quality Control.
The samples are white/red, hard gelatin capsules. There are no chemical symbols on the capsules which come in plastic bottles of 40 capsules/bottle. The label reads:
Heantos 2: 0.25g/capsule
Series no. 1, Manufacturing date: 20/04/1998
The powder in the capsules is off white.
Average weight of powder in capsules is 0.254g/capsule.

1.2 Animals
Healthy adult mice of both sexes weighing 20g ± 2 were used. The mice began fasting 16 hours before the tests began, with free access to water.
Healthy young adult rabbits of both sexes weighing 2.0kg ± 0.5 were used.

1.3 Method
Morphine hydrochloride was used at a dose shown to have significant analgesic effects in mice (cf. Pharmacology Department, Hanoi Medical College).
Heantos-2 was used at a dose equivalent to ½ infra-lethal dose in mice, and in the rabbits a dose 2/3 higher than that used in subchronic studies.
The protocol was designed by pharmacologist, Prof. Dr. Hoang Tich Huyen.

2. Experiment and results
2.1 Tests in mice
2.1.1 Reagent:
-Normal salin (NaCl 0.9%)
-Morphine HCl: 1/10 000 solution in water for injection (M)
-Heroin HCl: 1/10 000 solution in water for injection (H)
-Heantos-2: samples stored at the IDQC
Infra-lethal dose in mice: 0.74g/kg
Test dose: 0.37g/kg

Grind the content of the capsules in a porcelain mortar, gradually add purified water and mix well. Adjusted with water to achieve a suspension of 0.37g/20mL (H2)

2.1.2 Experimental design

Experiments are carried out with 6 groups of 10 mice, according to the following samples:

- Group 1: NaCl 0.9%, intraperitoneal, 0.1mL/10g
- Group 2: Morphine HCl 1/10 000, intraperitoneal, 0.1mL/10g
- Group 3: Heroin HCl 1/10 000, intraperitoneal, 0.1mL/10g
- Group 4: Heantos-2, (0.37g/20ml) oral, o.2mL/10g
- Group 5: Inject M as with Group 2 followed by intake of Heantos-2 as with Group 4
- Group 6: Inject H as with Group 3 followed by intake of Heantos-2 as with Group 4

The mice could eat and drink freely after administration.
Careful observations were made in the first 8 hours and again after 24 hours.

2.1.3 Results

- Group 1: mice showed signs of normal condition
- Group 2,3: Mice show normal activity and eating
- Group 4 (H2): After 5-10 minutes, the mice decreased movement after which they became immobile. Most of the mice fell asleep after 20 minutes. The sleep was heavy and some mice were observed to have periods of accelerated respiration, with fur raised a little. After 5-6 hours, some mice woke up for a few minutes, piloerection was noted after which they continued sleeping. At 8 hours most of the mice were still sleeping and returned to normal activity and eating after 24 hours.
- Group 5 and 6 (M + H2 and H + H2): The mice were observed to have conditions similar to those in Group 4 (H2). All of the mice slept heavily and appeared exhausted, but responding when stimulated.

Some of the mice in Group 5 (M + H2) experienced periods of accelerated breathing, some of the times respiration was very rapid for 3-5 minutes. After 5 hours, 3/10 mice were weak, with hypotonic muscles, light breath, exhaustion and weak reflex. By 24 hours all mice had returned to normal activity.
In Group 6 (M + H2) the lethargic condition of the mice was less than that observed in Group 4 and 5. After 5-6 hours, some mice awoke for some time when stimulated. All mice returned to normal condition after 24 hours.

2.2 Tests on rabbits

2.2.1 Reagent

-Normal salin (NaCl 0.9%)
-Morphine HCl: 1/5 000 solution in NaCl 0.9% (M)
-Heroin HCl: 1/5 000 solution in NaCl 0.9% (H)
-Heantos-2: samples stored at the IDQC
Grind the content of the capsules in a porcelain mortar, gradually add purified water and mix well. Adjusted with water to achieve a suspension of 5.0g/100mL (H2)

2.2.2 Experimental design

The experiment was designed in 4 groups of 3 rabbits.. The rabbits were given samples as follows:

- Group 1: NaCl 0.9%, intraperitonial, 5.0mL/kg
- Group 2: Heantos-2, (0.25g/kg) oral, 5.0mL/kg
- Group 3: Morphine HCl 1/ 5 000, intraperitoneal, 5.0mL/kg
- Group 4: Morphine HCl 1/5 000, intraperitoneal, 5.0mL/kg

Samples were fed by hose directly into the stomach. The rabbits were normally fed.

2.2.3 Results

- Group 1: Rabbits observed to be in normal condition
- Group 2,3,4: Shortly after administration, the rabbits showed normal activity and eating. After 15 minutes, some decreased movement, and after 30 minutes almost all rabbits were stationary, not eating but still responding when stimulated. A few rabbits showed exhaustion with glazed eyes for 1 hour. The rabbits remained still for 4-5 hours after which they step by step began moving again.

The rabbits did not sleep as had the mice, and they did not show any signs of tetanism or spastic paralysis. The rabbits responded when stimulated. After 24 hours, all of the rabbits became normal again.

4. Conclusion

Heantos-2, batch no.1, manufacturing date 20/4/1998, collected from the Central Psychiatric Hospital and stored at the Institute for Drug Quality Control, was tested in mice and rabbits at doses of: 0.37 g/kg (mice) and 0.25g/kg (rabbits) with co-administration of morphine and heroin (1mg/kg, intraperitoneal). The animals did not show any signs of convulsion, such as tetanism or spastic paralysis during observations. The animals showed signs of exhaustion, reduced activity and lethargy (in mice) up to 5-8 hours after administration. After 24 hours, most of the animals were in normal condition again.

30 January 1999
Prof. Trin Van Quy
(signed and sealed)
Institute of Drug Quality Control
Director

MINISTRY OF HEALTH
INSTITUTE OF DRUG
QUALITY CONTROL

SOCIALIST REPUBLIC OF VIETNAM
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REPORT ON THE EXPERIMENTAL PHARMACOLOGY OF HEANTOS-2

In compliance with the research contract signed with the Institute of Chemistry, National Center for Natural Science and Technology, the Institute of Drug Quality Control has carried out pharmacological experiments on Heantos-2 and hereby presents the following results.

1. MATERIALS AND METHODS

1.1 Samples

The sample used in this experiment was Heantos-2 (Batch: No 1, manufactured on 20 April, 1998), provided by the Central Psychiatric Hospital (sample-collecting note dated 11-May-1998). This sample was also used in the previous experiment (dated 30, Feb. 1999) for the toxic and pharmacological assessment and specimens were deposited at the Institute of Drug Quality Control.

Heantos-2 is manufactured in the form of non-marked capsule with white body and red cover, in white plastic bottles of 40 capsules each.

The bottle is labeled:

Heantos-2
0.25 g/cap (Batch: No 1, MFD: 20-April-1998)
Used as sleeping agent in detoxifying period

The capsule contains a fairly lumpy white powder, averaging 0.254 g/cap.

1.2 Animal treatments

White, healthy male mice, weighing 20g ± 2g, were fed the final time at 16 p.m. the day before the experiment was to be carried out.

1.3 Testing methods

Doses of morphine and heroin having alnagesic effects were used (according to the standards of the Department of Pharmacology, Hanoi School of Medicine).

The Heantos-2 dose for mice was half of the sub-lethal dose, the same dose applied in previous experiments (IDQC's report dated 30, Jan., 1999).

After administration, mice were given free access to food and water.

The mice were monitored continuosly for all activity and behavior within the first 8 hours and again 24 hours after administration.

When symptoms appeared in the mice like those observed in the previous experiment, the mice were killed to take out the organs: brain, muscle, lung, kidney and liver for macrocosm observation, fixation, and sampling microcosm specimen. Ten mice were killed at five different times: 15'-30'; 1 h30'- 2 h; 3 h30'- 4 h; 5h30'- 6 h and 24 h after administration, two mice for each time interval.

The macrocosm and microcosm assessments were based on the following features:

- Brain: vessel situation (flat or dilated, hematoma, edema), growth of Glia cell, level of necrosis.
- Lung: hematoma, pulmonary and subpleural hemorrhagenic edema, situation of alveoli (flat or bloated)
- Liver: change and degeneration of liver cells and structure: picture of lobule, ray, growth of Kupffer cells, and hematomic level of hepatic vein.
- Muscle: features of myodegeneration such as the appearance of fingerprints and the scaled-like sign in myofibril.
- Kidney: features of edema or hematoma at interstitial space and the degeneration of kidney duct cells.

The research plan was developed with the specialist advice from Prof. Dr. Hoang Tich Huyen, to meet the requirements of the Specialists Group, Drug Control Sub-Committee, Ministry of Health.

The experimental preparations, administration, monitoring, operation and macrocosm observation were carried out at the Department of Pharmacology, Institute of Drug Quality Control.

Fixation of microcosm specimen, microcosm evaluation of the organs was carried out at the Department of Anatomy, School of Medicine.

2. EXPERIMENTS AND RESULTS

2.1 Reagents

- 0.9 % NaCl solution for injection
- 1/10000 solution of HCl morphine in distilled water.

- 1/10000 solution of HCl heroine in distilled water (HCl heroin was provided by the Criminology Technical Section, Hanoi Police Department, Ministry of Public Security)
- Heantos-2: same dose as that used in the previous experiment and half of sublethal dose

  Sublethal dose: 0.74 g/kg body weight of mouse
  Testing dose: 0.37 g/kg body weight of mouse
  Testing sample was ground, mixed with distilled water, then added water to give 20 ml solution containing 0.37 g Heantos-2.

2.2 Experimental procedures

In this experiment, 40 mice were divided into 4 groups, 10 in each group and were administered once as follows:

- Group 1: intraperitoneal injection of 0.9 % NaCl solution at a dose of 0.1 ml/10 g
- Group 2: oral administration of Heantos-2 (H2) at a dose of 0.2 ml/10 g (0,37 g/kg)
- Group 3: intraperitoneal injection of solution of HCl morphine at a dose of 0.1 ml/10 g, then oral administration of Heantos-2 at same dose as group 2
- Group 4: intraperitoneal injection of solution of HCl heroine at a dose of 0.1 ml/10 g, then oral administration of Heantos-2 at same dose as group 2

2.3 Results

2.3.1 Observation of behaviors

After administration, mice showed symptoms similar to those that appeared in the previous experiment, details as follows:

Group 1: mice were active, ate and drank normally.

Groups 2,3 and 4: (Heantos-2 only or combined with morphine or heroine was administered to mice). From 5 to 10 min after administration, mice showed slow motion, then sat still. Most of mice slept after 20'. They slept very tiredly and deeply. Within the first 15-30', all mice with symbolic feather fluff were operated. After 5-6 h, some mice could be waken up by noise, then came back to sleep. The mice in deepest sleep or in an extremely tired situation were chosen to be operated firstly. About 8 h after administration, the rest (4 mice) were still in their deep sleep. In group 3 (M + H2), symptoms noticed were more serious than those observed in groups 2 and 4: Most of mice had shortness of breath, sometimes hyperpnea occurred within 3-5'. Then they lay prostratelly, breathed weakly, their tender leg muscle stretched out and had difficulty bending when stimulated. After 24 h, the rest (2 mice) were active, ate and drank normally.

2.3.2 Observation of organs

Group 1:

Macrocosm:
Injuries were observed in some mice: a little subpleural hemorrhage, underside (2/10) or both sides (2/10) at different points of time. A mouse had a fairly small lung. Two mice had a little stretched stomach.

Microcosm:
* Lung: Mice (8/10) had pulmonary injured signs such as hematoma, hemorrhage in alveolar walls, making some of alveoli flat or alveolar ducts narrower, accompanied with dilated alveoli. Microscopical hemorrhage was visualized even in some mice that did not show injured signs in macrocosm, sometime including large bleeding accompanied with hematocele (mouse No. 9). Bronchus may have increasingly secretive epithelium with edematous fluid, hemoglobin or empty, broadly dilated or flat epithelium. However the level of injury was not popular, not strong and nor symbolic. Inflammatory injury was not noticed yet.
* Muscle: Most of mice had their muscle structure in normal limit. However, two mice had local degeneration of myon. One of these mice had loss of myoideum, myoneme and had sealed-like sign in myofibril (in part of muscle).
* Liver: most of mice had their liver in normal limit. Some mice had injured signs similar to those of anemia rather than hematoma. There were features of degeneration in some hepatic cells such as: large cell, brighter hepatic serum, stretched membrane of cell, atrophic nucleus or loss of nucleus but only observed in a part of some hepatic lobules of Mouse No 5 and 6 (operated at 5-6h after ad.) or in some hepatic lobules of Mouse No 9 and 10 (operated 24h after ad.)
* Kidney: Most mouse kidneys were in normal limit. Only one mouse had several swollen, edematous glomeruli and translucent ureter with unclear wall and unclear border within epithelial cells.
* Brain: Most mouse brains were in normal limit. There were no proliferation or degeneration of neuroglia cells. Hematoma and edema of exo-intracellular were noticed but locally and slightly.

Group 2:

Macrocosm:
Organs were normal, intestines were shining but wet. Some mice had wet peritoneal socket with pink fluid. Stomach was flat in most case. Four mice had smaller and a fairy flat lung with some small hemorrhagic points. The bronchial system was not injured.

Microcosm:
* Lung: 7/10 mice had pulmonary hematoma and hemorrhage, many alveoli were flat and narrow; some dilated and fully filled with hemoglobin and edematous fluid. The

rest (3 mice) did not show the alveolar hemorrhage but got hematoma of alveolar wall in some places. Some alveoli were narrow, flat or dilated.
* Muscle: Most of mice in this group had got injured signs such as edema, hematoma, and small hemorrhage at interstitial space resulting in the split of myofibril at different levels. The signs of local myodegeneration were common but of different levels such as: loss of myoideum, myoneme, appearance of fingerprints and sealed-like sign. The myodegeneration was symbolic for mice No 1 and 2, but less and unclear for mice No 3, 4, and 5, and just slight for mice 9 -10, showing its recoverable posibility.
* Liver: most of mice showed hepatic injury at different levels: largely dilated vessels, empty or hematoma, fully stagnated with hemoglobin and fluid. Features observed were swollen translucent hepatic cells, degeneration, bloatly stretched membrane of cell, brighter hepatic serum, thick atrophic nucleus and loss of nucleus. There was slight proliferation of Kupffer cells or vice versa. The recoverable signs were not noticed after 24h.
* Kidney: Injury was not noticed clearly except for a little bit local hematoma and edema, dilated vessels.
* Brain: Most of mice's brains (8/10) were close to normal limit. Some signs of anemia rather than hematoma were visualized such as flat, or dilated, empty vessels and exo-intracellular edema at different levels.

Group 3:

Macrocosm:
Features of visceral anemia were noticed in all animals. All organs got brighter color than usual, especially the liver. Some mice got pink fluid in peritoneal socket. Stomach was flat in most case, but bloated for mouse No 5. Three mice showed a fairy big lung with hemorrhage (3/10).

Microcosm:
* Lung: There were irregular signs of injury resulting from circulatory disorder. Hematoma was found in most case. Some were noticed to have increasingly secretive epithelium, pulmonary hemorrhage mixed with edematous fluid in both bronchi and alveoli. However, these injuries were not common.
* Muscle: The muscle injuries observed in this group were similar to those of group 2. Degenerative features appeared some 30' after administration, then more clearly after that. By 5 h 30' after administration, there were recoverable signs but sealed-like sign still occurred (50 %).
* Liver: 30' after administration, hepatic injuries were visualized similar to those of group 2 but developed very irregular from time to time. Sometimes the abnormal hepatic cells were noticed. The recoverable signs were not noticed yet after 24h.
* Kidney and brain: Like two above groups, injured features observed in brain and kidney were not symbolic. Only one mouse showed the parietal thrombus.

Group 4:

Macrocosm:
Injuries resulting from circulatory disorder made all organs becoming brighter than usual. Some mice got the wet peritoneal socket, hematoma, or small pulmonary hemorrhage. There were recoverable signs in all animals after 24 h.

Microcosm:
* Lung: The symbolic signs of hematoma and small hemorrhage were noticed like that of groups 2 and 3. Some got local atelectasis and bleeding.
* Muscle: The muscle injuries observed in this group were similar to those of groups 2 and 3. Recoverable signs were noticed by 5 h 30' and 24 h after administration.
* Liver: 30' after administration, hepatic injuries were visualized similar to those of group 2 but developed very irregularly by the time. The hepatic vein was dilated , including hematoma or not. 3/10 mice showed their liver close to normal limit; 4/10 had injured features of degeneration but not clear; 3/10 showed clear features of injury such as hepatic cell becoming translucent, solid atrophy or little degeneration.
* Kidney: The injured features were not clear and symbolic.
* Brain: Like two above groups, injured features observed in brain were not symbolic. However, in some cases there were the injured features like flat, dilated vessel, edema, degeneration and the proliferation of Glia cell.

The detail descriptions and pictures of organs are illustrated in the enclosed appendix.

3. GENERAL COMMENTS

Microscopical observation showed injured features such as pulmonary hematoma and hemorrhage in all four groups, (including the control group No 1).

The muscle injury with the features of dilated striped fibril and the appearance of sealed-like sign were noticed in all four groups but at a higher level in groups administered Heantos-2. However, in mice operated after 5h and 24 h administration, recoverable signs were noticed.
In liver, the level of injuries in groups administered Heantos-2 was more severe than that of group 1. However, these injuries were not regular and not worse by the time and in some cases the recoverable features occurred.

Injuries in brain and kidney were not noticeable and symbolic. Brain and kidney situation was close to normal limit.

4. CONCLUSION

The Heantos-2 sample (MFD 20 April, 1998, Batch: No 1), provided by the Central Psychiatric Hospital (sample-collecting note dated 11-May-1998), deposited at the Institute of Drug Quality Control, was tested for pharmacological activities in white mice at dose of 0.37 g/kg mouse body weight (15 times the normal dose per day for

every patient: 5 capsule/day/person). Heantos-2, taken orally, was tested alone or in combination with morphine or heroin at a dose of 1 mg/kg by *i.p.* injection. The experiments showed mice had behavioral signs such as: tiredness, slowed motions or sleepiness, which were similar to those observed in the previous experiment (report dated 30/1/1999). In mice receiving Heantos -2 or Heantos-2 in cobination with morphine or heroin, possibilities for recovery from myo-injury was observed after 24 hours. Hepatic injuries were irregular, unequal and its restorative capacity was not clear (due to the small number of mice used and the testing period too short: 24 h after administration).

Hanoi, 14 May 1999
Head of Institute

Associate Prof. Dr. Trinh Van Quy

The study report on the assessment protocol of the Heantos medication in the treatment of drug addicts

1. Preface

This study has been carried out in accordance with instructions from a meeting of the scientific advisory council concerning the "assessment study of the Heantos medication", held on 12 June 1999 at the Ministry of Health.

In the pursuance of circular letter 75-YT-TT of the Ministry of Health - authorizing the Institute of Chemistry, NCNST in cooperation with the Central Psychiatric Hospital to carry out a study on the assessment protocol of the Heantos medication - we have conducted this research with the following objectives:

- to determine the appropriate dose of the different Heantos products
- to preliminarily assess the efficacy of Heantos in stopping drug addiction.

2. Object and Method of Study

2.1 Study Objects

2.1.1 Criteria for admission of patients:

- the patient participates in the treatment on a voluntary basis
- the patient is diagnosed as a drug addict according to the specification ICD10.

2.1.2 Criteria for excluding patients:

- the patient's first urine test is negative for drugs
- the patient suffers from chronic or acute diseases that has contra-indications to treatment with Heantos

2.2 Method of study

2.2.1 Study description

This is a comparative study of the clinical trials of various patient groups treated with different therapy protocols in order to determine the appropriate dose of the Heantos medicines. All patients are part of a designed study and all study components are conducted in full accordance with the research protocol, procedures for clinical investigations and treatment follow-up.

2.2.2 Treatment

2.2.2.1 The patient who arrives at the hospital will be met in a private room. The patient will complete formalities for admission, have the rules of the hospital explained to them and change into hospital attire.

2.2.2.2 The Doctor will interview the patient about their medical history as well as carry out a clinical check-up. A nurse will assist the patient in preparing for a urine test,

perform an electroencephalogram test as well as other necessary tests. Patients conforming to the admission criteria will be accepted for the Heantos treatment.

2.2.2.3 Arrangements will be made for a private room for each patient such that the patient can choose to be alone if so desired. The patient will be visited by a Doctor every day for clinical observation and to prescribe and administer medicine according to therapy protocol.

Every two days the patient's urine will be tested for drugs by the TLC method.

Psychological tests (Beck, Zung), biological tests (azotemia, grosmaclagan, SGOT, SGPT), hematology (blood formula, VSS) and electroencephalograms will be carried out for the second time from day 7.

2.2.2.4 After the patients are discharged (following 10 days of treatment) all data will be collated into a standardized patient record designed to meet the objectives of this study, i.e. to determine the appropriate dose of the Heantos medicines.

2.2.3 Study doses

- Dose according to inventor's protocol:

Heantos 1: - first two days, 6-8 capsules, twice a day at an interval of 8-12 hours
- day 3-5, 6-8 capsules, once before going to sleep
Heantos 3: - following days 6-10, 4-5 capsules, once before going to sleep

After 20 patients had been treated following this protocol, the Heantos scientific advisory council held a meeting on 24 July 1999 where they noted that the proportion of side-effects was still high and they consequently decided to modify the inventor's protocol.

- Dose according to the modified protocol:

Heantos 1: - first 3 days, the first administration is taken when patients experience 2-3 signs of withdrawal symptoms, 5-7 capsules, 1-2 times per day at an interval of at least 10 hours. Maximum of 5 doses in three days
- day 4-5, 5-7 capsules once a day, before going to sleep
Heantos 3: - following days 6-10, 3-4 capsules once before going to sleep

2.2.4 Evaluation

Evaluation is based on a grade system determined according to an evaluation table for 12 withdrawal symptoms (see appendix).

2.2.5 Data processing

The data is processed using statistical methods.

3. Study results

3.1 Patients

No. of patients who completed the 10 day treatment: 28
No. of patients who prematurely ended their treatment: 5

Of the 28 patients who completed the treatment, 15 were treated according to the inventor's protocol (Group I), 13 were treated according to the modified protocol (Group II).

There were 5 patients who had prematurely given up the treatment by day 4. Through our research we found that the reasons that these patients had initially agreed to take the anti-drug treatment were:
- 2 patients had been forced there by their families
- 2 wanted to avoid the law
- 1 had volunteered

However, on the way from Hoa Binh Center to the hospital these patients were informed of the nature of the tests they would be participating in which they reacted negatively towards by, for instance: refusing to take their medicine, hiding their medicine without taking it, speaking loudly to everyone, threatening to infect medical staff with HIV, etc. By the 4th day they collectively decided that they wanted to go home after having destroyed some hospital property such as test tubes. After this some Heantos medicine was found indicating that they indeed had not taken their prescribed doses. These patients were part of the group who were to be treated by the inventor's protocol. However, the treatment was not completed as the patients refused to take their medicine, hid the medicine or did not take the full dose. For this reason, these patients can be used as a control group (Group III).

3.2 Epidemiological characteristics of the patient groups

3.2.1 Sex

Sex	Group I	Group II	Group III
Male	14	13	5
Female	1	0	0
Total	15	13	5

3.2.2 Age

Age	Group I	Group II	Group III
≤ 20	0	2	1
21-30	9	8	2
31-40	5	3	2
≥ 41	1	0	0
Total	15	13	5

3.3 Characteristics of drug addiction in the Groups

3.3.1 Kind of drugs used

	Group I	Group II	Group III
Opium	7	1	1
Heroin	2	9	2
Opium + heroin	2	1	1
Opium + heroin + Pipolphene + Seduxen	2	1	1
Heroin + pipolphene	0	1	0
Opium + Dimedrol	1	0	0
Opium + Seduxen + Pipolphene + antirabid vaccine	1	0	0
Total	15	13	5

3.3.2 Form of drug administration

	Group I	Group II	Group III
Smoke	1	4	1
Injection	7	6	3
Smoke & injection	7	3	1
Total	15	13	5

3.3.3 Number of times drugs used per day

	Group I	Group II	Group III
1 time	5	3	2
2 times	7	5	2
3 times	2	5	1
4 times	1	0	0
Total	15	13	5

3.3.4 Duration of addiction

	Group I	Group II	Group III
Under 1 year	4	5	1
1-5 years	8	5	0
6-10 years	2	3	2
Over 10 years	1	0	2
Total	15	13	5

3.3.5 Number of previous anti-drug treatments

	Group I	Group II	Group III
None	3	5	1
1 time	4	5	0
2 times	3	3	2
More than 3 times	5	0	2
Total	15	13	5

3.3.6 HIV tests

	Group I	Group II	Group III
Positive	0	5	3
Negative	15	8	2
Total	15	13	5

3.4 Heantos use

3.4.1 Heantos 1, Group I

Heantos 1 was administered when the patients began showing signs of withdrawal symptoms.

In the first 2 days, 6-8 capsules, twice daily, at an interval of 8-12 hours.
From day 3 to 5, 6-8 capsules, once daily, before going to sleep

No.	Name	Day 1		Day 2		Day 3		Day 4	Day 5	Note
		1	2	1	2	1	2			
1	Pham Duy Tien	6	8	6	Sleep		8	8	8	
2	Le The Cuong	6	8	6	Sleep		8	8	8	
3	Nguyen Van Loi	6	8	6	8		8	8	8	
4	Dang Dinh Hoc	**6**		6	8		8	8	8	MC
5	Le Thanh Son	6	8	6	6		8	8	8	
6	Tran Duy Phuc		8	**6**	8		8	8	8	A
7	Dang Van Mau	8	8	**6**	8		8	8	8	MC
8	Nguyen Van Tien	8	8	6	**8**		8	8	8	A
9	Nguyen Thanh Tu	8	8	6	Sleep		**8**	6	8	MC
10	Vo Toan Tam	8	8	6	8		**8**	6	8	A
11	Pham Tien Phuc	8	8	6	8		8	8	8	
12	Tran Ngoc Thang	6	**8**		6		6	8	6	MC
13	Nguyen The Hung	6	8	Sleep	8		8	8	6	
14	Tran Quang Hung	6	8	**6**	8		8	8	6	A
15	Le Thanh Tra		8	**8**	6		4	6	6	MC

MC = muscle contractions
A = anxiety

3.4.2 Heantos 1, Group II

Heantos 1 was administered when 2-3 **withdrawal symptoms** had appeared in the patients.

First three days, 5-7 capsules, 1-2 times per day, at an interval of at least 10 hours and not more than 5 times in three days.
Day 4-5, 5-7 capsules once a day before going to sleep

No.	Name	Day 1		Day 2		Day 3		Day 4	Day 5	Note
		1	2	1	2	1	2			
1	Tran Van Chien		6	6	6		6	6	6	
2	Tran Thanh Hung			6	6	6	6	6	6	
3	Ngo minh Duc			6	6		6	6	6	
4	Duong Manh Cuong	6		6	6		6	6	6	A
5	Nguyen Si Hung		6	6	6		6	6	6	
6	Van Ba Ngoc			6	6		6	6	6	M
7	Le Manh Hung	5	5	5	7		6	6	4	
8	Nguyen Duy Thanh		5	5	5	5	6	6	6	M
9	Tran Van Nam		6	6	5		6	6	6	
10	Le Tien Hang	5	5	5	5	6	6	6	6	
11	Cao Nam Tien		5	5	5	5	6	6	6	
12	Nguyen Tan Dat		5	5	5	5	5	6	6	
13	Tran Viet Dung			6	6	6	6	6	6	

A = Anxiety
M=Myotonia

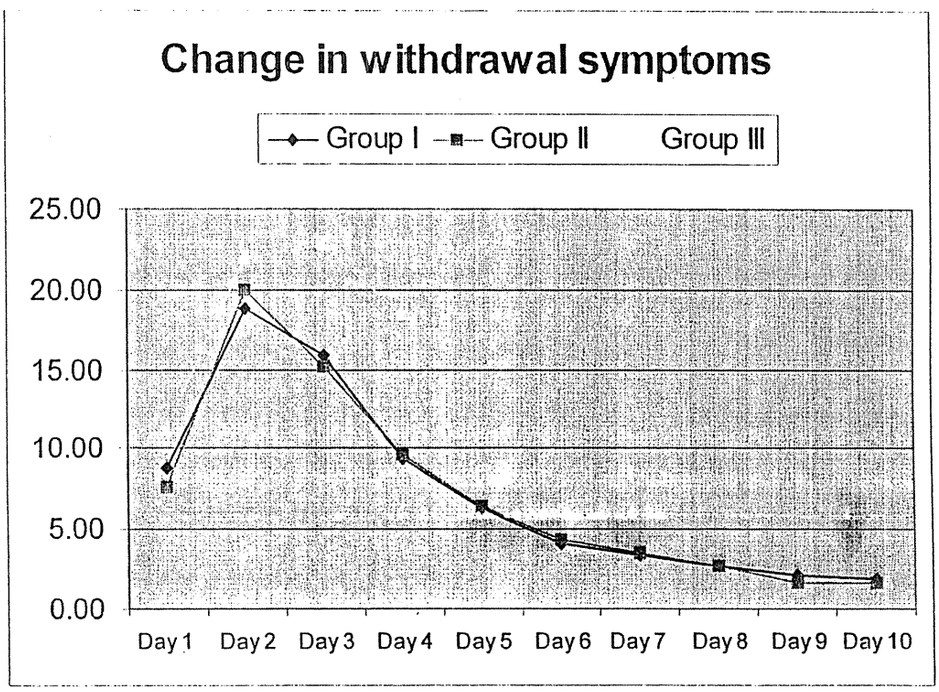
3.5 Treatment results

The detailed treatment result for each patient in 10 days (see appendix).

Grade table of withdrawal symptoms for the Groups

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
I	Σ	132	283	239	140	95	62	50	41	32	28
	Av.	8.8	18.86	15.93	9.33	6.33	4.13	3.33	2.73	2.13	1.86
II	Σ	99	259	197	124	84	56	45	35	22	22
	Av.	7.6	19.92	15.15	9.53	6.46	4.30	3.46	2.69	1.69	1.69
III	Σ	56	110	114	92						
	Av.	11.2	22	22.8	18.4						

Figure 1



Side effects in the Groups

	Group I n=15	Group II n=13	Group III n=5
Muscle contractions	5	0	0
Myotonia	0	2	0
Anxiety	4	1	0
Total	9	3	0

Some factors related to side effects

		Group I	Group II
The administration after which the side effects appeared	1st	1	1
	2nd	3	0
	3rd	2	1
	4th	2	0
	5th	1	1
	6th	0	0
Dose causing side effects	8 caps. H1	5	-
	7 caps.	-	0
	6 caps.	4	3
	5 caps.	-	0
Day in which side effects experienced	Day 1	2	1
	2	5	0
	3	2	2
	4	0	0

4. Comments and discussion

4.1 Comments on treatment effect

+ Effects on jactitation and paresthesia:

9/15 patients from Group I and 9/13 from Group II did not show signs of jactitation by day 3. 6/15 from Group I and 4/13 from Group II did not show signs of jactitation by day 4.

5/15 patients from Group I had a feeling of muscle contractions during which they claimed not to experience signs of paresthesia ("feeling of creeping maggots inside the body"). The patients claimed that such a feeling of muscle contractions was more endurable than paresthesia. 4/15 patients in the first three days experienced an increase in signs of paresthesia and anxiety after administration, but only for short amounts of time - about 2/3 of what they experience without taking Heantos. 10/13 patients from Group II experienced a reduction of paresthesia by 50%.

+ Effects on sleep:

In the first three days most patients only slept for 2-3 hours, falling in and out of a drowsy and light sleep and in the following days they slept 4-5 hours per night, more

deeply and felt more comfortable on waking up. After one week their sleep was close to normal hours.

+ Effects on cravings:

After the 4th and 5th days most of the patients did not experience any cravings, however some patients claimed that upon hearing any references to drugs at the times they would usually be using their drugs, they felt cravings but at a much less intense and endurable level.

+ Effects on other symptoms:

Heantos substantially reduced symptoms of digestive disorder though most of the patients did experience a dull and light pain in their stomach. In some cases they experienced watery stools 2-3 times but which stopped in day 3 or 4. Some patients vomited and experienced feelings of nausea in day 2 and 3, but not many times and only moderately. Yawning and runny eyes were reduced substantially. Goose flesh and hot/cold spells were still observed in the 5th and 6th days, after which they became less frequent.

Summary: Most of the patients experienced the most serious withdrawal symptoms in the second night and the third morning, and symptoms lessened from the afternoon of the third day, by the fourth evening they did not experience any signs of paresthesia, but they still experienced some signs of yawning, hot/cold spells and the feeling of cravings at the times they would usually be using drugs up to the 5th and 6th days. Heantos allowed a rapid health recovery and peace of mind. The patients became alert and regained their appetite in already the second and third days and their activity became normal by day 4. The average weight gained by each patient was 0.5-2 kilograms.

By comparison we found that the patients of Group III who had given up the treatment by day 4, experienced more serious and prolonged withdrawal symptoms than the other patients. By day 4 they still experienced signs of tiredness, a lot of yawning and intense paresthesia. 4/5 vomited green and yellow bile, 2/5 had to defecate several times a day, with signs of dehydration that needed treatment which the patients however refused.

4.2 Comments on side effects

- 5/15 patients in Group I showed light signs of muscle contractions. The muscle contractions often appeared 30 minutes after taking Heantos. Firstly, the patients experienced muscle fatigue and tetamus, after which their muscles contracted for short, discontinuous periods, each time lasting for almost one minute. The contractions were often observed in the facial, neck, leg and arm muscles, causing the muscle to lock in position in the patients. The patients were aware of this condition, but were unable to do anything about it. During these muscle contractions, the patients were fully alert, could communicate, being aware of and clearly describing this symptom. After 30 minutes the muscle contractions became increasingly less frequent as well as less intense and the patients could get sleep without any interruption. After waking up the patients felt

comfortable and were attentive. During the muscle contractions the patients' heart sound, pulse and blood pressure were within normal limits.

- muscle contractions were directly observed in 3 cases: the patient Dang Dinh Hoc experienced them after his first administration of 6 capsules of Heantos 1; the patient Le Thanh Tra experienced them after his second administration of 8 capsules of Heantos 1; and patient Dang Van Mau experienced them after his third administration of 6 capsules of Heantos 1.

- 2 other patients claimed also to have experienced muscle contractions after the second administration of capsules of Heantos 1 (patient Tran Ngoc Thang) and after the fourth administration of 8 capsules of Heantos 1 (Nguyen Thanh Tu).

In analyzing these patients' records we noted that:

- 1 was an opium addict, 2 were heroin addicts and 2 were both heroin and opium addicts;
- 2 patients injected, 1 smoked, 2 of them smoked and injected;
- 1 had been addicted for 6 months, 1 for 1 year, 1 for 2.5 years, 1 for 4 years and one for 5.5 years.

In most of the cases, as muscle contractions appeared the ensuing dosage of Heantos 1 was either reduced or stopped. We did not observe that the muscle contractions reappeared with the next administration even when taking the same dose that had caused the initial muscle contractions. There was however one case in which muscle contractions did not reappear until 10 hours after an administration of a higher dose than that which caused the muscle contraction in the first place.

2/13 patients in Group II claimed that 40 minutes after having taken their medicine signs of muscle fatigue and tightness inside the muscle appeared. Thereafter the patients experienced a stiffening of their muscles, as if they had muscle cramps. One patient experienced stiffness in his leg muscles while another in his neck muscles. They claimed that by shaking their legs or moving their neck they would feel better, and after 15 minutes these symptoms went away and the patient could sleep (patient Van Ba Ngoc experienced this symptom after his third administration of Heantos 1 (6 capsules); patient Nguyen Duy Thanh experienced it after 6 capsules of Heantos 1 for the 5th time; both patients were heroin addicts, 1 for 1 year, 1 for 2 years; 1 smoked and one injected). This symptom was not observed in either of the patients in the following administration.

4/15 patients in Group I claimed that shortly after taking Heantos 1 they felt signs of anxiety, discomfort, and restlessness in their body and thereby had to keep moving. This lasted from about 30 minutes to one hour and then lessened. The patients often felt a heaviness in their chest, and slight difficulties in breathing after inhaling strongly, then after taking deep breaths several times they felt better and could sleep. Upon waking up they felt comfortable and alert.

- After his first administration of Heantos 1 (6 capsules) patient Duong Manh Cuong experienced a sensation of anxiety and malaise. He kept moving around back and forth constantly, sometimes feeling pressure in his chest and slight shortness of breath. However, on checking his chest, he had regular respiratory movement and a clear pulmonary sound. His heart sound was regular. After 30 minutes, these symptoms were lessened and the patient could sleep for a while.

Of the 5 patients who felt anxiety and malaise:
4 patients were addicted to opium, 1 was addicted to heroin;
4 smoked, and 1 injected and smoked;
2 patients had been addicted for under 1 year, 3 patients were addicted from 1-3 years.

By analyzing the group of patients who had been subject to side effects we found that, in most cases, side effects were observed in those patients who injected their drugs (11/12 cases where side effects were experienced).

- Through our observations we noticed that the side effects often occurred within the first three days - from the first administration up until the 5th administration (the final administration of Heantos 1 in the first three days of the therapy protocol). From day 4 onwards side effects were not observed. The 5/12 patients who had taken a dose of 8 capsules of Heantos 1 per administration and the 7/12 patients who had taken 6 capsules of Heantos 1 per administration all experienced side effects. The dose of 5 capsules per administration did not cause any side effects in any of the cases. As seen in Figure 1 "Change in withdrawal symptoms" the dose of 5 capsules per administration was still as efficacious in stopping addiction as that used in therapy protocol 1 and in a time span shorter than that of the control group.

4.3 Some comments on the paraclinical tests

-The biochemistry and hematology studies showed no significant change before, during or after treatment. There was also no significant difference between the groups.

-6/15 patients in Group I; 2/13 patients in Group II and 2/5 patients in Group III tested positive for drugs in their second test (on the morning of day 3). They were all heavy addicts who had used a lot of drugs before starting the treatment at the center. Furthermore, most of them were admitted to the hospital in the afternoon and had their second test for drugs not more than 72 hours later. By the third urine test 100% of the patients tested negative for drugs.

-11/15 patients in Group I had electroencephalogram within the normal limit after treatment was completed. 4/15 had a Theta wave at a rate of 5-7 cycles/second, with an amplitude of 35-65 mV when breathing deeply.

11/13 in Group II patients had a normal electroencephalogram before and after Heantos treatment, 2/13 had an abnormal electroencephalogram before the treatment and had a normal electroencephalogram after treatment was completed.

-5/15 patients in Group I, 8/13 in Group II tested for depression (Beck Test) did not show signs of depression after treatment. 9/15 in Group I and 5/13 in Group II still showed signs of depression but at different levels.

5. Conclusion

Through our treatment, studies and comparison between the two therapy protocols we found that:
- The use of Heantos 1 at a dose of 5-6 capsules per administration in the detoxification phase and Heantos 3 at a dose of 3-4 capsules per administration in the following stabilizing phase, substantially reduced the proportion and level of muscle contractions and anxious feelings due to addiction, while still ensuring an efficacy in stopping addiction as good as that in the inventor's therapy protocol.

In general we found that the Heantos medicine supports the alleviation of withdrawal from drug addiction. The medicine has effects that reduce cravings, reduce paresthesia, reduce symptoms of digestive disorder, recover the patients' sleep habits and that help the patients recover their health rapidly as well as clear their minds.

6. Recommendation

In cases of drug injecting addicts, a dose of 5 capsules per administration of Heantos 1 is suitable. In cases where the addicts only smoke as well as for healthy addicts, a higher dose could be used.

We suggest that the Heantos scientific advisory council review and approve the use of the modified therapy protocol 2 for further assessment studies.

Comments on:

The study report on the assessment protocol of the Heantos medication in the treatment of drug addicts

Study group:
Le Xuan On, Luu To Phan, Nguyen Manh Hung

1. Document includes:

- study report: 10 pages
- appendix: 10 day clinical observation of 33 addicts in 3 different groups

2. Study objectives

To determine the appropriate dose of Heantos to alleviate withdrawal from drug addiction. Preliminary evaluation of the efficacy in stopping addiction. This objective is in accordance with the requirements of a Phase I clinical study as stipulated in decision 371 on the assessment of traditional medicine, issued by the Ministry of Health.

3. Objects and method of study

3.1 Objects:- identify criteria for admission of addicts suitable for study

3.2 Method of study:

The following steps were implemented:
- admission of patients on a voluntary basis
- recording of the patients' medical history
- treatment according to the approved therapy protocol, recording of clinical results, paraclinical tests and psychological evaluations
- reviewing of treatment results

3.3 Treatment in accordance with therapy protocols 1 and 2 with different dosages in order to identify appropriate dose.

a) First stage: using protocol 1, as provided by the inventor
- first 2 days: administration of Heantos 1, 6-8 capsules twice a day, at an interval of 8-12 hours
- following 3-5 days: administration of Heantos 1, 6-8 capsules once a day, before going to sleep
- following 6-10 days: administration of Heantos 3, 3-4 capsules once a day, before going to sleep

Number of treated patients: 20, of which 15 take the full treatment (Group 1) and 5 who did not receive treatment as they quit within the first 4 days (Group 3, can be regarded as the control group)

- after a preliminary review of the safety and efficacy of Heantos and following the analysis of the Heantos scientific advisory council, the inventor recommends therapy protocol 2

b) Second stage: using protocol 2 as provided by the inventor
- first 3 days: administration of Heantos 1, 5-7 capsules 1-2 times per day, with at least 10 hour intervals. Maximum of 5 doses in three days
- following 4-5 days: administration of Heantos 1, 5-7 capsules once a day, before going to sleep
- following 6-10 days: administration of Heantos 3, 3-4 capsules once before going to sleep

Number of patients treated: 13 (Group 2)

4. Study results

4.1 From the patients' medical history it is evident that 8/33 are HIV positive.

4.2 Clinical results

4.2.1 Side effects and effects on sleep

a) Group 1, 15 patients. The total number of capsules/patient in the first 5 days varies: 38 (1 patient), 40 (1 patient), 44 (6 patients), 50 (3 patients), 52 (2 patients), 54 (2 patients)

a1) Side effects:
- Muscle contractions: 5/15 of which 2 patients experience after 6 capsules on the morning of day 1 and day 2, 3 patients experience after 8 capsules on the morning of day 2, 2 patients in the afternoon of day 1 and day 3. Muscle contractions observed in the 5 patients only in the first 3 days.
-Anxiety: 4/15 of which 2 patients experience after 6 capsules in the morning of day 2, 2 patients experience after 8 capsules in the afternoon of day 2 and 3. Anxiety observed in the 4 patients only in the first 3 days.

a2) Effect on sleep:
4/15 experienced irregular sleep, of which 3 patients fell asleep in the afternoon of day 2 after 6 capsules taken in the morning, 1 patient slept in the morning of day 2 after 8 capsules taken in the afternoon of the day before.

Total number of Heantos 1 capsules taken before patients fell asleep: 1 patient after 14 capsules, 2 patients after 20 capsules, 1 patient after 22 capsules. In the patient who took 22 capsules, muscle contractions were observed after 8 capsules taken in the afternoon of day 3. The other patients didn't show any signs of muscle contraction.

b) Group 2, 13 patients. The total number of capsules/person in the first 5 days varies: 30 (2 patients), 35 (1 patient), 36 (5 patients), 37 (1 patient), 38 (1 patient), 44 (1 patient)

b1) Side effects:
- Myotonia: 2/13 experience an increase in signs of myotonia in the afternoon of day 3 after 6 capsules (with a total capsule intake of 18 and 26)
- Anxiety: 1/13 experience after the first administration of 6 capsules, thereafter no signs of anxiety were shown in the following administrations of the same dose.

In Group 2, 5/13 patients, received a dose of 5 capsules in their 3rd, 4th and 5th administration and thereafter received 6 capsules/administration. There was only 1 patient who received 7 capsules in one administration and 1 patient received 4 capsules in one administration. For all the 5 patients no side effects were observed, in comparison with those from Group 1 who received 6 capsules or 8 capsules per administration.

In Group 2 there were no patients who slept during the day time as was the case in group 1.

c) Group 3. There were no signs of muscle contraction, myotonia or anxiety resulting from insufficient dose of Heantos.

4.2.2 Efficacy of Heantos
As shown on the grade table for Groups 1, 2 and 3:

a) First 4 days: the average grade for group 1 and 2 was lower than that of group 3:

8.8 - 7.6/11.2 on the first day
18.86 - 19.92/22 on the second day
15.93 - 15.15/22.8 on the third day
9.33 - 9.53/18.4 on the fourth day

b) The dose used in therapy protocol 2 has a clinical efficacy similar to that of therapy protocol 1, however protocol 2 appears safer as it gives less side effects and reduces the experience of the side effects.

c) A possible conclusion is that Heantos helps patients overcome withdrawal

from drug addiction more easily, as indicated in the following symptoms:

Jactitation: for 18/28 patients signs of jactitation had stopped by the third day, for 10/28 patients jactitation stopped by the fourth day. The 5 patients who did not take Heantos (Group 3) still experience jactitation.

Paresthesia: Group 1 - 5/15 patients experienced muscle contraction but no signs of paresthesia ("feeling of creeping maggots inside the body"). 4/15 patients experienced anxiety while signs of paresthesia increased in intensity but shortened in time. Group 2 - 10/13 had their signs of paresthesia reduced by 50%.

Sleep: Patients in both Group 1 and 2 slept drowsily for 2-3 hours per night in the first three days. In the following days they slept 4-5 hours per night, more deeply and felt more comfortable after waking up. After one week they were basically back to their normal sleeping habits.

Cravings: Most of the patients experienced no cravings after 4-5 days of treatment.

Other symptoms: Digestive disorder was lessened. Yawning and runny eyes were reduced considerably. Goose flesh and hot/cold spells were still observed in the 5th and 6th days, after which they became less frequent.

Health recovery: By the 2nd and 3rd days of the treatment the patients became alert, attentive and regained their appetite. The activity of the patients became normal by day 4. The average weight gained by the patients was 0.5-2 kilograms.

4.2.3 Paraclinical tests

a) Biochemistry and hematology tests: no significant difference between the groups.

b) Urine tests: 10/33 patients still tested positive for drugs for the second time within 72 hours. By the third test they all tested negative for drugs.

c) Electroencephalography: Group 1 - 11/15 patients had a normal electroencephalogram after Heantos treatment. 4/15 had a Theta wave at a rate of 5-7 cycles/second, with an amplitude of 35-65 mV when breathing deeply. Group 2 - 13/13 patients had a normal electroencephalogram after Heantos treatment.

d) Psychological tests (Beck): 5/14 patients in Group 1, 8/13 in Group 2 did not show signs of depression after the treatment. The rest still showed signs of

depression but at different levels.

5. Comments

5.1 The objectives of the study are clear and in accordance with protocol.

5.2 Method and objects of study: There were a sufficient number of patients for study and the required procedures were carried out completely. The re-evaluation of each of the therapy protocols (with different doses of Heantos) was conducted using the non-collaborating patients as a control group.

5.3 Results

a) Heantos still caused muscle contraction (5/15) and anxiety (4/15) in Group 1 at a dose of 6-8 capsules/administration.

b) Heantos still caused an increase of myotonia (2/13) and anxiety (1/13) in Group 2 at a dose of 6 capsules/administration.

c) Heantos did not cause side effects in all 5 patients of Group 2 treated with a dose of 5 capsules/administration in the 3rd to 5th administrations.

d) Clinical and initial clinical efficacy for both Groups 1 and 2 are similar, basically helping the patients avoid or overcome withdrawal symptoms and to recover their health rapidly.

5.4 The dose of 5 capsules/administration in the first 2-3 days had an efficacy equal to doses of 6 or 8 capsules/administration, however they did not show the side effects characteristic of 6-8 capsules/administration. It may be noticed that the dose of 5 capsules/administration in the first 2-3 days is a suitable amount for using Heantos to alleviate withdrawal from drug addiction. Important note: this amount (0.5 g x 5 capsules x 2 administrations = 5.00 g), contains 6% *Stephania*-extract equal to 0.3 grams of tetrahydropalmatine.

According to Do Tat Loi: Rotundine hydrochloride (powder capsule) 0.05-0.1 g/day
According to Vo Van Chi: Tetrahydropalmatine 0.05 g x 2 = 0.1 g/day
Therefore the above amount is equal to three times the sleeping dose.
The addicts themselves could tolerate a high dose of morphine without intoxication, which indicates that they also might be able to tolerate a high dose of tetrahydropalmatine, or a high dose of seduxen (currently used in other therapy protocols as a tranquilizer). The studies show that the amount of 0.3g/day of tetrahydropalmatine does not cause side effects.

6. I fully concur with the recommendation of the study group for using the dose of 5 capsules/administration twice per day.

There is not sufficient evidence for the recommendation of using a higher dose for the group of addicts who smoke (because the number of patients was only 6/33), and for the healthy addicts (because this specification is not analyzed in the study).

Commentator:

Prof. MD. Hoang Bao Chau
Former Head of Institute of Medicine

Vietnamese documents

- Report on the standardization and stability of HEANTOS
  Insitute for Materia Medica
  Ministry of Health

- Report on the Safety of HEANTOS 1, 2 & 3
  Institute for Drug Quality Control
  Ministry of Health

- Report on the Experimental Pharmacology of HEANTOS 2
  Institute for Drug Quality Control
  Ministry of Health

- Report on the second Pharmacological test of HEANTOS 2
  Institute for Drug Quality Control
  Ministry of Health

- Study report on the assessment protocol of the Heantos medication in the treatment of drug addicts (short-term efficacy tests in humans)
  Central Psychiatric Hospital
  Minsitry of Health

- Comments on the Study Report by Prof. MD. Hoang Bao Chau
  Former Head of Institute of Medicine