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Kanglaite Injection
Study of General Pharmacology

Author: Wang Yicheng
Shanghai Institute of Pharmaceutical Industry (SIPI)

Sponsor: Zhejiang Kanglaite Pharmaceutical Co., Ltd.

Shanghai Institute of Pharmaceutical Industry (SIPI)

Personals Involved in This Study

Study Conductors: Wang yicheng, Yin Chengsheng

Animal Service Manager: Yan Yonggao

Quality Assurance: Liu Quanhai

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Summary

Kanglaite Injection (KLT) is a novel antitumor drug which was made from the efficacious parts extracted from Coicis Semen Yokuinin and is being developed by Zhejiang Kanglaite Pharmaceutical Co., Ltd. according to the traditional Chinese medicine theory. The results of pharmacological study of KLT showed significant antitumor and immune-enhancing effects. The purpose of this study was to determine whether KLT could influence the nervous, respiratory and cardiovascular system of the animals, so as to provide a reference for clinical prescription.

Nervous system: Mice were dosed intravenously with KLT (12.5, 25, 40 ml/kg), and the results of three dose levels of KLT indicated no significant influence on the nervous system of the mice.

Respiratory and cardiovascular system: 8 Beagle dogs, which were divided evenly into two groups, were administered intravenously with KLT or the vehicle at three dose levels of 2.6, 10 and 20 ml/kg. The statistical results indicated that three dose levels of KLT showed no significant influences on the respiratory, blood pressure and the electrocardiogram of dogs.

1. Purpose

The purpose of this study was to determine whether KLT could influence the nervous, respiratory and cardiovascular system of the animals, so as to provide a reference for clinical prescription.

2. Materials

Sample

KLT was provided by Zhejiang Traditional Chinese Medicine Hospital. (Lot No. 920608)

Animals

Kunming mice were supplied by the Shanghai Laboratory Animal Center. Beagle dogs were supplied by Laboratory Animal Center of SIPI.

3. Methods

Nervous system

80 mice of 19-21g body weight, 40 males and 40 females, were divided into four groups which were control, lower dose (0.25 ml), middle dose (0.5 ml) and higher dose (0.8 ml) respectively. The group of control was dosed with saline. The animals were dosed by intravenous route. The variation of each parameter was observed during the 48 hours after treatment and compared with the index before dosing and vehicle control. The indices were recorded according to Irwin's Classification of Action.

Cardiovascular and Respiratory system

8 Beagle dogs, divided into two groups, were anesthetized with 3% sodium pentobarbital intravenously. A polyethylene catheter was introduced into the femoral artery and connected with a pressure transducer. The diaphragm below xiphoid was connected with a mechanical-electrical transducer. ECG was recorded with lead II. The statistical indices were the respiratory frequency and amplitude, heart rate, QRS, TS, T, systolic pressure, diastolic pressure and average pressure respectively. Saline was dripped into the femoral vein before injecting KLT. Lower dose (2.6 ml/kg) or the vehicle was then dripped at 20 drops/min, and increased to 40 drops/min at 30 minutes later. The referring indices were

recorded at the end of dosing and 30', 60', 90', 120' after dosing, the effects of other two dose levels (10 ml/kg, 20 ml/kg) were studied afterwards by the same methods.

Statistics

The all data were expressed as mean \pm standards deviation ($\bar{X}\pm SD$) and the differences were analyzed by Students' T test.

4. Results

Nervous system

There were no abnormal changes in the parameters of nervous system compared with the vehicle control group in mice. KLT showed no significant influence on the nervous system of the mice.

Cardiovascular and respiratory system

The results indicated that three dose levels of KLT showed no significant variation on the respiratory frequency and amplitude. As to the blood pressure, there were no obvious changes on the systolic, diastolic and average pressure after administration with three dose levels of KLT. From the ECG, the rhythm of heart beating could be found to be normal and regular, and the QRS, ST and T not only remained within the normal range, but also showed no significant changes compared with those before dosing. However, the heart rate, decreased after dosing at each time point of three dose levels. Considering the same falling and the same shape of the curves in the group of the corresponding vehicle, therefore the variation of the heart rate could be induced by the corresponding vehicle.

Tab.1 KLT: Effect of KLT on the locomotor activity in mice

Item		Control	0.25ml	0.5ml	0.8ml
Awareness	Nimbleness	4	4	4	4
	Apparou	4	4	4	4
	Flounder	0	0	0	0
	Stereotype	0	0	0	0
Mood	Licking	4	4	4	4
	Shout	0	0	0	0
	Anxiety	0	0	0	0
	Excitement	0	0	0	0
	Fright	0	0	0	0
Movement	Reactivity	4	4	4	4
	Automatic movement	4	4	4	4
	Touch reaction	4	4	4	4
	Pain reaction	4	4	4	4
Center Nerve System	Surprise reaction	0	0	0	0
	Vertical tail	0	0	0	0
Excitability	Tremor	0	0	0	0
	Spasm	0	0	0	0
	Convulsion	0	0	0	0
Attitude	Body potential	4	4	4	4
	Waist potential	4	4	4	4
Ataxia	Titubation	0	0	0	0
	Different	0	0	0	0
	Righting reflex	0	0	0	0
Musculotonia	Four limb tension	4	4	4	4
	Shinning	4	4	4	4
	Body concave	0	0	0	0
	Body tension	4	4	4	4

	Waist tension	4	4	4	4	4
Automatic Nerve System function	Wiggle	0	0	0	0	0
	Piss	0	0	0	0	0
	Saliva	0	0	0	0	0
	Vertical hair	0	0	0	0	0
	Dacryorrhea	0	0	0	0	0
Death		0	0	0	0	0

Tab.2 KLT: Effect of KLT on the respiration in Beagle dogs

		Pretest	0	30	60	90	120min	
R/min iv. qtt n=4	2.6 ml/kg	\bar{X}	10.9	11.3	10.3	9.5	9.4	9.9
		SD	1.7	2.2	2.5	2.6	1.5	2.1
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	10.9	9.9	9.3	9.2	10.2	10.5
		SD	1.7	2.1	2.9	2.6	1.7	1.2
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	10.9	10.5	10.4	10.5	9.4	8.9
		SD	1.7	1.2	1.9	1.5	1.4	1.6
		p		>0.05	>0.05	>0.05	>0.05	>0.05
R mm iv. qtt n=4	2.6 ml/kg	\bar{X}	17.9	18.8	18.1	18.6	20.2	18.9
		SD	6.2	8.4	5.7	6.1	7.8	6.8
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	17.9	18.9	18.0	19.0	21.3	18.4
		SD	6.2	6.8	6.7	8.7	8.5	7.4
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	17.9	18.4	19.5	19.1	20.7	20.0
		SD	6.2	7.4	7.8	8.0	9.6	8.7
		p		>0.05	>0.05	>0.05	>0.05	>0.05

Tab.3 KLT: Effect of KLT on the systemic blood pressure in Beagle dogs

		Pretest	0	30	60	90	120min	
SBP MmHg iv. qtt n=4	2.6 ml/kg	\bar{X}	212.5	204.2	202.5	196.3	201.3	205.0
		SD	27.2	27.9	26.6	26.5	23.2	26.1
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	212.5	205.0	195.0	200.0	198.8	195.0
		SD	27.2	26.1	26.8	27.4	23.9	21.6
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	212.5	195.0	192.5	196.3	198.8	193.8
		SD	27.2	21.6	26.6	23.2	24.9	20.6
		p		>0.05	>0.05	>0.05	>0.05	>0.05
DBP mmHg iv. qtt n=4	2.6 ml/kg	\bar{X}	132.5	128.8	126.3	122.5	128.8	125.0
		SD	14.4	12.5	17.0	18.5	20.9	17.3
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	132.5	125.0	126.3	124.3	124.8	121.3
		SD	14.4	17.3	17.9	17.5	17.3	13.1
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	132.5	121.3	121.3	123.8	128.8	132.5
		SD	14.4	13.1	19.3	11.1	11.1	8.7
		p		>0.05	>0.05	>0.05	>0.05	>0.05
MAP mmHg iv. qtt n=4	2.6 ml/kg	\bar{X}	151.3	148.8	146.3	141.3	145.0	143.8
		SD	16.5	13.1	16.5	14.9	16.8	12.5
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	151.3	143.8	141.3	142.5	142.5	142.5
		SD	16.5	12.5	14.9	14.4	12.6	10.4
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	151.3	142.5	142.5	143.8	148.8	146.3
		SD	16.5	10.4	12.6	11.1	10.3	11.1
		p		>0.05	>0.05	>0.05	>0.05	>0.05

Tab.4 KLT: Effect of KLT on the electrocardiogram (ECG) in Beagle dogs

			Pretest	0	30	60	90	120min
HR/min iv. qtt n=4	2.6 ml/kg	\bar{X}	182.9	171.4	161.2	153.0	154.8	155.7
		SD	26.4	29.2	32.7	23.0	17.2	22.6
		p		<0.05	<0.05	<0.01	<0.05	<0.01
	10 ml/kg	\bar{X}	182.9	155.7	155.0	154.5	158.1	150.2
		SD	26.4	22.6	24.2	19.3	19.8	13.8
		p		<0.01	<0.01	<0.05	<0.01	<0.05
	20 ml/kg	\bar{X}	182.9	150.2	150.1	151.1	147.8	146.9
		SD	26.4	13.8	13.9	12.9	15.6	16.6
		p		<0.05	<0.05	<0.05	<0.01	<0.01
QRS S' iv. qtt n=4	2.6 ml/kg	\bar{X}	0.047	0.0487	0.048	0.0475	0.0475	0.0488
		SD	0.0035	0.0025	0.004	0.0029	0.005	0.0025
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	0.047	0.0488	0.049	0.048	0.0475	0.0488
		SD	0.0035	0.0025	0.0025	0.0024	0.0029	0.0025
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	0.047	0.0488	0.0488	0.0476	0.048	0.0475
		SD	0.0035	0.0025	0.0025	0.0028	0.0024	0.00288
		p		>0.05	>0.05	>0.05	>0.05	>0.05
ST mv iv. qtt n=4	2.6 ml/kg	\bar{X}	0.0525	0.05	0.04	0.05	0.0425	0.04
		SD	0.02	0.02	0.01	0.02	0.005	0.027
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	0.0525	0.04	0.055	0.005	0.0475	0.0475
		SD	0.02	0.027	0.002	0.02	0.015	0.015
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	0.0525	0.0475	0.0425	0.0375	0.045	0.0425
		SD	0.02	0.015	0.019	0.02	0.02	0.0189
		p		>0.05	>0.05	>0.05	>0.05	>0.05
T mv iv. qtt n=4	2.6 ml/kg	\bar{X}	0.16	0.17	0.18	0.16	0.17	0.18
		SD	0.06	0.07	0.06	0.06	0.07	0.08
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	0.16	0.18	0.16	0.16	0.18	0.17
		SD	0.06	0.08	0.06	0.06	0.07	0.08
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	0.16	0.17	0.19	0.17	0.17	0.17
		SD	0.06	0.08	0.07	0.08	0.08	0.08
		p		>0.05	>0.05	>0.05	>0.05	>0.05

Tab.5 KLT: Effect of vehicle on the electrocardiogram (ECG) in Beagle dogs

			Pretest	0	30	60	90	120min
HR/min iv. qtt n=4	2.6 ml/kg	\bar{X}	174.8	107.1	133.6	141.4	141.4	139.0
		SD	17.7	26.6	31.0	36.9	13.3	24.0
		p		<0.05	<0.05	<0.01	<0.05	<0.01
	10 ml/kg	\bar{X}	174.8	132.2	135.8	136.9	139.1	133.4
		SD	17.7	32.3	22.3	18.0	23.9	22.8
		p		<0.05	<0.05	<0.01	<0.05	<0.05
	20 ml/kg	\bar{X}	174.8	125.8	136.5	143.3	136.2	128.4
		SD	17.7	20.2	26.1	19.9	22.0	27.8
		p		<0.01	<0.05	<0.05	<0.05	<0.05
QRSS' iv. qtt n=4	2.6 ml/kg	\bar{X}	0.046	0.045	0.046	0.048	0.047	0.048
		SD	0.0026	0.003	0.0021	0.003	0.0025	0.001
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	0.046	0.048	0.048	0.047	0.047	0.046
		SD	0.0026	0.001	0.0012	0.0017	0.0009	0.0024
		p		>0.05	>0.05	>0.05	>0.05	>0.05

STmv iv. qtt n=4	20 ml/kg	\bar{X}	0.046	0.047	0.0488	0.048	0.047	0.048
		SD	0.0026	0.0014	0.0029	0.0016	0.0032	0.0038
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	2.6 ml/kg	\bar{X}	0.035	0.029	0.036	0.033	0.033	0.037
		SD	0.013	0.012	0.0079	0.015	0.018	0.018
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	0.035	0.02	0.03	0.03	0.03	0.003
		SD	0.013	0.008	0.014	0.002	0.002	0.002
		p		>0.05	>0.05	>0.05	>0.05	>0.05
20 ml/kg	\bar{X}	0.035	0.028	0.035	0.033	0.033	0.028	
	SD	0.013	0.009	0.019	0.018	0.018	0.015	
	p		>0.05	>0.05	>0.05	>0.05	>0.05	
Tmv iv. qtt n=4	2.6 ml/kg	\bar{X}	0.175	0.175	0.150	0.150	0.16	0.16
		SD	0.12	0.1	0.07	0.06	0.075	0.07
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	0.175	0.17	0.15	0.15	0.15	0.15
		SD	0.12	0.08	0.06	0.06	0.06	0.06
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	0.175	0.16	0.15	0.16	0.15	0.16
		SD	0.12	0.05	0.06	0.07	0.07	0.06
		p		>0.05	>0.05	>0.05	>0.05	>0.05

Tab.6 KLT: Effect of vehicle on the respiration in Beagle dogs

		Pretest	0	30	60	90	120min	
R/min n=4	2.6 ml/kg	\bar{X}	10.2	9.03	9.94	10.95	10.95	11.93
		SD	3.51	2.08	2.33	3.84	2.89	3.23
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	10.2	9.67	11.85	11.43	11.4	12.0
		SD	3.51	2.08	3.62	2.64	3.37	3.65
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	10.2	11.74	11.0	11.5	12.0	11.73
		SD	3.51	4.29	3.28	3.43	3.6	4.28
		p		>0.05	>0.05	>0.05	>0.05	>0.05
R mm n=4	2.6 ml/kg	\bar{X}	14.5	15.0	14.6	14.5	14.4	14.8
		SD	2.6	5.5	5.1	4.7	5.1	5.1
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10 ml/kg	\bar{X}	14.5	14.8	15.2	15.1	15.5	16.4
		SD	2.6	5.5	5.5	4.9	3.7	5.1
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20 ml/kg	\bar{X}	14.5	14.8	14.7	15.0	14.9	15.0
		SD	2.6	4.7	4.3	5.2	5.2	2.9
		p		>0.05	>0.05	>0.05	>0.05	>0.05

Tab.7 KLT: Effect of vehicle on the systemic blood pressure in Beagle dogs

			Pretest	0	30	60	90	120min
SBP MmHg n=4	2.6ml/kg	\bar{X}	200.0	198.8	205.0	201.2	191.3	200.0
		SD	12.2	11.1	33.9	32.7	6.3	23.8
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10	\bar{X}	200.0	202.5	195.8	188.8	202.5	191.3
		SD	12.2	18.5	19.9	8.5	20.6	12.5
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20	\bar{X}	200.0	200.0	190.0	200.0	188.8	187.5
		SD	12.2	21.6	7.1	24.8	24.9	17.0
		p		>0.05	>0.05	>0.05	>0.05	>0.05
DBP mmHg n=4	2.6	\bar{X}	131.3	138.7	136.3	133.8	128.8	131.3
		SD	10.3	2.5	9.5	12.5	2.5	4.8
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10	\bar{X}	131.3	140.0	136.3	131.5	131.3	131.8
		SD	10.3	7.1	9.5	3.0	7.5	2.4
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20	\bar{X}	131.3	140.0	130.0	135.0	131.8	132.8
		SD	10.3	14.1	4.1	10.8	2.4	6.4
		p		>0.05	>0.05	>0.05	>0.05	>0.05
MAP mmHg n=4	2.6	\bar{X}	150.0	153.8	154.5	155.0	147.5	148.8
		SD	8.2	4.8	12.5	14.7	6.5	6.3
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	10	\bar{X}	150.0	157.0	155.0	148.8	147.5	147.7
		SD	8.2	10.9	14.1	4.8	6.5	5.3
		p		>0.05	>0.05	>0.05	>0.05	>0.05
	20	\bar{X}	150.0	153.8	150.0	147.5	147.8	147.5
		SD	8.2	17.9	7.1	6.5	5.3	5.0
		p		>0.05	>0.05	>0.05	>0.05	>0.05