

中 药 研 究

择时服用淫羊藿对性激素水平的影响

王 菲* 郑 杨* 肖洪彬* 周 敏* 刘艳旭* 指导:李国清*

摘要 为了证实《黄帝内经》“择时服药”理论的科学性,本研究通过择时服用淫羊藿对幼鼠性激素水平的影响,探讨服药时间与药效的关系。结果显示:(1)淫羊藿煎剂具有性激素样作用,可以使雌性小鼠子宫增重,雌二醇(E_2)含量升高,雄性小鼠血清睾酮(T)含量升高。(2)卯时、酉时服药对雌性小鼠子宫增重, E_2 含量升高,雄性小鼠血清 T 含量升高有不同程度影响,卯时作用强于酉时。表明补肾壮阳药清晨服用效果最佳。

主题词 性激素/代谢 淫羊藿/治疗应用 择时服药

人体具有多种生理时间节律,药物在体内代谢同样具有节律性。“择时服药”是将时间因素与药物疗效紧密结合,利用生物体生理性节律和病理性周期变化及药物的时间效应等特点,选择最佳时间服药,使之最大程度地发挥药效并减免毒副作用和减少使用剂量的一种治疗方法。两千多年前《黄帝内经》就已认识到“择时服药”的重要性。主张“因天时而调气血”、“春夏养阳,秋冬养阴”以及“日未出时吐之”。本文从昼夜节律角度研究“择时服药”理论,选用临床常用补肾壮阳药淫羊藿,通过对雌性小鼠子宫、雌二醇(E_2)和雄性小鼠血清睾酮(T)的影响来观察其类性激素样作用,并为壮阳药的择时服用提供一定的实验依据。

1 实验材料

1.1 实验动物:昆明种健康纯系幼年小鼠,3 周龄,雌性或雄性,体重 11~13g,由黑龙江中医药大学实验动物中心提供。

1.2 实验药物:(1)淫羊藿购于黑龙江中医药大学科研门诊,经黑龙江中医药大学附属第一医院药剂科做外观鉴定。按传统方法制成水煎液,含生药 1g/ml。(2)乙烯雌酚、甲基睾丸素片由天津力生制药厂生产。(3)主要试剂: ^{125}I —血清 T 放射免疫分析试剂盒、 E_2 放射免疫分析试剂盒,购自中国原子能科学研究院。

1.3 主要仪器:JN-A 型精密扭力天平(上海产);FT-603 型闪烁计数器(国营二六一厂制造)。

2 实验方法

2.1 雌性激素样作用实验:取一定数量的雌性小鼠,分为卯时(05:00~07:00)和酉时(17:00~19:00)两个时辰进行实验,每个时辰分为 5 组,共 10 组,即生理盐水 I 组、生理盐水 II 组、乙烯雌酚对照组(以下称对照组)、淫羊藿高、低剂量组(以下称高、低剂量组)。除生理盐水 I 组给予等量生理盐水外,其余各组按每日 0.3mg/kg 灌服乙烯雌酚,连续给药 3 日。从第 4 日开始,每日分卯时、酉时两个灌服,生理盐水 I 组、生理盐水 II 组,按每日 20ml/kg 灌服生理盐水;对照组按每日 0.15mg/kg 灌服乙烯雌酚;高、低剂量组每日分别按 10g/kg、20g/kg 灌服淫羊藿煎剂,连续给药 14 天。于末次给药后禁食 24 小时,取血,离心取血清备用,然后将动物处死,切取子宫称重,换成子宫指数(mg/100g)。取上述备用血清测定 E_2 含量。

2.2 血清 T 含量测定:取一定数量的雄性小鼠,分为卯时和酉时两个时辰进行实验,每个时辰分为 4 组,共 8 组,即生理盐水组,每日给同体积水;甲基睾丸素对照组,每日灌服 10mg/kg 甲基睾丸素;淫羊藿高、低剂量组,每日分别灌服 10g/kg 和 2g/kg 淫羊藿煎剂。以上各组每日分酉时、卯时两个时辰灌服,连续给药 14 天。于末次给药后禁食 24 小时,取血,离心取血清,测定 T 含量。

3 结果

3.1 择时服药淫羊藿对雌性幼鼠子宫重量及血清 E_2 的影响:表 1 示,卯时、酉时各给药组分别同生理盐水 I 组、II 组相比,幼鼠子宫重量明显增重,血清 E_2 含量明显升高($P<0.01$),并且淫羊藿高剂量组作用强度明显优于低剂量组。卯时同酉时两个时辰相比较,高、低剂量组卯时的子宫增重、血清 E_2 含量明显高于酉时($P<0.05$)。说明淫羊藿口服给药具有雌激素样作用,而且择时服药(卯时、酉时)具有明显的差异性,卯时优于酉时。

3.2 择时服用淫羊藿对雄性幼鼠血清 T 含量的影响:表 2 示,卯时、酉时各给药组分别同生理盐水组相比,对幼鼠血清 T 含量有明显升高的作用($P<0.01$),

* 黑龙江中医药大学,哈尔滨市动力区和平路 14 号(150040)

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表1 择时服用淫羊藿对雌性幼鼠子宫重量
及血清 E₂ 的影响($\bar{x} \pm s$)

组别		子宫重量(mg/100g)	E ₂ (ng/dl)
生理盐水 I 组	卯时	96.2 ± 20.2(12)	71.41 ± 13.62(13)
	酉时	92.7 ± 21.6(13)	70.05 ± 10.61(12)
生理盐水 II 组	卯时	92.7 ± 13.1(12)	70.82 ± 13.58(14)
	酉时	97.3 ± 14.5(12)	71.26 ± 12.56(13)
高剂量组	卯时	386.3 ± 51.4(11)*△	129.22 ± 23.88(10)*△
	酉时	264.2 ± 33.9(10)*	108.00 ± 16.47(11)*
低剂量组	卯时	229.3 ± 40.4(11)*△	107.69 ± 13.11(11)*
	酉时	189.8 ± 35.5(11)*	94.33 ± 14.22(10)*
对照组	卯时	499.9 ± 98.9(10)*	149.10 ± 24.43(9)*
	酉时	410.2 ± 93.6(9)*	138.01 ± 18.11(10)*

与生理盐水 I、II 组比较, * $P < 0.01$; 与本组酉时比较, △ $P < 0.05$; 括号内为鼠数

表2 择时服用淫羊藿对雄性幼鼠血清 T 含量的影响($\bar{x} \pm s$)

组别		鼠数	T(ng/dl)
生理盐水组	卯时	14	69.61 ± 10.89
	酉时	14	70.13 ± 10.68
高剂量组	卯时	13	145.10 ± 25.35*△
	酉时	14	121.00 ± 23.12*
低剂量组	卯时	13	120.91 ± 15.20*△△
	酉时	12	101.44 ± 14.04*
甲基睾丸组	卯时	13	164.51 ± 32.42*
	酉时	12	153.46 ± 31.98*

与同时间生理盐水组比较, * $P < 0.01$; 与本组酉时比较, △ $P < 0.05$, △△ $P < 0.01$

淫羊藿高剂量组作用强度明显优于低剂量组;卯时同酉时两个时辰相比较,高、低剂量组卯时血清 T 含量明显高于酉时($P < 0.05$)。说明淫羊藿口服给药具有雄激素样作用,可以使幼鼠血清 T 含量升高,并且择时服用具有明显的差异性,卯时优于酉时。

4 讨论

中医理论认为,人体存在与昼夜相应的阴阳消长盛衰节律。卯时为日出之时,“朝则人气始生”,此时服用补肾壮阳药可借助人体阳气欲盛之势与药物作用协调一致,通过改善机体内的调节机制发挥药物作用。历

代医家大多主张清晨服用补肾壮阳药^[1]。李永浩等观察到择时服用益气补血汤治疗化疗期间白细胞减少,早、午服用优于早、晚服用,择时用药组化疗期间白细胞计数降低程度轻且回升快^[2]。黄青春报告,在相同条件下,采用择时服药改善肾功能和恢复肾阳虚功能状态比常规用药效果更佳^[3]。

淫羊藿是中医常用药,具有补肾壮阳,益精起萎,强腰固冲作用。现代药理研究已证明,淫羊藿有类性激素样作用^[4~6]。本文选用淫羊藿作为实验药物的目的,是在证实淫羊藿具有类性激素样作用的基础上,选择卯时、酉时两个不同时辰进行实验,以证明《黄帝内经》“择时服药”的科学性。

结果表明,淫羊藿煎剂具有性激素样作用,可以使雌性小鼠子宫增重, E₂ 含量升高,雄性小鼠血清 T 含量升高。卯时、酉时服药对雌性小鼠子宫增重、E₂ 含量升高、雄性小鼠血清 T 含量升高有不同程度影响,卯时作用强于酉时。

本文通过择时服用淫羊藿对雌性小鼠子宫、E₂ 和雄性小鼠血清 T 的实验观察,证实《黄帝内经》“择时服药”理论具有一定的科学性。补肾壮阳药清晨服用效果最佳,提示中药制剂的疗效,不但与剂量有关,而且相同剂量在不同时间给药,其作用强度是不同的。

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至错误的认识,为辛温药的正确运用建立了规矩准绳。在当前“火神心法”尤其值得深入研究,继承发扬。但应当指出的是,对于“火神心法”的正确运用,有一个长期临床历练的过程。在这一过程中,其关键点有二,一是正确辨证,只有真正掌握了郑氏提出的辨证要点,才能做到立法正确,用药无误。二是遣方用药循序渐进,遣方不要一下手就选取药力最雄峻的“重剂”,心知“重剂”所在,选用时退而求其次,再步步推进,层层深入,逐渐到位。既给自己留下了广阔的思维空间,又可防避

误诊误治,万一有误,也所误不深,救治不难;用药量不要轻率突破常规,而应从常规剂量开始,在实践中逐步把握不同程度的各种阳虚病症的最佳用量。只要把握住了上述关键,就能真正体会到学术上“无限风光在险峰”的莫可穷尽的理趣。

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ABSTRACTS FROM ORIGINAL ARTICLES

Clinical Observation on Treatment of 288 Cases of Correlative Gastric Diseases Infected by Pyloric Helicobacterium with Kang Wei Granules

Chen Feisong, Wei Beihai, Yao Wei, et al.

Kang Wei Granules which can strengthen the spleen, replenish Qi, clear away heat and remove dampness was used to treat 288 cases of correlative gastric disease infected by pyloric helicobacterium. Seventy-four cases were treated with triple therapy (Bismuth being the mainly ingredient) as control group. Results indicated that the treatment group was significantly superior to the control group in improvement of main symptoms, especially for the types of deficiency of spleen and stomach, and internal accumulation of dampness-heat ($P < 0.05$). There was no significant difference between the two groups in gastroscopy, pathological examination and the positive grade of pyloric helicobacterium ($P > 0.05$). It is suggested that Kang Wei Granules has a better clinical therapeutic effect for treatment of correlative gastric disease infected by pyloric helicobacterium.

Authors' address: Beijing Municipal Institute of TCM, Beijing 100010

Key words: Gastric diseases/microbiology infection of pyloric helicobacterium/ Chinese drug therapy @Kang Wei Granules
(Original article on page 599)

Effects of Jin Long She Oral Liquid Combined with Shen Mai Injectio on Tumor Marker and Immunological Function in the Patient of Intermediate and Late Gastric Cancer

Qin Zhifeng, Wei Pinkang, Li Xiangyong

Jin Long She Oral Liquid combined with Shen Mai Injectio was used to treat 35 cases of intermediate and late gastric cancer as treatment group, and chemotherapy was used to treat 16 cases as control. Results indicated that the index of physical strength (Karnofsky score assessment) and natural killer (NK) cell activity in the treatment group increased significantly, CD₄, CD₄/CD₈ increased and CD₈ decreased as compared with those before treatment ($P < 0.05$). In the chemotherapy group besides CD₄/CD₈ improved slightly, NK cell activity and CD₄, CD₈ decreased; tumor marker CEA and CA₁₉₋₉ decreased to a certain degree in the two groups, with no significant difference compared with those before treatment. It is suggested that combination of Jin Long She Oral Liquid and Shen Mai Injectio has a good effect on intermediate and late gastric cancer.

Authors' address: Shanghai Changzheng Hospital, Shanghai 200003

Key words: Gastric tumor/traditional drug therapy Shen Mai Injectio/therapeutic use @Jin Long She Oral Liquid
(Original article on page 605)

Effect of Administration of Herba Epimedii at the Optimal Time on Levels of Sexual Hormones

Wang Fei, Zheng Yang, Xiao Hongbin, et al

In order to confirm the theory of administration at the optimal time in *The Yellow Emperor's Internal Classic*, effects of administration of Herba Epimedii at the optimal time on the level of sexual hormones in young mice were investigated to explore the relationship between the time of administration and the effect. Results indicated that (1) Yin Yang Huo Decoction had sexual hormone-like actions, increasing weight of uterus and serum estradiol (E₂) content in the female mice, increasing serum testosterone (T) content in the male mice; (2) The administration at Mao (the period of the day from 5 a. m. to 7 a. m.) and You (from 5 p. m. to 7 p. m.), hours influenced the increases of uterus weight and serum E₂ content in the female mice and serum T content in the male mice to a certain degree, the action at Mao being stronger than that at the You. It is suggested that administration for tonifying the kidney and strengthening Yang in the early morning has the best effect.

Authors' address: Helongjiang University of TCM, Harbin 150040

Key words: Sexual hormones/metabolism Herba Epimedii
(Original article on page 619)

Cytologic Study on Prevention and Treatment of Primary Osteoporosis with Chinese Drugs for Tonifying the Kidney

Shi Yinyu, Zhan Hongsheng, Zhao Yongfang, et al.

In order to compare differences of effects of complex prescription for reinforcing the kidney on osteoblast (OB) and osteoclast (OC), MTT method was used to determine proliferous capability of OB, bone lacuna count was used for quantitative assessment of absorbent activity of OC. Results showed that the mean influencing rate of Jin Gui Shen Qi Pill, Bu Shen Yi Jing Prescription, Zhi Bai Di Huang Pill, and Western medicine Premarin tablet for proliferous capability of OB was 159.2%, 121.5%, 21.6% and 75.7% respectively; the mean influencing rate for bone lacuna count was 50.2%, 21.0%, 19.8% and 38.1% respectively, suggesting that the drug for even reinforcing Yin and Yang can improve proliferation of OB and inhibit activity of OC, and increase of the drug for warming Yang can strengthen the promoting action on proliferation of OB, but increase of the drug for nourishing Yin had opposed action, the drugs for nourishing Yin plus the drugs for purging the pathologic fire can inhibit activity of OC and proliferation of OB.

Authors' address: Shuguang Hospital Affiliated to Shanghai University of TCM, Shanghai 200021

Key words: Osteoporosis/bone and bone tissue/cytology
(Original article on page 621)