

## 地尔硫草与普罗帕酮在家兔体内的药动学相互作用研究

印绮平 王宏图 张静华 施孝金

(上海医科大学华山医院临床药理学研究室 上海 200040)

**摘要** 6 只家兔随机交叉实验,分别单用地尔硫草、普罗帕酮或合用两药,结果发现合用两药后,普罗帕酮的消除速率常数  $K_e$  和清除率  $cl_s/F$  较单用时明显减小,消除半衰期  $t_{1/2}(k_e)$  平均延长 0.701 小时,第一峰浓度和第二峰浓度分别升高 85.74% 和 75.55%,  $AUC_{0-\infty}$  增大 56.75%, 且均有显著性意义。地尔硫草的  $cl_s/F$  在合用药后显著降低,  $V_d/F$  显著减小,地尔硫草及其活性代谢物去乙酰地尔硫草的峰浓度则分别增大 129.83% 和 119.13%。表明两药合用后普罗帕酮的肝脏代谢受到抑制,同时普罗帕酮也影响了地尔硫草的体内吸收或处置过程。提示临床两药合用时应同时监测患者血液,避免不良反应的发生。

**关键词** 地尔硫草;普罗帕酮;药动学相互作用

### A study of pharmacokinetic interaction between diltiazem and propafenone in rabbits

Yin Qiping, Wang Hongtu, Zhang Jinghua, Shi Xiaojin

(Department of Pharmacy, Huashan Hospital

Shanghai Medical University 200040)

**ABSTRACT** A balanced, randomized and crossover study was conducted in six rabbits. Each rabbit was given diltiazem/propafenone alone or in combination. Pharmacokinetic parameters of propafenone were significantly changed when coadministration with diltiazem. Its  $K_e$  and  $cl_s/F$  were both  $C_{max}$  and  $AUC_{0-\infty}$  were increased. On the other hand, some pharmacokinetic parameters of diltiazem were also changed after combination treatment. Its  $cl_s/F$  and  $V_d/F$  were both decreased, while its  $C_{max}$  was elevated. In addition,  $C_{max}$  of deacetyldiltiazem, an active metabolite of diltiazem, was also elevated. It was suggested that the metabolism of propafenone in liver may be inhibited by diltiazem and meanwhile propafenone may have an effect on the absorption or elimination of diltiazem. From the above result, it is essential for clinicians to monitor drug concentration when diltiazem is coadministered with propafenone, and in some case, dosage of these drugs should be adjusted.

**KEY WORDS** diltiazem, propafenone pharmacokinetic interaction

地尔硫草(diltiazem DTZ)为苯并杂类钙拮抗剂,用于治疗心绞痛和高血压。普罗帕酮(propafenone PPF)属 I<sub>c</sub> 类抗心律失常药,用于治疗室上性、室性心动过速等。由于治疗的需要,临床上有时将 DTZ 和 PPF 联

合应用。但近来不良反应的报道提示<sup>[1]</sup>,两者不仅在药效学上存在协同作用,可能在药动学上也存在着相互作用,本文就它们之间的药动学相互作用作一探讨和研究。

#### 一、实验材料和条件

DTZ片:30mg/片,上海延安制药厂生产(批号921009);PPF片:50mg/片,上海东方制药厂生产(批号940402)。

仪器:Waters高效液相色谱仪,色谱柱规格200×4mm ID不锈钢柱。内填固定相YWG-C<sub>18</sub>(10μm)。岛津SPD-10A可变波长紫外检测器

## 二、实验方法

### 1. 实验对象

选取健康新西兰种家兔6只,雌雄各半,体重2.0±0.5kg。

### 2. 实验设计

将6只家兔随机分为3组,每组2只,分别先后给予DTZ36mg/kg,PPF50mg/kg及合用两药。清洗期两周。家兔每次试验前禁食12h,给药后4h再喂一饲料。于给药前及给药后0.25,0.5,0.75,1.0,1.5,2.0,3.0,4.0,6.0,8.0,10.0,12.0,14.0h分别采血3ml,离心后血清于-20℃保存,直至测定。

### 3. 血样分析

1ml血清中加入内标(美托洛尔)适量,用0.5ml pH9.0硼酸缓冲液碱化后,加入5ml重蒸乙醚,涡旋1min,4000rpm离心10min,上清液移至另一尖底试管中,用N<sub>2</sub>吹干,40μl 0.02mol/L稀硫酸溶解残渣,取25μl进样,HPLC分析。流动相为甲醇:水:0.3mol/L醋酸铵:二氯甲烷:三乙胺二65:25:5:5:0.5(V:V)流速1.2ml/min,柱温45±0.5℃。PPF、DTZ、DTZ代谢物去乙酰地尔硫草(deacetyldiltiacem, DADZ)及内标的检测波长分别为254nm、238nm、238nm和280nm。PPF、DTZ和DADZ的线性范围分别为20~1000ng/ml,10~1000ng/ml和0~1000ng/ml,三者的最低检测浓度均可达10ng/ml,方法回收率接近于100%,天内天间RSD小于10%符合测定要求

## 三、实验结果和处理

测得PPF、DTZ和DADZ的各药一时数据,采用3P87统计矩程序处理,求算有关药

动力学参数:Ke, t<sub>1/2</sub>(ke)、MRT、AUC<sub>0-∞</sub>cls/F、Vd/F;用三点抛物线拟合法求算达峰时t<sub>max</sub>和峰浓度C<sub>max</sub>;然后用自身对照t检验法对家兔单、合用药时的各药动力学参数进行统计学处理,以t值或p判别其间是否存在显著性差异。结果见表1、2、3。

## 四、讨论

1. 用3P87程序进行房室模型拟合时,发现DTZ在大多数家兔的体内过程符合二室模型,少数家兔则用一室模型拟合更合适。这种体内过程的差异,国外文献也见有报道<sup>[2]</sup>为统一和方便起见,采用3P87统计矩程序处理DTZ的药时数据。PPF、DADZ的药时曲线均有双峰,故也用统计矩程序处理。

2. 合用两药后,PPF的ke显著减小, t<sub>1/2</sub>(ke)平均延长0.701h,第一峰浓度C<sub>max1</sub>和第二峰浓度C<sub>max2</sub>分别增高85.74.%和75.55%,AUC<sub>0-∞</sub>增大56.75%。表明合用两药后PPF的代谢有所减慢。有资料表明<sup>[3]</sup>,DTZ为一潜在的肝药酶抑制剂,因此它有可能通过抑制肝药酶活性而抑制了PPF在肝脏的氧化代谢。合用药后PPF的cls/F明显减小,可能由于cls的减小或(和)F的增大引起,DTZ是否影响PPF吸收,需要进一步实验确证。

3. 合用两药后,DTZ的cls/F和Vd/F均显著减小,其C<sub>max</sub>和AUC<sub>0-∞</sub>分别增加129.83%和85.25%。同时DTZ的代谢物DADZ的峰浓度在合用药后也有明显升高。只是PPF是否增加了DTZ的吸收,抑或使得DTZ的全身清除率cls和表观分布体积Vd变小,也有待进一步的实验确证。

4. 本实验结果表明,合用DTZ和PPF时,不仅PPF的代谢减慢,引起其血浓度升高而可能产生不良反应,同时DTZ和DADZ的血浓度升高过多同样也会出现毒副作用。提示临床合用两药时,应同时对药效和血浓进行仔细观察和监测,并根据患者情况适当调整给药剂量,以避免发生不良反应。

表 1 DTZ 对 PPF 药动学参数的影响

参 数	1	2	3	4	5	6	$\bar{X} \pm SD$	t 值 P
Ke	0.5384	0.4187	0.3408	0.3342	0.3768	0.2470	0.3760±0.0978	3.044 * <0.05
(h <sup>-1</sup> )	0.2778	0.2616	0.3016	0.2216	0.3023	0.2282	0.2655±0.035	
t <sub>1/2</sub> (ke)	1.287	1.655	2.033	2.074	1.839	2.806	1.949±0.509	3.960 * <0.05
(h)	2.495	2.649	2.298	3.127	2.292	3.037	2.650±0.361	
Vd/F	64.829	95.660	313.826	165.164	64.626	450.676	192.464±157.57	1.36>0.05
(L.kg <sup>-1</sup> )	98.801	145.348	192.397	83.876	61.641	242.550	137.436±69.625	
cls	34.904	40.053	106.952	55.198	24.351	111.317	62.129±37.768	3.616 * <0.05
L.(h.kg) <sup>-1</sup>	27.447	38.023	58.027	18.587	18.634	55.350	36.011±17.559	
AUC <sub>0-∞</sub>	1.719	1.498	0.561	1.087	2.464	0.539	1.311±0.740	2.672 * <0.05
ug.h.ml <sup>-1</sup>	2.186	1.578	1.034	3.228	3.220	1.084	2.055±0.996	
MRT	5.056	5.248	3.678	3.195	4.559	4.745	4.376±0.766	0.238>0.05
(h)	5.332	4.660	4.009	3.910	4.646	3.507	4.344±0.659	
t <sub>max1</sub>	0.625	0.569	0.780	0.302	0.733	0.537	0.591±0.170	0.132>0.05
(h)	0.672	0.580	0.762	0.459	0.569	0.469	0.585±0.117	
t <sub>max2</sub>	5.639	5.416	3.018	1.409	4.159	2.304	3.658±1.707	1.800>0.05
(h)	3.060	2.959	2.984	1.482	4.497	2.219	2.700±1.199	
Cmax1	99.110	102.305	115.554	453.178	385.360	104.181	226.615±154.961	3.534 * <0.05
(ng.ml <sup>-1</sup> )	212.439	292.288	228.553	863.346	563.522	365.564	420.925±251.458	
Cmax2	326.369	245.586	205.354	353.04	339.456	85.181	259.164±103.078	3.616 * <0.05
(ng.ml <sup>-1</sup> )	438.824	385.546	227.942	735.108	649.483	292.887	454.965±199.602	

注:每组上行为单用 PPF 时的 PPF 药动学参数,下行为合用 PPF 和 DTZ 时的 PPF 药动学参数

表 2 PPF 对 DTZ 药动学参数的影响

参 数	1	2	3	4	5	6	$\bar{X} \pm SD$	t 值 P
Ke	0.3328	0.1484	0.2949	0.2292	0.2472	0.3804	0.27722±0.082	0.0306>0.05
(h <sup>-1</sup> )	0.1579	0.2751	0.2070	0.3112	0.3889	0.2442	0.2557±0.067	
t <sub>1/2</sub> (ke)	2.082	4.670	2.350	3.024	2.803	1.822	2.792±1.022	0.155>0.05
(h)	4.389	2.519	3.348	2.227	2.045	2.838	2.894±0.8666	
Vd/F	127.563	340.238	208.318	167.094	193.143	98.993	189.224±84.401	2.278 * <0.05
(L.kg <sup>-1</sup> )	116.560	95.104	103.826	95.47	69.068	130.229	101.706±20.913	
cls	42.453	50.491	61.433	38.298	47.745	37.657	46.346±8.989	4.172 * <0.01
L.(h.kg) <sup>-1</sup>	18.405	26.163	21.492	29.703	23.407	31.802	25.162±5.058	
AUC <sub>0-∞</sub>	0.848	0.713	0.586	0.940	0.754	0.956	0.800±0.143	4.224 * * <0.01
ug.h.ml <sup>-1</sup>	1.956	1.376	1.675	1.212	1.538	1.132	1.482±0.307	
MRT	4.637	7.586	4.083	4.986	3.997	3.614	4.817±1.441	0.452>0.05
(h)	7.056	3.195	5.376	3.614	3.195	3.835	4.378±1.539	
t <sub>max</sub>	1.196	2.340	2.002	1.558	0.587	0.561	1.374±0.731	1.462>0.05
(h)	2.108	0.538	0.750	0.364	0.585	0.319	0.777±0.670	
Cmax	61.482	112.129	151.380	168.880	183.693	264.718	173.714±50.687	4.484 * * <0.01
(ng.ml <sup>-1</sup> )	216.484	512.025	278.340	377.797	454.702	556.172	399.253±133.342	

注:每组上行为单用 DTZ 时的 DTZ 药动学参数,下行为合用 DTZ 和 PPF 时的 DTZ 药动学参数

表3 PPF对DTZ代谢物DADZ的影响

参数	1	2	3	4	5	6	$\bar{x} \pm SD$		t值 P
Ke	0.1292	0.3491	0.1619	0.1591	0.1993	0.151	0.1916	0.0804	0.565 > 0.05
(h <sup>-1</sup> )	0.1754	0.1592	0.2934	0.1262	0.4029	0.181	0.2231	0.1046	
t <sub>1/2</sub> (ke)	5.364	1.985	4.280	4.356	3.477	4.580	4.007	1.161	0.548 > 0.05
(h)	3.951	4.353	2.362	5.491	1.720	3.814	3.615	1.369	
AUC <sub>0-∞</sub>	2.451	1.547	4.326	4.696	3.189	3.277	3.248	1.165	2.238 > 0.05
ug·h·ml <sup>-1</sup>	3.808	6.439	7.924	5.102	3.079	4.016	5.061	1.827	
MRT	10.14	5.436	9.834	9.371	7.302	8.500	8.434	1.795	1.708 > 0.05
(h)	5.957	7.469	5.861	7.807	5.119	8.438	6.775	1.308	
t <sub>max1</sub>	0.632	1.391	2.084	2.146	0.344	0.576	1.196	0.795	1.544 > 0.05
(h)	0.924	0.756	0.359	0.360	0.740	0.392	0.588	0.248	
t <sub>max2</sub>	6.858	3.383	8.440	6.016	6.024	5.858	6.096	1.643	0.928 > 0.05
(h)	2.943	3.131	3.800	1.909	7.151	9.767	4.784	3.026	
C <sub>max1</sub>	336.950	127.821	351.704	338.471	676.453	321.765	358.861	176.956	3.515 * < 0.05
(ng·ml <sup>-1</sup> )	422.757	992.006	1012.366	599.018	579.800	812.274	786.370	232.412	
C <sub>max2</sub>	294.238	287.785	314.240	368.304	202.111	299.509	294.864	53.980	2.080 > 0.05
(ng·ml <sup>-1</sup> )	315.461	625.548	930.490	614.170	626.240	264.999	502.157	268.294	

注:每组上行为单用DTZ时的DADZ药动学参数,下行为合用DTZ和PPF时的DADE药动学参数

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