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地尔硫草缓释片在不同肾功能高血压患者中的药物动力学和药效学

陈绍行, 顾天华, 宋代军, 郭冀珍, 王孝铭, 龚兰生 (上海市高血压研究所, 上海200025, 中国)

Pharmacokinetics and pharmacodynamics of slow release tablet of diltiazem in hypertensive patients with various renal functions

CHEN Shao-Xing, GU Tian-Hua, SONG Dai-Jun, GUO Ji-Zhen, WANG Xiao-Ming, GONG Lan-Sheng (*Shanghai Institute of Hypertension, Shanghai 200025, China*)

ABSTRACT Twenty hypertensive patients were equally divided into 2 groups; A) with normal renal function (NRF) and B) with impaired renal function (IRF) according to creatinine clearance, blood urea nitrogen and creatinine levels. The pharmacokinetic and pharmacodynamic effects of diltiazem (Dil, 90 mg, bid × 7 d, po) were studied. The pharmacokinetic parameters in IRF patients (K_a 0.7 ± 0.2 h⁻¹, $T_{1/2}$ 3.7 ± 0.7 h, C_{max} 45 ± 4 ng · ml⁻¹, T_{max} 3.1 ± 0.4 h) did not differ from those in NRF patients (0.7 ± 0.5 h⁻¹, 4.1 ± 1.3 h, 41 ± 5 ng · ml⁻¹ and 3.4 ± 0.4 h, $P > 0.05$). Antihypertensive efficacy of Dil in patients with IRF was similar to that in those with NRF, and the hypotensive effect lasted over 24 h. The plasma Dil concentrations were strongly correlated with a decrease in BP in

both groups. It was concluded that IRF did not affect the disposition of slow release Dil tablet under a steady state. No dosage adjustment of Dil is necessary in hypertensive patients with IRF.

KEY WORDS diltiazem; delayed-action preparations; pharmacokinetics; blood pressure; kidney function tests

A 摘要 肾功能正常和受损两组高血压病人作 diltiazem 缓释片 7 d (Dil, 90 mg, bid) 的药物动力学和药效学研究。结果: 两组病人的主要药动学参数 K_a , K_e , $T_{1/2a}$, $T_{1/2e}$, C_{max} 和 T_{max} 相比较无显著性差异。降压幅度相同, 降压作用达 24 h, 血药浓度与血压变化呈正相关。因此, 肾功能损害并不影响 Dil 缓释片稳态期的体内消除过程, 无需调整剂量。

关键词 地尔硫草; 迟效制剂; 药物动力学; 血压; 肾功能试验

地尔硫草(diltiazem, Dil)用于高血压治疗日趋广泛^[1], 其降压作用长, 不良反应轻且服用方便的缓释剂型也已问世^[2,3]。Dil 缓释片是一种新剂型^[4], 我们曾报道了该药在正常人中的药动学和药效学^[5], 本文进一步对肾功能

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正常和受损两组高血压病人作 Dil 血药浓度达到稳态后的药动学和药效学比较,旨在了解肾功能减退是否影响 Dil 缓释片的体内消除过程以及观察 Dil 缓释片的降压疗效。

MATERIALS AND METHODS

20例住院高血压患者按内生肌酐清除率(Cl_{cr}),尿素氮(BUN)和肌酐(Cr)水平分为肾功能正常组和肾功能受损(轻、中度)组,凡 $Cl_{cr} > 90 \text{ ml} \cdot \text{min}^{-1}$, BUN $< 6.5 \text{ mmol} \cdot \text{L}^{-1}$, Cr $< 110 \mu\text{mol} \cdot \text{L}^{-1}$ 为肾功能正常组,凡 $Cl_{cr} 30-90 \text{ ml} \cdot \text{min}^{-1}$, BUN $6.5-21.5 \text{ mmol} \cdot \text{L}^{-1}$ 和 Cr $110-440 \mu\text{mol} \cdot \text{L}^{-1}$ 为肾功能受损组,每组10人,前组根据病史,体检和实验室检查,排除肾脏疾患,系原发性高血压,高血压病程 $10 \pm 3 \text{ a}$;后组包括肾实质性高血压3人和原发性高血压伴肾功能不全7人,病程 $12 \pm 3 \text{ a}$ 。两组病人无肝脏疾病且肝功能正常 (Tab 1)。

Tab 1. Clinical characteristics of subjects. $n=10$, $\bar{x} \pm s$. * $P < 0.01$ vs normal renal function.

	Renal function	
	Normal	Impaired
Sex (M:F)	10:0	9:1
Age/a	44±7	49±9
Duration/a	10±3	12±3
$Cl_{cr}/\text{ml} \cdot \text{min}^{-1}$	102±18	46±12*
BUN/ $\text{mmol} \cdot \text{L}^{-1}$	5.0±1.0	12.5±1.5*
Cr/ $\mu\text{mol} \cdot \text{L}^{-1}$	80±20	260±50*

方法 两组病人停药各类降压药物2 wk后,服用 Dil 缓释片90 mg 每日2次,共7 d. 给药时间7 am 和2 pm. 两组病人在服药后d 7作血药浓度测定,血标本采自给药前(7 am)和给药后的1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 23 h,每次从肘静脉取血2.5 ml. 同日,用台式自动血压监测仪(日本产, Accutorr 1 A)作24 h 坐位血压测定。

血浆样品的预处理,按文献(5)的方法。

Dil 血药浓度用高效液相色谱-紫外检测器测定,内标法。灵敏度 $5 \text{ ng} \cdot \text{ml}^{-1}$ 。色谱条件

为,流动相: $\text{CH}_3\text{OH}-\text{NH}_4\text{H}_2\text{PO}_4$ ($0.01 \text{ mol} \cdot \text{L}^{-1}-(\text{C}_2\text{H}_5)_3\text{N}$ (45:55:0.25)), 流速: $1 \text{ ml} \cdot \text{min}^{-1}$, 柱温: $40 \text{ }^\circ\text{C}$, UV 检测波长: 237 nm , 色谱柱: Zorbax-CN 柱, $250 \text{ mm} \times 4.6 \text{ mm}$ ID, 校正液浓度: 维拉帕米(Verapamil, Ver), 内标, $20 \mu\text{g} \cdot \text{ml}^{-1}$, Dil $3 \mu\text{g} \cdot \text{ml}^{-1}$ 。在此色谱条件下,保留时间 Ver 13.7 min , Dil 9.8 min 。

Dil 药物动力学参数的计算 根据中国科学院计算中心提供的临床药理应用程序库(CPAPL)多剂量血药浓度数据求药物动力学参数程序(MDP),按1房室模型进行拟合计算。

药物 Dil 缓释片系漂浮型缓释制剂,每片45 mg,由上海医药工业研究院研制⁽⁴⁾, Ver 和 Dil 标准品均由上海医药工业研究院提供。

RESULTS

Dil 缓释片药动学参数比较 服用 Dil 缓释片d 7肾功能受损组 LT $0.6 \pm 0.1 \text{ h}$, K_e $0.7 \pm 0.2 \text{ h}^{-1}$, $T_{1/2}$ $3.7 \pm 0.7 \text{ h}$ 与肾功能正常组(LT $0.4 \pm 0.2 \text{ h}$, K_e $0.7 \pm 0.5 \text{ h}^{-1}$, $T_{1/2}$ $4.1 \pm 1.3 \text{ h}$)相比较无显著性差异($P > 0.05$),提示肾功能受损时,对 Dil 缓释片的吸收、消除过程无不良影响。两组病人的药动学参数列于 Tab 2。

在7 am 和2 pm 服药后出现2个血药浓度峰。两组病人之间 C_{max_1} , C_{max_2} , T_{max_1} 和 T_{max_2} 相比较也无显著性差异($P > 0.05$),两组病人的血药浓度曲线都较平坦,在服药后23 h,肾功能正常组病人的血药浓度 $13.4 \text{ ng} \cdot \text{ml}^{-1}$, 肾功能受损组病人 $12.0 \text{ ng} \cdot \text{ml}^{-1}$, Fig 1。

Dil 缓释片时对血压的作用 自动24 h 血压监测提示,两组病人服药后收缩压(SBP)和舒张压(DBP)与同日服药前(7 am)相比,均呈平稳下降,直至24 h. 在7 am 和2 pm 服药后,最大降压作用均出现在3-6 h. 在肾功能受损组,最大SBP 平均下降值为 $1.3 \pm 0.6 \text{ kPa}$

Tab 2. Pharmacokinetic parameters of diltiazem slow release tablet (45 mg/tablet). $n=10$, $\bar{x} \pm s$. $^*P > 0.05$ vs normal renal function.

	Renal function	
	Normal	Impaired
Age/a	44 ± 7	49 ± 9
K_e/h^{-1}	0.7 ± 0.5	0.7 ± 0.2 [*]
K_r/h^{-1}	0.19 ± 0.06	0.19 ± 0.03 ^a
$T_{1/2\alpha}/h$	1.3 ± 0.5	1.1 ± 0.4 [*]
$T_{1/2\beta}/h$	4.1 ± 1.3	3.7 ± 0.7 ^a
LT/h	0.4 ± 0.2	0.6 ± 0.1 [*]
$C_{max_1}/ng \cdot ml^{-1}$	41 ± 5	45 ± 4 ^a
T_{max_1}/h	3.4 ± 0.5	3.1 ± 0.4 [*]
$C_{max_2}/ng \cdot ml^{-1}$	57 ± 6	61 ± 6 ^a
T_{max_2}/h	2.8 ± 0.3	2.8 ± 0.3 [*]
V:F	1.5 ± 0.5	1.3 ± 0.2 [*]

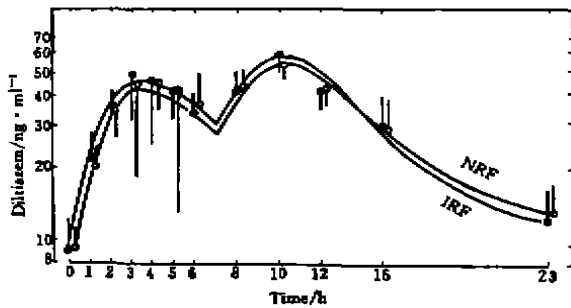


Fig 1. Concentrations in plasma of diltiazem (90 mg, bld, po) on d 7 of treatment. $n=10$, $\bar{x} \pm s$. NRF: normal renal function (○), IRF: Impaired renal function (●).

和 1.4 ± 0.7 kPa, 最大 DBP 平均下降值为 1.5 ± 0.4 kPa 和 1.8 ± 0.9 kPa. 肾功能正常组最大 SBP 和 DBP 平均下降值依次为 1.4 ± 0.6 kPa, 1.4 ± 0.5 kPa, 1.7 ± 0.5 kPa 和 1.6 ± 0.6 kPa, 两组相比, 无显著性差异 ($P > 0.05$), Fig 2.

血药浓度与血压之间的关系 Diltiazem 缓释片

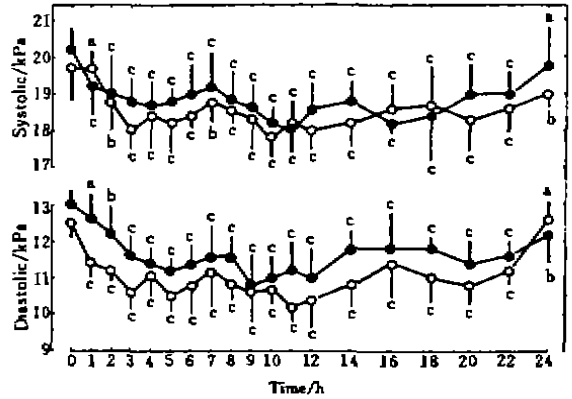


Fig 2. Blood pressure on d 7 of treatment. $n=10$, $\bar{x} \pm s$. $^*P > 0.05$, $^bP < 0.05$, $^cP < 0.01$ vs 0 (self-control). NRF: (○), IRF: (●).

的血药浓度与 SBP, DBP 的变化呈正相关, Fig 3. 相关系数 r 值, 在肾功能正常组是 0.803 ($P < 0.01$) 和 0.864 ($P < 0.01$), 肾功能受损组是 0.881 ($P < 0.01$) 和 0.833 ($P < 0.01$).

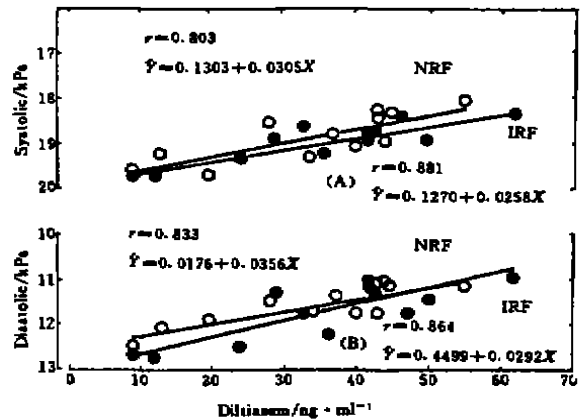


Fig 3. Correlation between diltiazem concentrations in plasma and blood pressure. NRF: (○), IRF: (●).

DISCUSSION

本文通过在肾功能正常和减退两组高血压病人中, Dil 缓释片血药浓度达到稳态后的药动力学研究, 证实了 Dil 体内的吸收、分布和消

除过程不因肾功能受损而受影响^[6,7]。从缓释剂型而言,主要通过药物缓慢释放,延长吸收而发挥长效作用,药动学上表现为 K_e 减小, T_{max} 推迟和 $T_{1/2}$ 延长,而并非剂型本身对药物消除过程有影响^[8],故肾功能正常与否对药动学影响不大。从药物体内消除过程而言,Dil的蛋白结合率较高,主要经肝脏生物转化代谢为脱乙酰地尔硫^[9],以原形在尿中出现的药量仅占所给药量的0.1—0.4%^[10],因而在肾功能受损时,对肾脏清除原药的影响甚微。脱乙酰地尔硫^[9]又进一步代谢为脱乙酰基-O-或-N-脱甲基地尔硫^[11],在肾功能不全者,这些代谢物无积蓄现象^[6]。我们因缺乏必要的实验条件,未作代谢物测定。

可能是2 pm 给药是在7 am 给药后血药浓度尚未完全下降的基础上,故 C_{max_2} 、 T_{max_2} 比 C_{max_1} 和 T_{max_1} 稍有提高和提前。

两组病人的 $T_{1/2}$ 比正常人单次口服给药^[6]的 $T_{1/2}$ 短,可能系本次实验在bid 给药后有2个血药浓度高峰,使计算机对数据处理方式不同所致,鉴于两组病人间 $T_{1/2}$ 值并无差异,故药动学意义不大。

Fig 2反映了Dil缓释片降压作用持久且平稳的特征,这种特征对于提高降压治疗的顺应性具有重要的临床意义。首先,Dil缓释片bid 给药,能控制24 h 血压,并减少服药次数,方便患者,有利于慢性高血压的长期治疗。其次,高血压病人靶器官损害,除与24 h 血压平均值高低有关外,也决定于24 h 血压波动幅度,尤其是夜间血压水平^[11]。Dil缓释片服后,血药浓度平稳,两组病人昼夜血压均能得到控制,起伏减小,有利于减轻或预防靶器官的损伤。

Dil血药浓度与血压变化的正相关关系,能指导临床医生依照Dil缓释片的 T_{max} ,结合患者24 h 血压起伏规律,合理地调整给药时

间,以有效地控制血压波动高峰,避免夜间血压过低而影响重要脏器的灌流。

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