临床常用中西药血药浓度的比较与分析

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摘要: 血药浓度在一定程度上决定了药物效应的发挥。目前普遍认为中药体内化合物血药浓度较低, 但对其低的程度及是否可以在此浓度水平下发挥药效, 尚无充分的研究依据及文献报道。本文通过检索 Scifinder、Pubmed 和 CNKI 中英文数据库, 对 69 篇文献进行了整理汇总, 统计了 73 种西药在人体内的最小有效血药浓度及 40 种中药 (单味或复方) 给药后 211 种化学成分的最大血药浓度, 分析比较了临床常用西药的最小有效血药浓度及中药体内成分最大血药浓度。结果发现, 中药绝大多数体内化合物的最大血药浓度远小于西药最小有效血药浓度, 即分别有 17 种西药 (占所统计西药数量的 23%) 最小有效血药浓度和 143 种中药体内化合物 (占所统计中药化学成分数量的 68%) 最大血药浓度小于 100 ng·mL^{-1}; 31 种西药 (占所统计西药数量的 42%) 最小有效血药浓度和 20 种中药体内化合物 (占所统计中药化学成分的 9%) 最大血药浓度大于 1 000 ng·mL^{-1}。本文根据文献资料对中西药血药浓度进行较为系统的综述与比较, 为深入探讨中药药效物质基础及其作用机制的研究提供新的思路及参考。

关键词: 血药浓度; 西药; 中药; 药效物质基础; 药理作用机制

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Comparision and analysis on the blood concentration of common Chinese medicine and Western medicine

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Abstract: To a certain extent, the drug effect is determined by its blood concentration. It is generally accepted that the blood concentrations of constituents of Chinese medicines are very low. There is no sufficient experimental bases and references on its degree and the possibility of taking effect. In this study, 69 papers were collected and analyzed by searching the database of Scifinder, Pubmed, CNKI. The minimum effective blood concentrations of 73 common Western medicines and the maximum blood concentrations of 211 *in vivo* constituents of 40 Chinese medicines (single herb or compound Chinese medicine) were summarized. It was found that the maximum blood concentrations of the most *in vivo* constituents of Chinese medicines were much less than the minimum effective blood concentrations of the Western medicines. Specifically, the minimum effective blood concentrations of 17 Western medicines (23% of total) and the maximum blood concentrations of the 143 *in vivo* constituents of Chinese medicines (68% of total) were less than 100 ng·mL^{-1}; the minimum

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effective blood concentrations of 31 Western medicines (42% of total) and the maximum blood concentrations of the 20 *in vivo* constituents of Chinese medicines (9% of total) were more than 1 000 ng·mL^{-1}. In this paper, a systematic summary and comparison of the blood concentrations in traditional Chinese medicines and Western medicines were conducted, which could provide a new ideas and references for the study of the pharmacodynamical material basis and its mechanism in traditional Chinese medicine.

Key words: blood concentration; Western medicine; Chinese medicine; pharmacodynamical material basis; pharmacological mechanism

一般认为, 药物在生物体内能够发挥各种药理作用, 本质在于药物经给药部位进入生物体血液循环 (肠道直接作用与外用药除外), 一定浓度的药物分子与靶点分子产生特异性或非特异性结合进而引起相应的生物效应。对大多数药物而言, 药理作用的强弱和持续时间的长短, 与药物分子在靶点部位的浓度呈正比。然而目前直接测定药物分子在靶点部位的浓度较为困难。药物分子进入人体后, 可经血液运送至作用部位 (靶点部位)。血液中的游离药物通过扩散进入细胞外液, 到达细胞膜或进而扩散至细胞内与靶点结合。血液中的药物浓度与细胞外液及细胞内的药物浓度间可形成可逆平衡, 故血液中的药物浓度可间接地反映药物在靶点部位的浓度[1]。因此, 血药浓度在一定程度上决定了药物效应的发挥。

虽然目前普遍认为中药含有多种化学成分, 各成分含量通常较低, 而其入血成分 (包括中药化学成分原形及其代谢产物) 的血药浓度更低。但是究竟中药体内成分血药浓度有多低? 在这样的浓度下, 单一成分发挥药效的可能性有多大? 还没有充分的依据和认识。西药成分单一, 血药浓度与效应间关系明确; 而作为复杂体系的中药, 其入血成分浓度与药效间的关系较难阐明。为此, 本文拟通过检索和分析临床常用中西药血药浓度的相关文献, 将常规剂量下中药体内化合物最大血药浓度和西药最小有效血药浓度进行比较, 为深入探讨中药药效物质及其作用机制提供思路和参考。本文首先采用中国学术期刊全文数据库、Pubmed 和 Scifinder 对相关文献进行检索。中文检索词分别为:“血药浓度”, 二次检索词为“西药”、“中药”, 通过主题词、关键词、摘要和全文等多个字段进行检索查找。根据西药血药浓度的中文文献检索结果, 对相应西药继续进行英文文献追踪。中药血药浓度文献检索的英文检索词分别为:“pharmacokinetics”, 二次检索词为“tratidional Chinese medicine”, 通过“research topic”进行检索查找, 并将文献类型限制为“Journal”。为防止检索结果与已检索出的中文文献重复将语言限制为“English”。同时, 本文所列西药均为收载于《临床常用药物手册》[2]中的临床常用西药, 且文献中要有明确的有效血药浓度下限。中药最大血药浓度的文献需标明确切的给药量, 且在临床常用剂量下开展的研究, 需以中药单味药、提取物 (以提取物入药的中药, 文中提及折合生药量, 并根据此折合剂量判断是否为临床常用剂量) 或复方入药, 排除以单体成分直接给药情况。对上述检索结果, 筛选出相关文献。最后, 记录西药药品名称、最小有效血药浓度、中药名称、样品类型、给药方式、剂量、化合物、化合物类型、最大血药浓度和文献来源。

1 临床常用中西药血药浓度的文献资料来源

临床常用西药最小有效血药浓度数据来源: ① 临床药代动力学研究文献报道。如 Koup 等[3]建立了氨茶碱治疗呼吸系统疾病危重患者的指导原则及其临床药代动力学研究方法。静脉给予 72 例患者氨茶碱 (负荷剂量 5.6 mg·kg^{-1}, 维持剂量 0.9、0.68、0.45 mg·kg^{-1}·h^{-1}), 采用高效液相色谱法测定血清茶碱含量。结果发现, 72% 研究对象 (52 例) 在血药浓度为 8～20 mg·L^{-1} 时起效, 只有 2 例静脉滴注氨茶碱后, 在有效血药浓度 5～25 mg·L^{-1} 范围之外起效。② 血药浓度监测文献报道。血药浓度监测是以药代动力学原理为指导, 分析测定药物在血液中的浓度, 用以评价疗效或确定给药方案, 使给药方案个体化, 以提高药物治疗水平, 达到临床安全、有效和合理用药的目的, 通常用于治疗窗窄、毒性强、服药周期长和服药后个体差异大的药物。在此类文献中通常会标明所研究西药的最低有效血药浓度。如 Xiao 等[4]用放射免疫分析法对 229 例患者体内地高辛血药浓度进行了监测。结果发现, 治疗血药浓度范围 (0.5～2 ng·mL^{-1}) 内有 152 例 (占 66.2%)。由此可知, 地高辛吸收个体差异大, 治疗指数低, 应及时监测血药浓度。③ 临床用药相关专著。如《现代临床药物学》[5]、《Pediatric Dosage Handbook》[6]。西药有效血药浓度

是通过对大量临床资料进行统计而确定，而中药作为复杂体系，药效物质基础较难明确，目前尚未见开展此方面研究的报道。中药血药浓度信息多通过对人血浆或动物血浆中目标成分的药代动力学研究得到最大血药浓度。虽然动物血浆中的中药成分的最大血药浓度值不能等同于人体内血药浓度情况，然而有文献认为基础代谢率、热卡、肝肾功能、血药浓度、药−时曲线下面积、肌酐、血液循环等与体表面积基本成正比[7]。如 Zhou 等[8]采用 HPLC 法研究了大鼠灌胃给予 11.5 mg·kg^{-1} (相当于人口服给药 200 mg) 氨茶碱后血浆药代动力学，结果发现氨茶碱 C_{max} 为 74.349 ± 7.599 μg·mL^{-1}，$AUC_{0-\infty}$为 457.664 ± 61.173 μg·mL^{-1}·h。Li[9]对 20 名志愿者口服 200 mg 氨茶碱缓释片后血浆药代动力学进行了研究，结果发现氨茶碱 C_{max} 为 2.862 ± 0.374 μg·mL^{-1}，$AUC_{0-\infty}$为 43.323 ± 7.362 μg·mL^{-1}·h。比较上述实验结果，相同剂量下氨茶碱在大鼠血浆中最大血药浓度大于人血浆。与血药浓度与体表面积成正比的理论一致。故在此理论下，动物用药剂量与人用药剂量进行折合换算，换算后剂量下的动物血药浓度在一定程度上也可以反映人体内的情况。

因此，本文除了总结中药给药后化合物在人体内的血药浓度外，也加入了动物体内血药浓度。如 Liu 等[10]开展了生脉注射液中 ginsenoside-Rg1 的药代动力学研究。采用 LC-ESI-MS/MS 法对 10 名健康志愿者 (男女比例 1∶1，年龄 20～30 岁，身体质量指数为 19～25 kg·m^{-2}) 静脉注射 60 mL (常规剂量) 生脉注射液后 0、5、15 和 30 min，1、2、3、4、6、8、12 和 24 h 血浆中的 ginsenoside-Rg1 含量进行测定。采用 WinNonlin® software 对数据进行分析，得到了相应药动学参数 (AUC、C_{max}、T_{max} 等)。此外，Liu 等[11]研究了痛经模型大鼠灌胃香附四物汤后 4 种主要活性成分小檗碱、原阿片碱、四氢黄连碱和延胡索乙素的药代动力学。采用 LC-MS/MS 测定了痛经模型大鼠 (220～250 g) 给予香附四物汤 3.78 g·kg^{-1} (相当于人 0.6 g·kg^{-1}，常规剂量) 后 0、5、15、30、60、120、240、360、480 和 1 920 min 时血浆中指标成分的含量，经 WinNonlin® software 分析，得到了相应药动学参数 (AUC、C_{max} 和 T_{max} 等)。

2 中西药血药浓度概况

查阅文献总结得到了 73 种西药在人体内的最小有效血药浓度及 40 种中药 (单味或复方) 给药后体内 211 种化合物的最大血药浓度，其中以人血浆为研究对象的体内化合物共 42 种 (包括原形成分 25 种，代谢产物 18 种)；以大鼠血浆为研究对象的体内化合物共 169 种。中药研究部分涉及的人或动物用药剂量均与临床常用剂量相符，未见明显超出临床常用剂量的情况。具体数据见表 1、2。

3 临床常用中西药血药浓度的比较与分析

73 种西药最小有效血药浓度和 211 种中药体内化合物 (代谢产物) 最大血药浓度的分布情况见表 3。其中西药人体最小有效血药浓度值最低的为氟奋乃静 (0.13 ng·mL^{-1})，最小有效血药浓度值最高的为水杨酸类药物 (100 000 ng·mL^{-1})；中药体内化合物在人血浆中，最大血药浓度值最小的为直肠给予广痛消气雾剂后人血浆中盐酸小檗碱 (0.31 ng·mL^{-1})，最大的为静脉给药黄芪总皂苷注射液后人血浆中的 astragaloside IV (5 190 ng·mL^{-1})；中药体内化合物在动物血浆中，最大血药浓度值最小的为灌胃茵陈术附汤后大鼠血浆中的 ononin (0.34 ng·mL^{-1})，最大的为灌胃生脉散后大鼠血浆中的 5,8-dihydroxy-1,4-naphthoquinone (9 965.75 ng·mL^{-1})。

就整体而言，血药浓度小于 100 ng·mL^{-1} 的中药化学成分 (代谢产物) 共 143 种，占总统计所得成分数量的 68%，西药共 17 种，占总统计所得的 23%；血药浓度处于 100～1 000 ng·mL^{-1} 区间内的中药化学成分 (代谢产物) 共 48 种，占总统计所得成分数量的 23%，西药共 25 种，占总统计所得的 34%；血药浓度处于 1 000～100 000 ng·mL^{-1} 区间内的中药化学成分 (代谢产物) 共 20 种，占总统计所得成分数量的 9%，西药共 31 种，占总统计所得的 42%。见表 3 和图 1～3。

由此可知，中西药血药浓度分布总体趋势：随着血药浓度由低到高，西药数量呈由少到多的变化，中药体内化合物 (原形/代谢产物) 数量则由多到少。即西药最小血药浓度多分布在较高的浓度区间 (1 000～100 000 ng·mL^{-1})；中药体内化合物 (原形/代谢产物) 最大血药浓度较集中分布在低浓度区间 (< 100 ng·mL^{-1})；高浓度区间中药体内化合物分布尤为少，且所调查的中药化学成分最大血药浓度值未见超出西药最小有效血药浓度值范围，最大血药浓度最高值是西药最小有效血药浓度最高值的 1/10。本文所列的中药体内化合物最大血药浓度，均是在人或动物给药剂量与临床常用剂量相符的情况下测定得到的。根据本文总结的数据可知，中药体内化学成分的最大血药浓度比西药最小有效血药浓度低，且二者之间差距较大，推测中药起效时体内各个化合物 (代谢产物) 实际血药浓度可能并未达到单独起作用所

Table 1 The minimum effective blood concentrations of 73 Western medicine chemicals. Document types: (1) Pharmacokinetic studies; (2) Therapeutic drug monitoring studies; (3) Clinical monograph

Western medicine	Minimum effective blood concentration/ng·mL^{-1}	Document type	Reference	Western medicine	Minimum effective blood concentration /ng·mL^{-1}	Document type	Reference
Digoxin	0.5	(2)	4	Darenthin	500	(3)	29
Nifedipine	25	(2)	12	Digitoxigenin	9	(3)	29
Trovafloxacin	60	(3)	6	Propiram	2 000	(3)	29
Erythromycin	60	(3)	6	Flecainide	200	(3)	29
Clonazepam	16	(2)	13	Lidocaine	1 500	(3)	29
Cyclosporine	100	(2)	14	Mexiletine	500	(3)	29
Gentamicin	125	(3)	6	Procaine	4 000	(3)	29
Ciprofloxacin	125	(3)	6	Propranolol	50	(3)	29
Clorimipramine	160	(2)	15	Quinidine	2 000	(3)	29
Quetiapine	250	(2)	16	Tocainide	4 000	(3)	29
Aripiprazole	350	(2)	17	Verapamil	80	(3)	29
Clozapine	370	(2)	18	Amrinone	3 700	(3)	29
Cordarone	500	(2)	19	Hydralazine	100	(3)	29
Amikacin	500	(2)	20	Primidone	5 000	(3)	29
Teicoplanin	500	(2)	21	Amitriptyline	110	(3)	29
Rifampin	500	(2)	22	Amoxapine	200	(3)	29
Lamotrigine	1 000	(2)	23	Bupropion	25	(3)	29
Fosfomycin	1 000	(3)	6	Clomipramine	80	(3)	29
Human activated protein C	1 040	(1)	24	Desipramine	125	(3)	29
Isoniazid	3 000	(2)	23	Doxepin	100	(3)	29
Oxcarbazepine	3 470	(3)	6	Imipramine	200	(3)	29
Oxacillin	4 000	(3)	6	Maprotiline	200	(3)	29
Carbamazepine	4 000	(2)	25	Nortriptyline	50	(3)	29
Aminophylline	5 000	(1)	6	Protriptyline	100	(3)	29
Vancomycin	5 000	(2)	4	Trazodone	800	(3)	29
Micafungin	5 000	(2)	13	Chlorpromazine	30	(3)	29
Cephazolin	8 000	(1)	26	Fluphenazine	0.13	(3)	29
Phenytoin sodium	10 000	(2)	13	Haloperidol	5	(3)	29
Pyrazinamide	12 500	(1)	27	Trilafon	0.8	(3)	29
Phenobarbital	15 000	(2)	16	Thiothixene	2	(3)	29
Penicillin	16 000	(2)	23	Amantadine	300	(3)	29
Sodium valproate	50 000	(1)	28	Salicylates	100 000	(3)	29
Kanamycin	15 000	(3)	29	Terbutaline	0.5	(3)	29
Netilmicin	6 000	(3)	29	Flucytosine	25 000	(3)	29
Streptomycin	20 000	(3)	29	Chloramphenicol	15 000	(3)	29
Sulfonamides	50 000	(3)	29	Ethosuximide	40 000	(3)	29
Amiodarone	500	(3)	29				

Table 2 The maximum blood concentration of *in vivo* constituents of traditional Chinese medicine in human/animal plasma. iv: Intravenous injection; ip: Peritoneal injection; ig: Intragastric administration; *po*: Oral administration

Sample	Chinese medicine	Administration	Dose	Constituent	Category	C_{max} /ng·mL^{-1}	Reference
Rat plasma	Xiangfu-Siwu decoction	ig	3.78 g·kg^{-1}	Tetrahydropalmatine	Prototype	49.0	11
				Protopine	Prototype	510	11
				Berberine	Prototype	8.9	11
				Tetrahydro corydaline	Prototype	3.4	11
Human plasma	Astragalosides injection	iv	45 mg	Astragaloside IV	Prototype	5 190	30
Rat plasma	Danggui-Shaoyao-San	ig	3.54 g·kg^{-1}	Paeoniflorin	Prototype	8 280	31
Rat plasma	Chrysanthemi Flos extract	ig	100 mg·kg^{-1}	Apigenin	Prototype	3 310	32
				Luteolin	Prototype	1 684	32

Continued

Sample	Chinese medicine	Administration	Dose	Constituent	Category	C_{max} /ng·mL^{-1}	Reference
				Diosmetin	Prototype	329.4	32
				Chrysoeriol	Prototype	93.1	32
Rat plasma	Longdan-Xiegan-decoction	ig	10 g·kg^{-1}	Gentiamarin	Prototype	5 767	33
				Geniposide	Prototype	1 164	33
				Baicalin	Prototype	2 008	33
				Swertiamain	Prototype	13.0	33
Rat plasma	Verbenae herba	ig	10 mL·kg^{-1}	Luteolin	Prototype	1 620	34
				Kaempferol	Prototype	590	34
				Apigenin	Prototype	6 690	34
				Quercetol	Prototype	820	34
				Quercetin	Prototype	6 360	34
Rat plasma	Coptidis Rhizoma aqueous extracts	ig	10 mL·kg^{-1}	Berberine	Prototype	153.33	35
				Coptisine	Prototype	106.81	35
				Palmatine	Prototype	114.86	35
				Jatrorrhizine	Prototype	28.08	35
				Epiberberine	Prototype	96.69	35
				Magnoflorine	Prototype	310.26	35
				Columbamin	Prototype	123.19	35
				Noroxyhy-drastinine	Prototype	10.94	35
				Oxyberberine	Prototype	6.78	35
				8-Oxocoptisine	Prototype	10.48	35
Rat plasma	Wu-Jin pill	ig	15 g·kg^{-1}	Jatrorrhizine	Prototype	18.62	36
				Berberine	Prototype	89.57	36
				Coptisine	Prototype	33.33	36
				Palmatine	Prototype	25.80	36
				Evodiamine	Prototype	21.22	36
				Peoniflorin	Prototype	210.59	36
Rat plasma	Danmu injection	im	2 mL·kg^{-1}	Naucleamide A-10-*O*-*β*-*d*-glucopyranoside	Prototype	74.83	37
				Naucleamide G	Prototype	22.92	37
				Pumiloside	Prototype	102.06	37
				3-Epi-pumiloside	Prototype	19.59	37
				Strictosamide	Prototype	720.76	37
				Vincosamide	Prototype	36.30	37
Human plasma	Puerariae Lobatae radix	*po*	2.56 g	Puerarin	Prototype	11.07	38
				7,4'-Dihydroxy isoflavone	Metabolites	2.10	38
Human plasma	Guanxin II	*po*	3 g·kg^{-1}	Ferulic Acid	Prototype	26.20	39
Rat plasma	Xiao-Xu-Ming decoction	ig	2.0 g·kg^{-1}	Oroxylin A-7-*O*-glucuronide	Prototype	1200	40
				Wogonoside	Prototype	2 362	40
				Liquiritigenin	Prototype	20.3	40
				5-*O*-Methylvisammiol	Prototype	338	40
				Cimifugin	Prototype	2 018	40
				Glycyrrhizic acid	Prototype	23.24	40
				Glycyrrhetinic acid	Prototype	760.7	40
Mice plasma	Astragali radix	ig	80 mg·kg^{-1}	Calycosin-7-*O*-glucoside	Prototype	33.41	41
				Ononin	Prototype	51.38	41
				Calycosin	Prototype	32.98	41
				Formononetin	Prototype	47.93	41
				Astragaloside IV	Prototype	128.95	41
Rat plasma	Buyang-Huangwu-Tang	ig	10 g·kg^{-1}	Astragaloside I	Prototype	55	42
				Astragaloside II	Prototype	30	42

Continued

Sample	Chinese medicine	Administration	Dose	Constituent	Category	C_{max} /ng·mL^{-1}	Reference
				Astragaloside IV	Prototype	100	42
				Formononetin	Prototype	98	42
				Ononin	Prototype	19	42
				Calycosin	Prototype	1 231	42
				Calycosin-7-*O*-glucoside	Prototype	18	42
				Ligustilide	Prototype	7.8	42
				Peoniflorin	Prototype	97	42
Human plasma	Guang-Tong-Xiao aerosol	Rectal administration	0.165 g·kg^{-1}	Tetrahydropalmatine	Prototype	0.55	43
				Berberine hydrochloride	Prototype	0.31	43
Human plasma	Chaihu-Shugan-San	*po*	4 g·kg^{-1}	Meranzin hydrate	Prototype	199	44
				Ferulic acid	Prototype	317	44
Human plasma	Wuzhi capsule	*po*	6 capsules	Schisandrol A	Prototype	126.88	45
				Schisandrol B	Prototype	65.18	45
				Schisantherin A	Prototype	400.27	45
				Deoxyschizandrin	Prototype	63.21	45
				Schizanhenol	Prototype	31.00	45
Human plasma	Yigu capsule	*po*	15 capsules	LcariinII	Prototype	2.76	46
Human plasma	Panax Quinquefolius radix	*po*	10 g	Ginsenoside Rb1	Prototype	19.90	47
				Compound K	Prototype	7.32	47
Human plasma	Notogenseng radix et Rhizoma	*po*	27 g	Ginsenoside Ra3	Prototype	4.94	48
				Ginsenoside Rb2	Prototype	39.05	48
				Ginsenoside Rd	Prototype	8.98	48
				Ginsenoside F2	Prototype	4.45	48
				Compound K	Prototype	154.88	48
				20(*S*)-Protopanoxadiol	Prototype	4.19	48
				Notoginsenoside R1	Prototype	1.07	48
				Ginsenoside Rg1	Prototype	7.25	48
				Ginsenoside F1	Prototype	3.06	48
				20(*S*)-Protopanaxatriol	Prototype	23.39	48
				M16	Metabolites	2.56	48
				M17	Metabolites	6.08	48
				M19	Metabolites	8.30	48
				M20	Metabolites	2.69	48
				M21	Metabolites	15.23	48
				M22	Metabolites	4.25	48
				M4	Metabolites	11.66	48
				M5	Metabolites	20.04	48
				M6	Metabolites	7.63	48
				M7	Metabolites	4.73	48
				M8	Metabolites	160.70	48
				M10	Metabolites	20.62	48
				M11	Metabolites	59.52	48
				M12	Metabolites	391.82	48
				M13	Metabolites	10.79	48
				M14	Metabolites	10.15	48
				M15	Metabolites	3.74	48
Rat plasma	Baihe-Zhimu-Tang	ig	10 g·kg^{-1}	Mangiferin	Prototype	522.83	49
				Neo-mangiferin	Prototype	336.7	49
				Timosaponin B II	Prototype	434.6	49
				Timosaponin B III	Prototype	36.4	49
				Timosaponin A III	Prototype	94.4	49

Continued

Sample	Chinese medicine	Administration	Dose	Constituent	Category	C_{max} /ng·mL^{-1}	Reference
Rat plasma	Zi-Shen pill	ig	1.94 g·kg^{-1}	Palmatine	Prototype	3.8	50
				Berberine	Prototype	6.8	50
				Timosaponin E1	Prototype	15.2	50
				Timosaponin B	Prototype	35.0	50
				Timosaponin B Ⅱ	Prototype	63.5	50
				Mangiferin	Prototype	874.9	50
				Neo-mangiferin	Prototype	71.4	50
Rat plasma	Kai-Xin San	ig	9.4 g·kg^{-1}	Tumulosic acid	Prototype	5.88	51
				Ginsenoside Rg1	Prototype	8.75	51
				Ginsenoside Re	Prototype	69.14	51
				Polygalaxanthone III	Prototype	65.15	51
				Ginsenoside Rd	Prototype	78.91	51
				Ginsenoside Rb1	Prototype	275.9	51
Rat plasma	Fuzi-Xiexin decoction	ig	30 g·kg^{-1}	Emodin	Prototype	3.30	52
				Jatrorrhizine	Prototype	2.26	52
				Berberine	Prototype	5.83	52
				Palmatine	Prototype	6.27	52
				Coptisine	Prototype	7.78	52
				Wogonoside	Prototype	125.73	52
				Wogonin	Prototype	33.98	52
				Aloe-emodin	Prototype	40.88	52
				Rhein	Prototype	2 496.96	52
				Baicalin	Prototype	121.03	52
Rat plasma	Tang-Ming-Ling pill	ig	16 g·kg^{-1}	Chrysin	Prototype	19.47	53
				Naringenin	Prototype	133.8	53
				Oroxylin A	Prototype	155.9	53
				Hesperidin	Prototype	190.3	53
				Wogonin	Prototype	1378	53
				Berberine	Prototype	156.2	53
				Coptisine	Prototype	16.94	53
				Jatrorrhizine	Prototype	7.884	53
				Palmatine	Prototype	16.52	53
Rat plasma	Jiao-Tai-Wan	ig	300 mg·kg^{-1}	Epiberberine	Prototype	2.86	54
				Berberine	Prototype	10.19	54
				Palmatine	Prototype	0.85	54
				Coptisine	Prototype	4.09	54
				Jatrorrhizine	Prototype	1.04	54
Rat plasma	Yinchen-Zhufu decoction	ig	1.5 g·kg^{-1}	Ononin	Prototype	0.34	55
				Liquiritin	Prototype	11.77	55
				Ginkgolides III	Prototype	16.07	55
				Glycyrrhizinic acid	Prototype	57.90	55
				Cinnamylic acid	Prototype	81.33	55
				Glycyrrhetinic acid	Prototype	431.17	55
Rat plasma	Danggui-Buxue decoction	ig	20 g·kg^{-1}	Ononin	Prototype	6.42	56
				Butyl lactone	Prototype	7.35	56
				Campanulin	Prototype	9.28	56
				Astragalin	Prototype	24.70	56
				Caffeic acid	Prototype	34.43	56
				Ligustilide	Prototype	34.18	56
				Ferulic acid	Prototype	61.03	56
Rat plasma	Ke-ke capsule	ig	0.18 g·kg^{-1}	Morphine	Prototype	8.921	57

Continued

Sample	Chinese medicine	Administration	Dose	Constituent	Category	C_{max} /ng·mL^{-1}	Reference
				Ephedrine	Prototype	46.85	57
				Pseudoephedrine	Prototype	12.58	57
Rat plasma	Chaihu-Shugan-San	ig	30 g·kg^{-1}	Meranzin hydrate	Prototype	58.66	58
Rat plasma	Bushen-Huoxue formula	ig	1.0 g·kg^{-1}	Formononetin	Prototype	1.79	59
				Emodin	Prototype	8.26	59
				Tanshinone ⅡA	Prototype	22.64	59
Beagle plasma	Niuhuang-Jiedu pill	ig	380 mg·kg^{-1}	Dimethylarsinic acid	Prototype	57.0	60
Rat plasma	Wu-Zhu-Yu decoction	ig	6.67 g·kg^{-1}	Evodiamine	Prototype	9.01	61
				Rutecarpine	Prototype	10.13	61
				Ginsenoside Rd	Prototype	14.56	61
				Ginsenoside Rb1	Prototype	63.99	61
				Ginsenoside Re	Prototype	2.98	61
				Ginsenoside Rg1	Prototype	4.42	61
				Limonin	Prototype	630.90	61
				Dehydroevodiamine	Prototype	432.40	61
Rat plasma	Juglandis Mandshuruicae cortex extract	ig	15 g·kg^{-1}	Quercetin	Prototype	33.57	62
				Myricetin	Prototype	54.10	62
				Naringenin	Prototype	64.83	62
				Myricetrin	Prototype	103.36	62
				Texifolin	Prototype	110.24	62
				Gallic acid	Prototype	3 443.76	62
				Quercitrin	Prototype	111.29	62
				5,8-Dihydroxy-1,4-naphthoquinone	Prototype	9 965.75	62
Rat plasma	Sheng-Mai formula	ig	5 mg·kg^{-1}	Schizandrin	Prototype	4.51	63
				Schisandrol B	Prototype	3.61	63
				Schisantherin A	Prototype	3.80	63
				Schizandrin B	Prototype	11.46	63
				Deoxyschizandrin	Prototype	7.64	63
Rat plasma	Schisandra chinensis	ig	150 mg·g^{-1}	Schisandrol A	Prototype	449.0	64
				Schisandrol B	Prototype	100	64
				Gomisin N	Prototype	240	64
				Tigloylgomisin H	Prototype	29.4	64
				Schizandrin A	Prototype	96.2	64
				Schizandrin B	Prototype	54.9	64
				Angeloylgomisin H	Prototype	70.3	64
				Schisandrin C	Prototype	68.7	64
Rat plasma	Licorice	ig	5 g·kg^{-1}	Liquiritin	Prototype	553.20	65
				Isoliquiritin	Prototype	145.80	65
				Liquiritigenin	Prototype	68.40	65
				Isoliquiritigenin	Prototype	44.70	65
				Glycyrrhizic acid	Prototype	1 210.50	65
				Glycycoumarin	Prototype	7.40	65
				Formononetin	Prototype	13.90	65
Rat plasma	Borneol	ig	20 mg·kg^{-1}	Borneol	Prototype	17.864	66
				Camphor	Prototype	18.36	66
Rat plasma	Suan-Zao-Ren decoction	ig	8 g·kg^{-1}	Spinosin	Prototype	44.20	67
				Mangiferin	Prototype	1576	67
				Ferulic acid	Prototype	151.5	67
Rat plasma	Corydalis Decumbentis rhizoma	ig	2.0 g·kg^{-1}	Tetrahydropalmatine	Prototype	435.8	68
				Protopine	Prototype	347.9	68
				Palmatine	Prototype	8.53	68

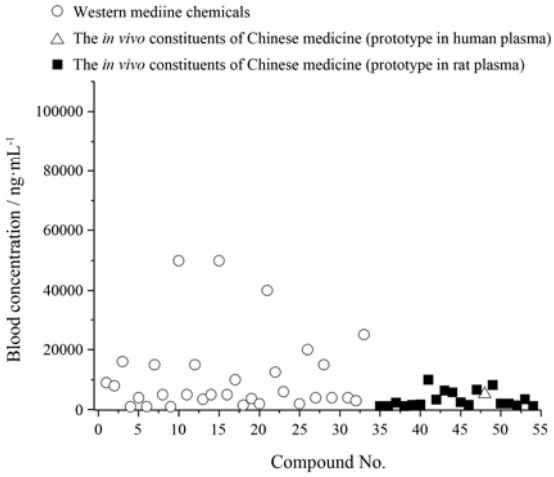

Figure 1 The distribution of 31 Western medicines and 20 Chinese medicines blood concentration in the interval of 1 000−10 000 ng·mL^{-1}

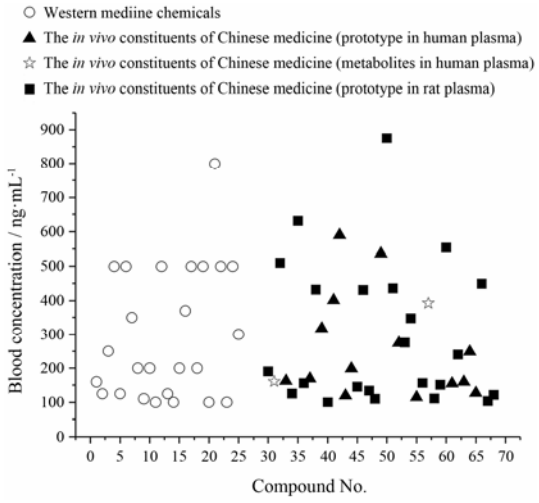

Figure 2 The distribution of blood concentrations of 25 Western medicines and 48 *in vivo* constituents of Chinese medicines (including 2 metabolites) in the interval of 100 −1 000 ng·mL^{-1}

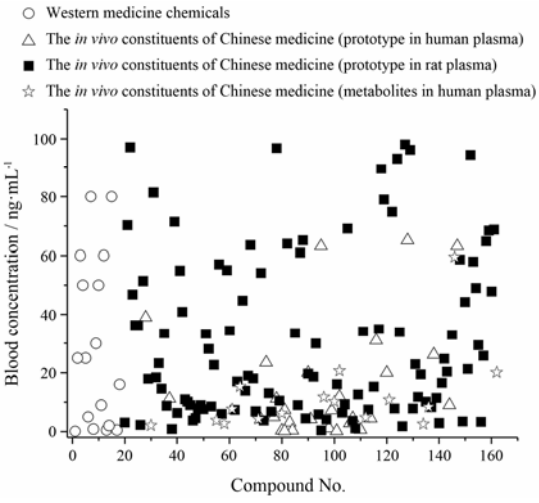

Figure 3 The distribution of blood concentrations of 17 Western medicines and 143 *in vivo* constituents of Chinese medicines (including 16 metabolites) in the interval of 0 −100 ng·mL^{-1}

Table 3 The distribution of blood concentrations of Western medicines chemicals and Chinese medicines

Blood concentration /ng·mL^{-1}	Western medicine chemical	Chinese medicine
10 000 − 100 000	11	0
5 000 − 10 000	7	6
1 000 − 5 000	13	14
100 − 1 000	25	48
10 − 100	10	89
0 − 10	7	54

需的血药浓度。

4 展望与思考

本文通过比较总结临床常用西药血药浓度 (最小有效血药浓度) 及中药体内化合物血药浓度 (最大血药浓度), 发现中药绝大多数体内化合物的最大血药浓度远远低于西药最小有效血药浓度。

根据本文分析的结果, 关于“中药药效物质如何产生药效作用”思考如下: 目前中药多成分多靶点的协同作用的理论是对中药作用机制的一个公认的重要解释[69, 70], 但是由本文分析的结果可见, 中药体内 (大多数) 单一化学成分的浓度远低于西药最小有效血药浓度, 这能激动相关靶点而引起相应药理效应吗? “多成分的协同作用”也许提示不需要达到一定的血药浓度, 亦或许所需要的浓度可明显低于西药的最低有效浓度? 然而本文总结发现, 有 90% 以上的中药体内成分的最大血药浓度低于 1 000 ng·mL^{-1}, 却有 42% 西药的最小有效血药浓度处于 10 000～100 000 ng·mL^{-1}, 即至少有 90% 中药体内成分的血药浓度低于血药浓度较高的西药的最小有效血药浓度的 1/10～1/1 000。同时, 由于血液中的药物浓度可间接地反映药物在靶点部位的浓度, 因此, 在这样低浓度下单一的中药体内成分激动相应靶点引起药理效应的可能性, 值得进一步思考和研究。或许中药成分发挥药效作用还存在其他机制? 作者最近报道[71], 中药土茯苓主要成分花旗松素灌胃给药后在大鼠体内共鉴定出 191 个代谢产物, 活性预测结果显示其中 60 个代谢产物有 5 个相同的靶点 (nucleoside diphosphate kinase 等); 预测有 41 个代谢产物或通过作用于靶点 glycogen synthase kinase-3 beta 发挥抗肿瘤活性, 其中有 6 个代谢产物已有抗肿瘤活性的文献报道。上述研究结果表明, 中药的原形成分及其代谢产物有可能作用于相同的靶点以共同发挥药理活性。“中药最大血药浓度低于西药最小有效血药浓度”提示, 这种叠加作用会不会是中药发挥药理作用的重要机制之一[72]? 总之, 本文对常用

中西药血药浓度情况的综述虽然不能涵盖所有情况, 但在一定程度上反映了中西药体内情况的显著差异, 这为今后如何定义中药药效物质基础的概念提供新的思考, 为研究中药药理作用机制提供新的思路。

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