Effectiveness evaluation of cardiovascular drugs based on CYP2C9 target protein

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Abstract: This study is to discuss the effectiveness evaluation of cardiovascular drugs based on CYP2C9 target protein. Multilevel fuzzy comprehensive evaluation method was taken to evaluate the individualized medication effectiveness for cardiovascular drug under the function of CYP2P9 target protein. Then, it was established for the index system to affect drug efficacy and index weight was settled. This index system was applied on the study of valsartan drugs to evaluate the drug efficacy rate of sample. Results corresponded with the actual drug treatment, and received better verification. The beneficial exploration was performed for the effectiveness evaluation of individualized administration.

Keywords: CYP2C9, cardiovascular drugs, effectiveness evaluation, multilevel fuzzy comprehensive evaluation method.

INTRODUCTION

According to statistics, cardiovascular disease is the first cause of causing death. With the improvement of living standard, the changes of people's diet structure, activity decreasiing, increasing intakes of cholesterol and body mass index had become the risk factors for cardiovascular disease. The individual effective dose of many cardiovascular drugs were considerable different, such as anticoagulants, anti-arrhythmic drugs, antihypertensive drugs, antilipemic agents, and so on. The main factor of these difference was genetic polymorphism of drug reaction (Suehiro and Hinoda, 2012). Clinical and body physical factors were the vital reason for individual medication differences.

ARBs was the WHO approved new generation of antihypertensive drugs. Compared with ACEI, ARBs had more comprehensive inhibition on RAS (renin-angiotensin system), and with more curative effect, if combined with ACEI. Valsartan drugs were mainly metabolized by cytochrome oxidase P450 in human body. CYP2C9 was not only the action targets of valsartan cardiovascular drugs, but also the action target of central nervous system drugs, hypoglycemic drugs, antibacterial and anti-inflammatory drugs and stomach ulcer drugs. The individualized medication efficiency difference of cardiovascular drugs developed CYP2C9 target protein had the positive significance to establish individualized medication effectiveness evaluation.

The establish of cardiovascular drugs effectiveness evaluation index system based on cyp2c9 target protein

Through Uniprot data base, 73 kinds of medicine related CYP2C9 protein were extracted, including 19 kinds of cardiovascular medicine, 27 kinds of antibacterial and anti-inflammatory drugs, 11 kinds of central nervous system drugs, 6 kinds of hypoglycemic drugs, 4 kinds of antiallergic agent, 4 kinds of stomach ulcer drugs, 1 kind of medicine in deal with acute vomiting drugs of breast cancer and after chemotherapy. The typical cardiovascular valsartan drugs were taken as example in this study.

Basic principles for establishment of index system

pertinence principle

The establishment of index system was based on individualized medication characteristics, and revolved in effects on the individualized medication.

Operability principle

Index system establishment should comprehensively and correctly reflect the individual basic connotation differences, and with medical operable.

Scientific principle

The established index system could perform quantitative or qualitative analysis and scientific evaluation.

Independence principle

Based on the related study at home and aboard and the work results of People's Hospital of Zhengzhou, the established index system was relatively independent. The indicators did not overlapped between, and easy to determine the index weight, and index score.

Establishment of index system

While on the establishment of index system, the individual drugs should be used to reflect the effectiveness, especially through evaluation of these indexes. At the same time, such errors should be avoided, such as mass, confusing, overlapping and linear correlation. Based on the influence factors of individual drug efficacy at home and abroad, this study proposed the individual medication effectiveness evaluation index

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system. The target level was based on the cardiovascular drug effectiveness evaluation of CYP2C9 target protein; Index level was the main factors for evaluation, which contained the interactions of drugs, target protein and clinical and physical factors; Principle level was the main factor of each elements. Influence factors mainly focused on impact factors and some descriptive elements. Through the evaluation of these elements, it could truly reflect what aspects could affect the drug efficacy and degree of influence. When the index of each factors were determined, the index should be relative independent, and could calculate the quantitative or qualitative description. 10 indicator elements were finally chosen through screening, as seen in table 1 and table 2.

To establish the hierarchical structure model

Drug effectiveness evaluation model contained a multitude of indicators. In order to establish a reliable drug evaluation model, firstly, it need correctly evaluate the weight of each index overall. Only the reasonable determined index weight between, accurate assessment model was established. Analytic hierarchy method (Wollmann *et al*, 2012; Hummel *et al*, 2012; Suner *et al*, 2012; Liu *et al*, 2011; Do *et al*, 2013; Wang *et al*, 2012) was in accordance with the requirement, then established a described system function or internal independence pass class hierarchy, then the two factors of relative importance were compared, and concluded the corresponding proportion scale. Finally, the judgment matrix of upper level to lower level related elements and gave the related elements of the upper level relative importance.

Determination of the weights

After the establishment of hierarchy, comparison between each had token to determine the weight of each factor in B, C and D level. Its basic principle was in accordance with their relative importance degree of its level, it need give the corresponding weights, specific standard as shown in table 3.

Solutions of the judgment matrix $A(a_{ij})$, then concluded the characteristic roots and characteristic vectors, and consistency confirmed each matrix. In the process of building judgment matrix, the importance of the comparison results should be delivered; This suggested the judgment was logic self-consistent, namely the importance was not contradictory. If the consistency condition did not content, it need to modify the judgment matrix, until satisfied. For a consistent judgment matrix and its each column after normalization was the corresponding weight vector. When $A(a_{ij})$ was not consistent, each column after normalization was to the weight vector. The plus method was applied to figure out arithmetic average of the columns as the weight vector. It was the most commonly used weight calculation method weight).

In the evaluation of influencing factor D for single factor evaluation, the membership degree of each index of each level were concluded and marked as the fuzzy relationship matrix $R=(r_{ij})$ n×m. When the membership function were determined, in order to avoid figure between numerical difference was not big, and the evaluation grade difference level jump phenomena, fuzzy processing was done first, made a smooth transition between the membership function in each level; For intermediate level, if on the interval midpoint of membership degree, it was 1.0; if on the edge points of membership degree, it was0.5; For the left and the right level, of the membership degree faraway from the critical value were bigger, at critical level on both sides of the membership degree of 0.5. If let k_1, k_3, k_5, k_7 respectively as v_1 and v_2、v_2 and v_3、v_3 and v_4、v_4 and v_5 were critical value of level. K_2, k_4, k_6 were respectively the mid-range of v_2、v_3、v_4 degree, also as $k_2=(k_1+k_3)/2$, $k_4=(k_3+k_5)/2$, $k_6=(k_5+k_7)/2$. Then established the formula of relative membership function, d_i representative the i parameter values:

$$\mu_{v1}(d_i)\begin{cases}0.5(1+\dfrac{d_i-k_1}{d_i-k_2}), d_i \ge k_1\\ 0.5(1-\dfrac{k_1-d_i}{k_1-k_2}), k_2 \le d_i < k_1\\ 0, d_i < k_2\end{cases} \quad (1)$$

$$\mu_{v2}(d_i)=\begin{cases}0.5(1-\dfrac{d_i-k_1}{d_i-k_2}), d_i \ge k_1\\ 0.5(1+\dfrac{k_1-d_i}{k_1-k_2}), k_2 \le d_i < k\\ 0.5(1+\dfrac{d_i-k_3}{k_2-k_3}), k_3 \le d_i < k_2\\ 0.5(1-\dfrac{k_3-d_i}{k_3-k_4}), k_4 \le d_i < k_3\\ 0, d_i < k_4\end{cases} \quad (2)$$

$$\mu_{v3}(d_i)=\begin{cases}0, d_i \ge k_2\\ 0.5(1-\dfrac{d_i-k_3}{k_2-k_3}), k_3 \le d_i < k_2\\ 0.5(1+\dfrac{k_3-d_i}{k_3-k_4}), k_4 \le d_i < k_3\\ 0.5(1+\dfrac{d_i-k_5}{k_4-k_5}), k_5 \le d_i < k_4\\ 0.5(1-\dfrac{k_5-d_i}{k_5-k_6}), k_6 \le d_i < k_5\\ 0, d_i < k_6\end{cases} \quad (3)$$

$$\mu_{v4}(d_i)=\begin{cases}0\ ,\ d_i \geq k_4\\ 0.5(1-\dfrac{d_i-k_5}{k_4-k_5}), k_5 \leq d_i < k_4\\ 0.5(1+\dfrac{k_5-d_i}{k_5-k_6}), k_6 \leq d_i < k_5\\ 0.5(1+\dfrac{d_i-k_7}{k_6-k_7}), k_7 \leq d_i < k_6\\ 0.5(1-\dfrac{k_7-d_i}{k_6-d_i}), d_i < k_7\end{cases} \quad (4)$$

$$\mu_{v5}(d_i)=\begin{cases}0, d_i \geq k_6\\ 0.5(1-\dfrac{d_i-k_7}{k_6-k_7}, k_7 \leq d_i < k_6\\ 0.5(1+\dfrac{k_7-d_i}{k_6-d_i}), d_i < k_7\end{cases} \quad (5)$$

Formula (1) to (5) were the crescendo index membership function was used to calculate the index membership function with positive impact on evaluation results; decresendo index membership function formula was used to calculate the index membership degree with negative impact on evaluation results. Based on the above 5 formula, the decreasendo index index membership function formula.

Through the fuzzy transformation: B=W×R (6)

Fuzzy comprehensive evaluation vectors were B=(b1,b2,…,bn), then the fuzzy comprehensive index was calculated FCI=B×P (7)

FCI was fuzzy comprehensive index, P=(5,4,3,2,1) was remark set

RESULTS

The blood sample and efficacy data of patients treated with valsartan medication were collected to detect CYP2C9 gene polymorphism through gene chip method. Two representative samples were selected as the research objective, then index membership degree under each criterion level were calculated, samples was seen as attached table 4. Sample parameter values Y_1={1,0,0,0,2,2,0,5,3,2,1}, Y_2={1,0,0,1,2,2,2,54,70,3}

Fuzzy relationship matrix

$$R=\begin{bmatrix}0 & 0 & 0\ 1 0\\ 0 & 0 & 0\ 0 1\\ 1 & 0 & 0\ 0 0\\ 1 & 0 & 0\ 0 0\\ 0.7 & 0.3 & 0\ 0 0\\ 0 & 0 & 1\ 0 0\\ 1 & 0 & 0\ 0 0\\ 0.6667 & 0.3333 & 0\ 0 0\\ 0 & 0.7 & 0.3 0 0\\ 0 & 1 & 0\ 0 0\end{bmatrix}$$

By the fuzzy transformation: B=W×R. The results of fuzzy comprehensive evaluation vectors are obtained B=(0.5028,0.0893,0.0409,0.1835,0.1835). The fuzzy comprehensive index method were applied to calculate value FCI=B×S=70.8871. From the evaluation of FCI results, $S=(100,80,60,40,20)^T$ was the comment set. Same way. The sample 2 evaluation value was 60.8980.

From the results, two samples age range was large, and were respectively 32 years old and 70 years old. Because the metabolic ability of elderly person was poor, which affected drug metabolism ability. Long medication time, it was easy to create the drug resistance. A variety of drugs were applied to increase the chances of interaction between the drugs. Drug interactions could be divided into the synergism and antagonism. Generally, a variety of drug combination could greatly increase the possibility of drug in antagonism effect between, thereby, to reduce the drug's effectiveness. And the synergy of drugs also often caused non-security treatment due to various ratio and dosage of different drug, and even lead to excessive treatment. Secondly, in the sample 2, the change of genotype could lead to the change of the target protein conformation and reduce the effectiveness of drugs. In this study, as the design of indicators involved in drugs and the body of clinical and two kinds of indexes, this example mainly discussed the performance evaluation of the same drug in different populations, the drug indicators tended to be the same for the main consideration of clinical and the body. This study could also be used to evaluate the same individuals to different drugs, the individual was more suitable for what kind of drugs. If drug index weight occupied a large part, result of significance may be stronger than that of different individual drug use.

From the result of fuzzy analytic hierarchy process, the weight of drugs and target protein interaction factor accounted for a larger part. It could brought a significant difference for the bonding situation of amino acid residues, gene polymorphism and locus mutation for individual drug use and effectiveness. And the side effects of drugs and drug resistance also should not be ignored, the mainstream multiple targets for drug development mode were for the treatment of complex diseases, but also increased the side effects of drugs. CYP2C9 protein were token as the sample, the protein was as hypoglycemic, anti-inflammatory drugs, cardiovascular drugs, gastric ulcer drugs and antifungal drugs common targets, which caused more side effects in each treatment. So, the efficiency of the drug should not only consider the effect of the treatment of diseases, but also its possible side effects.

Table 1: Effectiveness evaluation index system and index weight of cardiovascular drugs based on CYP2C9 protein

Target level A	Index Level B	Principle Lebel C	Impact Factor D
	Interaction between drug and target protein factors b_1(0.8333)	Bonding situation of drugs and targets c_1(0.4403)	Hydrogen bonding d_1(0.5) PI bonding d_2(0.5)
Effectiveness evaluation of cardiovascular drugs based on CYP2C9 target protein		Target locus mutation or target gene polymorphism c_2(0.3245)	Locus mutation d_3(0.5)
			Gene polymorphism d_4(0.5)
		Drug side effects and drug resistance c_3(0.2352)	Drug known target quantity d_5(0.8333)
			Similar drugs common target quantity d_6(0.1667)
	Clinical and physical factors b_2(0.1667)	Clinical factors c_4(0.75)	Drug combination d_7(0.8333)
			Prescription days d_8(0.1667)
		Clinical factors c_4(0.25)	Age d_9(0.6584)
			Disease condition d_{10}(0.3416)

Fuzzy balance vector W= [0.1835, 0.1835, 0.1352, 0.1352, 0.1633, 0.0327, 0.1042, 0.0208, 0.0274, 0.0142]

Table 2: Individualized cardiovascular drug effectiveness evaluation standard

Indicator	type	V1	V2	V3	V4	V5
Hydrogen bond d_1	positive	>3	3	2	1	0
PI bond d_2	positive	>3	3	2	1	0
Locus mutation d_3	negative	0	1	2	3	4
Gene polymorphism d_4	negative	0	1	2	3	>3
Drug known target quantity d_5	negative	1 ~3	3~6	6~9	9~12	>12
Similar drugs common target quantity d_5	negative	0	1	2	3	>3
Drug combination d_7	negative	0	1	2	3	>3
Prescription days d_8	negative	<7	7~15	15~30	30~60	>60
Age d_9	negative	<20	20 ~ 35	35~50	50-65	>65
Disease condition d_{10}	negative	0	1	2	3	>3

Positive was for the positive effect of the index on individual drug effectiveness; Negative was for negative effects

Table 3: The meaning of AHP ratio scale

Scale	Meaning
1	Comparison between two elements, both were same importance
3	Comparison between two elements, former element was slightly important than latter one
5	Comparison between two elements, former element was obviously important than latter one
7	Comparison between two elements, former element was strongly important than latter one
9	Comparison between two elements, former element was extremely importantly than latter one
2,4,6,8	The intermediate value between above judgment
reciprocal	The importance ratio of element i and element j was α_{ij}, and the ratio of element j and element i was $\alpha_{ji} = \frac{1}{a_{ij}}$

in the comparison between in level of same index, it formed a judgment matrix $A(a_{ij})$.

Based on the fuzzy comprehensive evaluation method, this study evaluated the individualized cardiovascular drug effectiveness. The method profoundly considered the evaluation indicators and evaluation level of uncertainty, the evaluation result could reflect the level of drug efficacy, but also when to evaluate various levels to determine the main factors influencing the individual drug use efficiency. Evaluation results was accordance with the actual situation of drug treatment, it could be used as a cardiovascular drug individualized medication evaluation standard of reference in the future. However, the limited statistical data source, which increased the difficulty of quantifying, affected the establishment of evaluation index system and index system of the design need further optimized.

Table 4: sample 1 indicators of membership hierarchy of sample 1

Target level A	Principle level B	Principle level C	Impact factor D	Evaluation hierarchy				
				V_3	V_2	V_3	V_4	V_5
Cardiovascular drug effectiveness evaluation based on CYP2C9 target protein	Interaction between drug and target protein factors b_1 (0.8333)	Drugs and targets for the bonding situation c_1 (0.4403)	Hydrogen bonding d_1 (0.5)	0	0	0	1	0
			PI bonding d_2 (0.5)	0	0	0	0	1
		Target locus mutation or target gene polymorphism c_2 (0.3245)	Locus mutation d_3 (0.5)	1	0	0	0	0
			Gene polymorphism d_4 (0.5)	1	0	0	0	0
		Drug side effects and drug resistance c_3 (0.2352)	Drugs known to target quantity d_5 (0.8333)	0.7	0.3	0	0	0
			Similar drugs contain common target quantity d_6 (0.1667)	0	0	1	0	0
	Clinical and body factors b_2 (0.1667)	Clinical factors c_4 (0.75)	Drug combination d_7 (0.8333)	1	0	0	0	0
			Long-term drug use d_8 (0.16667)	0.6667	0.3333	0	0	0
		Body factors c_5 (0.25)	Age d_9 (0.6584)	0	0.7	0.3	0	0
			Disease condition d_{10} (0.0887)	0	1	0	0	0

REFERENCES

Do HT, Lo SL and Phan Thi LA (2013). Calculating of river water quanlity sampling frequency by the analytic hierarchy process (AHP). Environ *Monit. Assess.*, **185**(1): 909-916.

Hummel MJ, Volz F and van Manen JG *et al* (2012). Using the analytic hierarchy process to elicit patient preferences: Prioritizing multiple outcome measures of antidepressant drug treatment. *Patient*, **5**(4): 225-237.

Liu SF, Lee YL and Liang JC (2011). Shape design of an optimal comfortable pillow based on the analytic hierarchy process method. *J. Chiropr. Med.*, **10**(4): 229-239.

Suehiro Y and Hinoda Y (2012). Genetic and epigenetic changes in colorectal cancer and genetic testing for personalized medicine. *Rinsho. Byori.*, **60**(10): 976-981.

Suner A, Celikoglu CC and Dicle O *et al* (2012). Sequential decision tree using the analytic hierarchy process for decision support in rectal cancer. *Artif. Intell. Med.*, **56**(1): 59-68.

Wang H, Zheng T and Sun JZ (2012). The Index system establish of military hospitals to deal with bioterrosim construction ability. *Military Medicine*, **36**(10): 765-767.

Wollmann D, Steiner MT and Vieira GE *et al* (2012). Evaluation of health service providers by consumers through the analytic hierarchy process method. *Rev. Saude. Publica.*, **46**(5): 777-783.