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Quantitative design of drug compatibility by weighted modification method[1]

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KEY WORDS combination drug therapy; drug interaction; drug synergism; drug antagonism; drug dose-response relationship; biometry; dexamethasone; metronidazole; allantoin

ABSTRACT

AIM: To set up a new method for designing and quantitatively analyzing drug compatibility. **METHODS**: Drugs for compatibility were divided into 6 dose levels which were evenly distributed to 6 compound groups according to a fixed design. A new mathematical model was set up to fit the dose-effect data of 6 groups. The coefficients, obtained from the model, reflected the dose-effect relationship and the important degree of every drug in combination. According to the coefficients, the drugs in compatibility could be distinguished into principal drug, synergist, inferior, antagonist, and assistant. Because compatibility in the maximal effect group was nearly (or was) an optimal one in 6 groups, the doses in the group were taken as a base for further modification which considered interaction among drugs. The results of the modification were demonstrated by further experiment. This method was applied to design and to quantitatively analyze the compatibility of allantoin, metronidazole, and dexamethasone sodium phosphate by 2 effect indices in mice. **RESULTS**: This new method was able to effectively determine important degree of drugs in combination, and to optimize their doses for designing compatibility. **CONCLUSION**: This weighted modification method is a highly efficient, accurate, and practical means for designing and quantitatively analyzing drug compatibility.

INTRODUCTION

The quantitative analysis of drug compatibility is an important aspect for studying new compound drugs, and is also a key technique for studying traditional Chinese medical formulas. But at present, there are few methods to find an optimal compatibility from multidrug and multidose. For example, if 3 drugs make up a description and each drug is divided into 6 levels, the optimal compatibility must be obtained from the total 18 dose levels of 3 drugs. By the orthogonal design for overall analysis, it is laborious that 216 groups will be set in experiments. To the formula uniform design[1], we find that uniformity is obtained only when the number of groups is up to 11. There are so many dose levels in an effective dose range that dose-effect relationship can not be shown in experiment, and valid dose-effect equation can not be obtained as well. On the other hand, the result of this method is often beyond the limit of special field. So in this paper, based on our previous optimal (super) Latin square design[2], the principle of the uniform design, and the character of dose-effect relationship, a new method was proposed to solve the problem.

To evaluate this new method, the compatibility of allantoin (Alt), metronidazole (Met), and dexamethasone sodium phosphate (Dex), was designed and quantitatively analyzed by this method.

PRINCIPLE AND STEPS

Principle All drugs for compatibility are

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divided into 6 dose levels which are evenly distributed to 6 compound groups. A new mathematical model is set up to fit the dose-effect data of 6 groups, the obtained coefficients from the model can reflect the dose-effect relationship of all drugs and decide their important degree in combination. Because compatibility of the maximal effect group (G_{Emax}) in 6 groups is nearly (or is) an optimal one, the doses in the group are taken as a base for further modification which can consider interaction among drugs. The drugs with apparent dose-effect relationship are adjusted to high dose in combination, the drugs with slight dose-effect relationship are limited to a certain dose, and the drugs without effect or with antagonism are deleted. This result of modification must be demonstrated by further experiment.

Design The number of drugs for compatibility is generally 3 – 4 and no more than 6. Each drug is divided into 6 dose levels in the range from an allowed maximal dose (D_{max}) to a weak effect dose (D_{min}), which are evenly distributed to 6 compound groups. The compatibility design table (Tab 1) is composed. The table is enough to meet practical need for compatibility.

Tab 1. Compatibility design table.

No of drugs	1	2	3	4	5	6
Row selected	A	C	B	F	D	E
No of Row	A	B	C	D	E	F
Group 1	1	2	3	4	5	6
Group 2	2	4	6	1	3	5
Group 3	3	6	2	5	1	4
Group 4	4	1	5	2	6	3
Group 5	5	3	1	6	4	2
Group 6	6	5	4	3	2	1

Rows are selected from Tab 1 according to the number of drugs in combination. For example, if there are 4 drugs for compatibility, the 1st drug is corresponding to Row A, the 2nd to Row C, 3rd to Row B, and 4th to Row F. Six dose levels in every Row is uniformly distributed to 6 compound groups. This uniformity has been confirmed by mathematicians[3].

If the drugs for compatibility are more than 6, some drugs, fixed doses as a background, are not arranged into Tab 1. In another experiment, these drugs are arranged into Tab 1, and the other drug doses are fixed.

Effect (E) indice Effect indice selected must be able to be exactly determined and repeated well in experiment.

G_{Emax} As 6 dose levels are evenly distributed to 6 groups, it is enough to indicate that compatibility in G_{Emax} is nearly (or is) an optimal one. In G_{Emax}, the mean value of the effect and its standard deviation are expressed as $E_{max} \pm s_{max}$, and doses in compatibility are labeled as D_{Emax1}, $D_{Emax2} \cdots D_{Emaxn}$, respectively.

Standardized doses In order to simplify doses and easily judge results without changing dose-effect relationship, 6 doses of each drug are divided by their mean value respectively. Six quotients obtained are called standardized doses (d) (no unit).

Dose-effect equation In mathematics, the relation between compound doses ($d_1 + d_2 + \cdots + d_n$) with their corresponding E can be expressed as hyperbola (Equation 1) or a part on hyperbola in range of D_{max} to D_{min}.

$$E = E'_{max} \cdot \frac{b_1 d_1 + b_2 d_2 \cdots + b_n d_n}{1 + b_1 d_1 + b_2 d_2 \cdots + b_n d_n} \qquad \text{Equation 1}$$

where n = the number of drugs in combination, and b is a variable coefficient of d. E'_{max} is fixed as a maximal effect in fitting equation, and $E'_{max} = E_{max} + s_{max}$. To effect rate (p), $E'_{max} = p + \sqrt{p(1-p)/n}$.

Fitting of dose-effect equation Independent variables (d) and the corresponding E of 6 compound groups were taken into Equation 1 for curve fitting. A variable coefficient (b) of one drug is a mark of its dose-effect relationship, and is also a mark of its important degree in compatibility. Actually, b is a weighted coefficient. The larger b value, the more important is the drug. The most important drug is called the principal drug. If b is small or negative, it indicates that the drug has little dose-effect relationship, or no effect, or antagonism.

Interaction between the principal drugs and other drugs, called the mutual elements, can be observed with Equation 1, in which d is substituted by the mutual elements, such as $d_1 d_2$, $d_1 d_3$. b of a mutual element expresses the degree of interaction between 2 drugs. The larger is b, the stronger is synergism. If b is small or negative, it indicates that there is not

interaction or it may be of antagonism. As the number of variables is more than 6, the mutual elements of every principal drug with other drugs are fitted by Equation 1 separately.

Statistical test of variable coefficient *b* *F* test is used by Equation 2.

$$F=\frac{\upsilon_2\times\sum(\hat{E}-\bar{E})^2}{\upsilon_1\times\sum(E-\hat{E})^2}=\frac{4\times\sum(\hat{E}-\bar{E})^2}{\upsilon_1\times\sum(E-\hat{E})^2} \qquad \text{Equation 2}$$

where $\hat{E}$ = the fitted value of E in the dose-effect equation, $\bar{E}$ = the mean value of E, freedom degree $\upsilon_2 = 4$ and υ_1 = the number of variables. υ_1 can be decreased by degrees according to statistical result of $P(\upsilon_1)$ (Tab 2). For example, when 3 drugs for compatibility, $\upsilon_1 = 3$ and $F > 6.59$ calculated by Equation 2, indicates that 3 variables are of statistical significance [see Tab 2, $P_{(3)} < 0.05$]. If $F < 6.59$ [$P_{(3)} > 0.05$], υ_1 is decreased to 2 ($\upsilon_1 = 2$) and F is recalculated by Equation 2. $F > 6.94$ ($\upsilon_1 = 2$) indicates that the larger 2 variables are certainly of statistical significance [$P_{(2)} < 0.05$]. Otherwise, $F < 6.94$, $\upsilon_1 = 1$, and F is recalculated again. $F > 7.71$ ($\upsilon_1 = 1$) indicates that the largest variable is certainly of statistical significance [$P_{(1)} < 0.05$], and $F < 7.71$ ($\upsilon_1 = 1$) indicates that effects among drugs in compatibility have not significant difference [$P_{(1-3)} > 0.05$]. To mutual elements, the statistical test is the same as above.

Modifying doses According to coefficient and statistical test, drugs in compatibility could be classified into some types. Drugs with $b > 0$ and $P < 0.05$ are called principal drugs, the doses of which are adjusted to D_{max}; drugs with synergizing principal drugs are called synergists, the doses of which are adjusted to range ($D_{Emax} - D_{max}$); drugs with $b < 0$ and $P < 0.05$ are called inferiors, the doses of which are adjusted to range ($D_{min} - D_{Emax}$), or inferiors are deleted from compatibility. Antagonists with antagonizing principal drugs are the same as inferiors. Other drugs with $P > 0.05$, called assistants, take D_{Emax} for compatibility. Modified doses must be kept within D_{max} and satisfy special field demand. These modified doses can constitute one or several modified groups (Tab 3).

Demonstration experiment and the optimal test The effect of a modified group ($\bar{x}_1 \pm s_1$, n_1) must be confirmed by further experiment (the demonstration experiment) and compared with that of $G_{Emax}(x_0 \pm s_0, n_0, \bar{x}_0 \pm s_0 = E_{max} \pm s_{max})$ by the optimal test. This test is similar to an equieffective test[4] with taking special field demand and experiment error into account. Equieffective cutoff L is calculated by

$$L = |s_x \times T - x_0 \times w| \qquad \text{Equation 3}$$

where w = a special equieffective standard (generally $w = 0.05 - 0.1$), it indicates that a modified group must

Tab 2. Variable coefficient (b) of F test table.

Number of b tested	$P_{(\upsilon 1)} > 0.05$	$P_{(\upsilon 1)} < 0.05$
$\upsilon_1 = 6$	$F < 6.16$, then $\upsilon_1 = 5$, F recalculated	$F \geqslant 6.16$, 6 coefficients $P < 0.05$
$\upsilon_1 = 5$	$F < 6.26$, then $\upsilon_1 = 4$, F recalculated	$F \geqslant 6.26$, 5 coefficients $P < 0.05$
$\upsilon_1 = 4$	$F < 6.39$, then $\upsilon_1 = 3$, F recalculated	$F \geqslant 6.39$, 4 coefficients $P < 0.05$
$\upsilon_1 = 3$	$F < 6.59$, then $\upsilon_1 = 2$, F recalculated	$F \geqslant 6.59$, 3 coefficients $P < 0.05$
$\upsilon_1 = 2$	$F < 6.94$, then $\upsilon_1 = 1$, F recalculated	$F \geqslant 6.94$, 2 coefficients $P < 0.05$
$\upsilon_1 = 1$	$F < 7.71$, all coefficients $P > 0.05$	$F \geqslant 7.71$, 1 coefficient $P < 0.05$

Tab 3. Modified dose by the weighted modification method.

$b > 0$ and $P < 0.05$		$b < 0$ and $P < 0.05$		$P > 0.05$	
Drugs	Modified dose	Drugs	Modified dose	Other drugs	Modified dose
Principal drugs	D_{max}	Inferiors	$D_{min} - D_{Emax}$ or no	Assistants	D_{Emax}
Synergists	$D_{Emax} - D_{max}$	Antagonists	$D_{min} - D_{Emax}$ or no		

D_{Emax} = the dose in G_{Emax}, D_{max} = the maximal dose in compatibility design table.

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be superior to G_{Emax} up to certain degree. For example, when influence of a modified group on blood pressure is only up to +5 % or −5 % ($w = 0.05$) higher than that in G_{Emax}, the difference can be taken as a significant change in special field. T = one side $t_{0.05}$ from t-value table or calculated by the formula $T = 1.644 + 1.55/(f - 0.75)$ as $f \geqslant 10$. $f = n_1 + n_0 - 2$. s_x = the common standard error of $\bar{x}_1$ and $\bar{x}_0$, calculated by

$n_1 \neq n_0$,

$$s_x = \sqrt{\frac{s_1^2 \times (n_1 - 1) + s_0^2 \times (n_0 - 1)}{n_1 + n_0 - 2} \times \left(\frac{1}{n_1} + \frac{1}{n_0}\right)}$$

Equation 4

When $n_1 = n_0$, the above formula is simplified as

$$s_x = \sqrt{\frac{s_1^2 + s_0^2}{n_1}}$$

Equation 5

Judge that (1) if $\bar{x}_1 - \bar{x}_0 \geqslant L$, $P < 0.05$, indicating that the optimal test is valid and compatibility in a modified group is an optimal one; (2) if $\bar{x}_0 - \bar{x}_1 \geqslant L$, $P > 0.05$, indicating that the optimal test is invalid and compatibility in G_{Emax} is an optimal one; (3) if $|\bar{x}_0 - \bar{x}_1| < L$, either compatibility in a modified group or G_{Emax} can be selected as an optimal one.

EXPERIMENTS

Materials Alt powder was obtained from Jiangsu Huanghai Pharmaceutical Factory and the purity = 99.6 %, Met powder from Tianjing Hebei Pharmaceutical Factory and the purity = 99.85 %, and Dex powder from Roussel Uclaf Co and the purity = 99.6 %. The assay kit of tissue-type plasminogen activator (t-PA) was purchased from Fujian Taiyang Co, № 980906.

Kunming strain mice (weighing 19 − 21 g) of both sex were purchased from the Animal Center of Nanjing Medical University (Grade Ⅱ, Certificate № 97001).

Compatibility design D_{max} of Alt was decided by a previous experiment as 400 mg·kg^{-1}, D_{max} of Met as 8 mg·kg^{-1} and D_{max} of Dex as 400 mg·kg^{-1}. Each D_{max} was diluted into 6 doses at the same proportion (1 : 0.8) by 5 % glucose (5% GS), and then all doses were evenly distributed to Row A, C, and B from Tab 1, and 6 compound groups were formed as Tab 4.

Tab 4. Compatibility design of Alt, Met, and Dex by the weighted modification method.

Groups	Alt /mg·kg^{-1}	Dex /mg·kg^{-1}	Met /mg·kg^{-1}
1	131 (1)	3.3 (2)	205 (3)
2	164 (2)	5.1 (4)	400 (6)
3	205 (3)	8.0 (6)	164 (2)
4	256 (4)	2.6 (1)	320 (5)
5	320 (5)	4.1 (3)	131 (1)
6	400 (6)	6.4 (5)	256 (4)
$\bar{x}$	246	4.917	246
Control	–	–	–

Ordinal number of dose level was expressed in ( ).

Determination of t-PA activity Mice, fasted for 8 h, were randomly divided into 7 groups of 10 mice. Drugs of Group 1 − 6 were administered (20 mL·kg^{-1}, ip) according to Tab 4, and the control group was given 5 % GS (ip). At the same time, 1 % acetic acid was injected (10 mL·kg^{-1}, ip). After 30 min, the mice were killed and peritonitis exudate of each animal was collected to 1 mL from abdominal cavity opened. The exudate was put into anticoagulated silicic tube and centrifuged at 1500 × g for 10 min. 200 μL supernatant was used. Other procedure of the experiment was done according to the t-PA assay kit introduction. Exudate absorbance (A) in 96-well plate was determined at 405 nm with a microplate photometer (Yutai Yanghang Co, Hong Kong). The differences ($A_{405}\uparrow$), A of each well in Group 1 − 6 minus the mean value of A in control group, were recorded.

Determination of anti-exudation[5] Groups and administration were the same as above. Thirty minutes after the administration, 0.5 % Evans blue normal saline was injected (10 mL·kg^{-1}, iv) by tail vain, and 1 % acetic acid was given (10 mL·kg^{-1}, ip). After 20 min, the mice were killed, and peritonitis exudate of each animal was collected from abdominal cavity opened. Abdominal cavity was washed by normal saline and the washing liquid was collected to 6 mL, which was added to 10 mL by normal saline and centrifuged at 1500 × g for 15 min. The absorbance (A) of supernatant was measured at 590 nm with 721 Spectrometer. Then A was transformed into Evans blue concentration (C_{EB}, mg·L^{-1}) by the standard curve of Evans blue concentration

and A. Differences ($C_{EB}\downarrow$, mg·L^{-1}), C_{EB} of each animal in Group 1 – 6 minus the mean value of C_{EB} in control group, were recorded.

Demonstration experiment Some modified groups were composed of modified doses, and further observed by the demonstration experiment. The experimental results were analyzed by the optimal test.

Data analysis Dose-effect equations were fitted by Simplex method. Computer completed all calculations, and the program was provided on APPENDIX.

RESULTS

Dose-effect data Compared with the control group, all compound groups had stronger effect on $A_{405}\uparrow$ and $C_{EB}\downarrow$ ($P<0.05$ or $P<0.01$) (Tab 5).

Analysis of compatibility of Alt, Met, and Dex on $A_{405}\uparrow$ Group 6 was G_{Emax} (Tab 5). $E'_{max}=\bar{E}_{max}+s_{max}=1.1+0.5=1.6$ (Tab 5). d_1, d_2, and d_3 with E ($A_{405}\uparrow$) were taken into Equation 1 for fitting. The dose-effect equation was obtained.

$$\hat{E}(A_{405}\uparrow)=1.6\,\frac{0.28d_1+1.00d_2-0.49d_3}{1+0.28d_1+1.00d_2-0.49d_3}$$

The variable coefficients (b) in the above equation were tested as follows according to Equation 2 and Tab 2.

$\nu_1=3$, $F=4\times\sum(\hat{E}-\bar{E})^2/[3\times\sum(E-\bar{E})^2]=3.913$, $P_{(\nu1)}=P_{(3)}>0.05$.

$\nu_1=2$, $F=4\times\sum(\hat{E}-\bar{E})^2/[2\times\sum(E-\bar{E})^2]=5.870$, $P_{(\nu1)}=P_{(2)}>0.05$.

$\nu_1=1$, $F=4\times\sum(\hat{E}-\bar{E})^2/[1\times\sum(E-\bar{E})^2]=11.740$, $P_{(\nu1)}=P_{(1)}<0.05$,

namely the largest b ($1.00\ d_2$), $P<0.05$. It indicated that Dex (d_2) was a principal drug.

Then the mutual elements between the principal drug (d_2) and other drugs, with $A_{405}\uparrow$ (E) were taken into Equation 1 for fitting.

$$\hat{E}(A_{405}\uparrow)=1.6\,\frac{0.81\ d_1d_2-0.05\ d_2d_3}{1+0.81\ d_1d_2-0.05\ d_2d_3}$$

$\nu_1=2$, $F=5.913$, $P_{(\nu1)}=P_{(2)}>0.05$. $\nu_1=1$, $F=11.817$, $P_{(\nu1)}=P_{(1)}<0.05$, namely the larger b ($0.81\ d_1d_2$), $P<0.05$. It indicated that Alt (d_1) was a synergist.

The dose in compatibility was adjusted to form a modified group (Tab 6) according to the important degree of each drug in compatibility and special field demand. The effects of the group and G_{Emax} were obtained by further demonstration experiment (Tab 7).

The optimal test of modified group (Tab 7): $\bar{x}_0\pm s_0=1.1\pm0.3$, $\bar{x}_1\pm s_1=1.3\pm0.3$, $n_0=n_1=10$, $f=10+10-2=18$, $w=0.1$, $T=1.644+1.55/(18-0.75)=1.734$; $s_\lambda=\sqrt{(0.3^2+0.3^2)/10}=0.134$; $L=10.134\times1.734-1.1\times0.11=0.122$, $\bar{x}_1-\bar{x}_0=0.2>L=0.122$, $P<0.05$. So the optimal test of Modified group was valid. It indicated that the compatibility in Modified group was an optimal one.

Analysis of compatibility of Alt, Met, and Dex on $C_{EB}\downarrow$ Group 6 was G_{Emax} (Tab 5). $E'_{max}=E_{max}+s_{max}=3.5+0.8=4.3$ mg·L^{-1}. d_1, d_2, d_3 and the corresponding E ($C_{EB}\downarrow$) were taken into Equation 1 for fitting, and a dose-effect equation was obtained,

$$\hat{E}\ (C_{EB}\downarrow)=4.3\,\frac{0.96d_1+0.39d_2+0.22d_3}{1+0.96d_1+0.39d_2+0.22d_3},$$

$P_{(\nu1)}=P_{(1-3)}>0.05$

Tab 5. Standardized doses (d) of Alt, Dex, and Met in combination, their mutual elements and corresponding effects (E). n = number of mice.

Groups	Alt + Dex + Met			Mutual elements			$A_{405}\uparrow$ ($\times10$) ($\bar{x}\pm s$, $n=10$)	$C_{EB}\downarrow$ /mg·kg^{-1} ($\bar{x}\pm s$, $n=10$)
	d_1	d_2	d_3	d_1d_2	d_1d_3	d_2d_3		
1	0.533	0.671	0.833	0.357	0.444	0.559	0.25±0.08	1.4±0.5
2	0.667	1.037	1.626	0.692	1.084	1.687	0.63±0.26	2.7±0.6
3	0.833	1.627	0.667	1.356	0.556	1.085	0.84±0.29	2.6±0.7
4	1.041	0.529	1.301	0.550	1.354	0.688	0.20±0.08	2.8±0.8
5	1.301	0.834	0.533	1.085	0.693	0.444	0.79±0.25	2.3±0.6
6	1.626	1.302	1.041	2.117	1.682	1.355	1.1±0.5	3.5±0.8

d = a dose divided by the mean of doses in the same row (see Tab 4).

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Tab 6. Modified doses of Alt, Dex, and Met in compatibility by $A_{405}\uparrow$.

$b>0$ and $P<0.05$		$P>0.05$	
Drugs	Modified dose /mg·kg^{-1}	Drugs	Modified dose /mg·kg^{-1}
Principal drug: Dex(d_2)	8	Assistant: Met(d_3)	256
Synergist: Alt(d_1)	400		

Tab 7. Modified group compared with G_{Emax} in demonstration experiment. $\bar{x} \pm s$. $n=10$ mice. $^bP<0.05$ *vs* G_{Emax} by the optimal test.

Groups	Alt + Dex + Met /mg·kg^{-1}			$A_{405}\uparrow$ ($\times 10$)
G_{Emax}	400	6.4	256	1.1 ± 0.3
Modified group	400	8.0	256	1.3 ± 0.3^b

Contribution of Alt, Met, and Dex to anti-exudation effect in compatibility was similar ($P_{(1-3)}>0.05$), and the drugs in compatibility can not be distinguished into principal drug, inferior and assistant. So their mutual elements did not need to be observed. The compatibility in the G_{Emax} was an optimal one, and a demonstration experiment was avoided.

DISCUSSION

This weighted modification method has some advantages: 1) it is a highly efficient method: for example, to total 18 dose levels of 3 drugs in combination, the optimal compatibility obtained only needs 6 compound groups and another 2 – 4 groups for a demonstration experiment; 2) the dose for compatibility is limited in the range allowed by a special field, and the modified doses accord with practical demands; 3) the interaction among drugs can be considered in modified doses for compatibility; 4) because of a demonstration experiment, the result of compatibility is reliable.

Some problems must be taken into account:

The effect of compound groups, at least part of groups, should be stronger than that of a negative control group (no drug used).

A large or small variable coefficient (b) only indicates a dose-effect relationship. To a drug with small coefficient, it is not certain that the drug has no effect. The comparison between coefficients must be limited in the same equation.

D_{max}, an allowed maximal dose in practice, is often determined by a pre-experiment. The range from D_{max} to D_{min} should be wide enough to be divided into 6 groups, but some drugs have a narrow dose range so 6 dose levels in this design need be reduced. For example, continuous 2 doses in 6 dose levels can be the same, dose level 1 = level 2 or level 5 = level 6.

Effect indices should be repeated well in experiment. Because of experimental error, a modified dose is only taken as a clue, and a demonstration experiment is necessary.

Taking changed effect (increased or decreased value) as an indice of effect, it is helpful to accurately fit the dose-effect equation. Moreover, it must be prudent in deleting a drug from compatibility according to a certain indice, because a prescription often has many effect indices. For example, in this study, if taking antibacterial effect as an indice, Med maybe a principal drug. So it is necessary to make a comprehensive indice for compatibility.

APPENDIX

A QBASIC program of the modification method (DATA in the program from the compatibility of Alt, Met, and Dex on $A_{405}\uparrow$ (in this paper):

```
DECLARE SUB
sub1 (Emax!,m!,n!,p! (),x! (),y! (),yy! ())
DECLARE SUB
sub2 (Emax!,s!,n!,t! (),x! (),y! (),yy! ())
CLS
E = .0001: a = 2: B = .5
READ n, Emax
m = n + 1
DIM p(m,m),x(6,n),y(6),yy(6),t(n),SE(6)
FOR i = 1 TO 6
  FOR j = 1 TO n
    READ x(i, j)
  NEXT j
NEXT i
meany = 0
FOR i = 1 TO 6
  READ y(i)
```

```
  meany = meany + y(i)
NEXT i
meany = meany/6
FOR i = 1 TO n
  p(1, i) = 1
NEXT i
FOR i = 2 TO m
  FOR j = 1 TO n
    IF i = j + 1 THEN
     p(i, j) = p(1, j) + 1
    ELSE
     p(i, j) = p(1, j)
    END IF
  NEXT j
NEXT i
CALL sub1(Emax,m,n,p(),x(),y(),yy())
PRINT "Do..."
q = 0
DO
  q = q + 1
  LOCATE 2, 1
  PRINT "Pass"; q
    FOR i = 1 TO n
     FOR j = i + 1 TO m
      IF p(i, m) > p(j, m) THEN
       FOR k = 1 TO m
        SWAP p(i, k), p(j, k)
       NEXT k
      END IF
     NEXT j
NEXT i
IF ABS((p(1,m) - p(m,m))/p(1,m)) < E THEN
EXIT DO
FOR j = 1 TO n
  f = 0
FOR i = 1 TO n
    f = f + p(i, j)
  NEXT i
  w(j) = f/n
  p(m, j) = 2 * w(j) - p(m, j)
NEXT j
FOR i = 1 TO n
  t(i) = p(m, i)
NEXT i
CALL sub2(Emax,s,n,t(),x(),y(),yy())
IF s<p(m, m) THEN
IF s<p(1, m) THEN
    FOR i = 1 TO n
    t(i) = w(i) + a * (p(m,i) - w(i))
  NEXT i
  CALL sub2(Emax,ss,n,t(),x(),y(),yy())
  IF ss < s THEN
    FOR i = 1 TO n
      p(m, i) = t(i)
    NEXT i
    p(m, m) = ss
  ELSE
   p(m, m) = s
  END IF
 ELSE
  p(m, m) = s
 END IF
ELSE
  IF s < p(m, m) THEN
   FOR i = 1 TO n
    t(i) = w(i) + B * (p(m, i) - w(i))
   NEXT i
   CALL sub2(Emax,ss,n,t(),x(),y(),yy())
   IF ss < s THEN
    FOR i = 1 TO n
      p(m, i) = t(i)
    NEXT i
    p(m, m) = ss
   ELSE
    p(m, m) = s
   END IF
ELSE
  FOR i = 1 TO n
    t(i) = w(i) - B * (p(m, i) - w(i))
  NEXT i
  CALL sub2(Emax,ss,n,t(),x(),y(),yy())
  IF ss < p(m, m) THEN
    FOR i = 1 TO n
      p(m, i) = t(i)
    NEXT i
    p(m, m) = ss
  ELSE
    FOR i = 2 TO m
      FOR j = 1 TO n
        p(i,j) = (p(1,j) + p(i,j))/2
      NEXT j
    NEXT i
    CALL sub1(Emax,m,n,p(),x(),y(),yy())
  END IF
```

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```
 END IF
END IF
LOOP
R1 = 0: R2 = 0: R3 = 0: yy = 0
FOR i = 1 TO 6
  FOR k = 1 TO n
    yy = p(1, k) * x(i, k) + yy
  NEXT k
  E = Emax * yy/(yy + 1)
  yy = 0
  R1 = (y(i) - E)^2 + R1
  R2 = (y(i) - meany)^2 + R2
  R3 = (meany - E)^2 + R3
NEXT i
PRINT "E'max = "; Emax
FOR i = 1 TO n
  PRINT " b"; i; " = "; p(1, i)
NEXT i
FOR i = n TO 1 STEP -1
  R = 1 - R1/R2
  F = 4 * R3/(R1 * i)
  PRINT " v1 = "; i;", F(v"; i;") = "; INT(F *
1000)/1000;
  IF i = 6 AND F > = 6.16 THEN
    PRINT ",P < 0.05"
  ELSEIF i = 5 AND F > = 6.26 THEN
    PRINT ", P < 0.05."
  ELSEIF i = 4 AND F > = 6.39 THEN
    PRINT ",P < 0.05."
  ELSEIF i = 3 AND F > = 6.59 THEN
    PRINT ",P < 0.05."
  ELSEIF i = 2 AND F > = 6.94 THEN
    PRINT ",P < 0.05."
  ELSEIF i = 1 AND F > = 7.71 THEN
    PRINT ",P < 0.05."
  ELSEIF i = 1 AND F < 7.71 THEN
    PRINT ",P > 0.05."
  ELSE
    PRINT ",P > 0.05."
  END IF
NEXT i
REM Number of variables(d1,d1d2...),E'max
DATA 3,1.6
REM Standardized doses of 6 compound groups
DATA 0.533,0.671,0.833
DATA 0.667,1.037,1.626
DATA 0.833,1.627,0.667
DATA 1.041,0.529,1.301
DATA 1.301,0.843,0.533
DATA 1.626,1.302,1.041
REM Effects in 6 compound groups
DATA 0.25,0.63,0.84,0.2,0.79,1.1

SUB sub1 (Emax,m,n,p(),x(),y(),yy())
  yy = 0
    FOR j = 1 TO m
      p(j, m) = 0
    FOR i = 1 TO 6
      FOR k = 1 TO n
        yy = p(j, k) * x(i, k) + yy
      NEXT k
      yy(i) = Emax * yy/(1 + yy)
      p(j,m) = p(j,m) + (yy(i) - y(i))^2
      yy = 0
    NEXT i
  NEXT j
END SUB

SUB sub2 (Emax,s,n,t(),x(),y(),yy())
  s = 0: yy = 0
  FOR i = 1 TO 6
    FOR j = 1 TO n
      yy = t(j) * x(i, j) + yy
    NEXT j
    yy(i) = Emax * yy/(1 + yy)
    s = s + (yy(i) - y(i))^2
    yy = 0
  NEXT i
END SUB
```

EFERENCES

1 Fang KT. Uniform design and uniform design tables. 1st ed. Beijing: Science Press; 1994. p 55-63.
2 Sun RY. Design and statistical analysis of pharmacological experiment. In: Xu SY, Bian RN, Cheng X, editors. Methodology of the pharmacological experiments. 2nd ed. Beijing: People's Medical Publishing House; 1994. p 173-4.
3 Fang KT. Uniform design-Number theory method is applied to experimental design. Acta Math Appl Sin 1980; 3: 363-72.
4 Zheng QS, Sun RY. Analysis of multidrug effects by parameter method. Acta Pharmacol Sin 1998; 19: 234-7.
5 Yu CB. Experimental method of capillary permeability. In: Xu SY, Bian RN, Cheng X, editors. Methodology of the pharmacological experiments. 2od ed. Beijing: People's Medical Publishing House; 1994. p731.

权重配方法定量设计药物组方[1]

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关键词 联合药物治疗; 药物相互作用; 药物协同作用; 药物拮抗作用; 药物剂量效应关系; 生物统计学; 地塞米松; 甲硝唑; 尿囊素

目的: 建立一种药物组方设计和定量分析的新方法. **方法**: 将配方设计规范为 6 个配伍组, 根据新的数学模型, 确定各药的量效关系和交互影响, 从而判断各药在配方中重要程度. 以此为基础, 调整配伍剂量, 向最优结果逼近. 其调整的优化剂量由进一步试验来验证其效应. 并以尿囊素, 地塞米松磷酸钠和甲硝唑组方为例, 选用 2 个指标, 作配方设计和定量分析. **结果**: 本法能有效地分析实验中各药在组方中的地位(如主药, 辅药, 协同药等), 并据此调整剂量, 构成新的配伍, 经配方优方检验, 确定了最佳配伍结果. **结论**: 权重配方法是一种高效, 严谨和实用的方法, 可用以设计药物组方, 并作药物配伍的定量分析.

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