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COMMUN. STATIST.—SIMULA., 31(2), 301–312 (2002)

NONPARAMETRIC IDENTIFICATION OF THE MINIMUM EFFECTIVE DOSE FOR RANDOMIZED BLOCK DESIGNS

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ABSTRACT

One primary purpose in a dose–response study for drug development is to identify the minimum effective dose (MED), which is the lowest dose level producing an effect over that of the zero-dose control. Proposed herein is a nonparametric step-down closed testing procedure for identifying the MED in a randomized block design with one or more observations per cell. The associated *p*-value of the identified MED is then obtained. Numerical examples further demonstrate the feasibility of the proposed testing procedure. Finally, the comparative results of a Monte Carlo investigation of the relative error rate and power performances are presented and discussed.

Key Words: Adjusted *p*-value; Dose–response study; Step-down closed test

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1. INTRODUCTION

To investigate the effect of a substance in a dose–response study, several increasing dose levels of the substance are usually compared with a zero-dose control. One factor of interest in such a study is to identify the lowest dose level producing a desirable effect over that of the zero-dose control, which is commonly referred to as the minimum effective dose (MED, see, for instance, Ruberg, 1989). An example of this arises in studies of the effect of laboratory animals to a substance such as a drug, a food additive, or a pesticide.

Nonparametric procedures for identifying the MED in a one-way layout have been extensively studied by many authors. Shirley (1977) and Williams (1986) considered multiple tests for identifying the MED based on the isotonic regression estimators of the Kruskal–Wallis (1952) average ranks under the assumption of a monotonic (or an ordered) dose–response relationship. Chen and Wolfe (1993) further suggested multiple tests for contrasting increasing dose levels based on the rank-based isotonic regression estimators under an up-and-down dose–response relationship, which is also known as an umbrella pattern (Mack and Wolfe, 1981). To make the MED identification procedure easy to implement, Chen (1999) proposed a multiple test based on the Mann–Whitney (1947) statistics incorporated into the step-down closed testing scheme suggested by Tamhane et al. (1996). Notice that the power performance of Chen's test is at least competitive to that of the isotonic regression-based procedures for an ordered dose–response relationship. Moreover, Chen's test is more powerful than the Chen-Wolfe procedure for an umbrella pattern dose–response relationship.

In a one-way layout, however, existing differences between the increasing dose levels and the zero-dose control may be obscured by relatively large variability of subjects within the samples. This problem can often be alleviated by conducting a randomized block design where the subjects are divided into more homogeneous blocks and the subjects in each block are randomly assigned to receive different dose levels under study. For the randomized block design with one observation per cell, House (1986) extended Williams' (1986) test based on the isotonic regression estimators of Friedman's (1937) average ranks for a monotonic dose–response relationship. Lim and Wolfe (1997) further proposed isotonic regression-based multiple tests under the assumption of an umbrella pattern dose–response relationship. Note that a variety of general randomized block designs in which the control is allowed to appear more often than the individual treatments have been discussed for multiple comparisons with a control, see, for example, Bechhofer and Tamhane (1981) and Spurrier

(1988,1993). However, the problem of the MED identification has not yet been addressed for any more general block design. In this paper, we extend Chen's (1999) test for the more general randomized block design with multiple observations per cell. The associated p-value of the identified MED is further obtained which is defined to be the smallest level of significance at which the dose level would be declared to be the MED.

In Section 2, an extension of Chen's (1999) test to a general randomized block design is proposed. Two examples illustrating the use of the test procedure are given in Section 3. Finally, in Section 4, the results of a Monte Carlo simulation investigation of the relative error rate and power performances of the competing tests are presented and discussed.

2. PROPOSED TEST

Let $Y_{ij1}, Y_{ij2}, \ldots, Y_{ijn_{ij}} (i = 1, 2, \ldots, \text{b},\ j = 0, 1, \ldots, k$ and $n_{ij} \geq 1)$ be independent continuous random variables with the distribution function of Y_{ijt} given by $F(x - \beta_i - \theta_j)$, where the β_i are block effects that are not of direct interest and the θ_j are treatment effects. Suppose that the zero treatment ($j = 0$) is the zero-dose control and the other k treatments correspond to increasing dose levels. In this paper, specifically, we consider identification of the MED which is the smallest dose level producing a better treatment effect than does the zero-dose control; namely,

$$\text{MED} = \min\{j : \theta_j > \theta_0,\ j = 1, 2, \ldots, k\}$$

As noted in Tamhane et al. (1996), the family of null hypotheses $H = \{H_{0j}\}$, where

$$H_{0j} : (\theta_0 = \theta_1 = \cdots = \theta_{j-1} = \theta_j), \quad j = 1, 2, \ldots, k,$$

is closed under intersection in the sense that $H_{0i} \in H$ and $H_{0j} \in H$ imply $H_{0i} \cap H_{0j} \in H$ (Marcus et al., 1976). Hence, a level α closed procedure, which includes separate level α tests of individual H_{0j} applied in a step-down manner, can be employed in finding the MED. Moreover, the closed testing scheme strongly controls the family-wise error rate (FWE), which is the probability that at least one true H_{0j} is rejected. Therefore, we consider using nonparametric statistics incorporated into a step-down closed testing scheme to identify the MED for the general randomized block design with one or more observations per cell.

Let T_{ij} be the Mann–Whitney (1947) statistic comparing the jth dose level with all the lower dose groups combined in the ith block, namely,

$$T_{ij} = \sum_{u=0}^{j-1} \sum_{s=1}^{n_{ij}} \sum_{r=1}^{n_{iu}} I(Y_{ijs} - Y_{iut}), \quad i = 1, 2, \ldots, b, \;\; j = 1, 2, \ldots, k,$$

where $I(a) = 1$ if $a > 0, = 0$, otherwise.

Notice that, for each $i = 1, 2, \ldots, b$, the T_{ij} are uncorrelated under H_{0k} (Terpstra, 1952). Let $N_j^i = \sum_{s=0}^{j} n_{is}$, $i = 1, 2, \ldots, b$, $j = 1, 2, \ldots, k$. Set $T_j = \sum_{i=1}^{b} T_{ij}$, $j = 1, 2, \ldots, k$. Since observations in different blocks are independent, the null (H_{0k}) mean and variance of T_j are respectively given by

$$\mu(T_j) = \sum_{i=1}^{b} n_{ij} N_{j-1}^i \Big/ 2$$

and

$$\sigma^2(T_j) = \sum_{i=1}^{b} n_{ij} N_{j-1}^i (N_j^i + 1) \Big/ 12$$

If there are ties among the N_j^i observations, a modification of the $\mathrm{Var}(T_j)$ is then obtained by replacing the $(N_j^i + 1)$ with $(N_j^i + 1) - \sum_{u=1}^{g_i} (t_u^3 - t_u)/\{N_j^i (N_j^i - 1)\}$, where g_i is the number of tied groups in block i and t_u is the size of the tied group u. Let

$$T_j^* = \{T_j - \mu(T_j)\}/\sigma(T_j), \quad j = 1, 2, \ldots, k,$$

where $\sigma(T_j) = \sqrt{\sigma^2(T_j)}$. Notice that, under H_{0k}, the statistics $T_1^*, T_2^*, \ldots, T_k^*$ are uncorrelated. The Projection Theorem (see, for example, Randle and Wolfe, 1979) then implies that, the asymptotic null (H_{0k}) distribution of $(T_1^*, \ldots, T_k^*)$ is a k-variate normal with zero mean vector and identity covariance matrix. Let $z(c)$ be the upper cth percentile of a standard normal distribution. Then, the asymptotic independence of $T_1^*, \ldots, T_k^*$ implies that, for each $j = 1, 2, \ldots, k$.

$$1 - \alpha \approx P\{\max(T_1^*, \ldots, T_j^*) \le z(\alpha(j)) | H_{0j}\},$$

where $\alpha(j) \approx 1 - (1 - \alpha)^{1/j}$.

As an extension of Chen's (1999) test, we describe a step-down closed testing scheme suggested by Tamhane et al. (1996) together with the test statistics $T_1^*, \ldots, T_k^*$ for a general randomized block design in the following: To identify the MED at level α, we first let $k_1 = k$ and find

$T^*_{(k_1)} = \max(T^*_1, \ldots, T^*_{k_1})$. Define $d(k_1)$ to be the anti-rank of $T^*_{(k_1)}$; that is, $T^*_{(k_1)} = T^*_{d(k_1)}$. Then, if $T^*_{(k_1)} \geq z(\alpha(k_1))$, we reject H_{0j}, $j = d(k_1), \ldots, k_1$, and go to the second step with $k_2 = d(k_1) - 1$; otherwise, stop testing and accept all the null hypotheses. In general, at the ith step, let $k_i = d(k_{i-1}) - 1$. If $\max(T^*_1, \ldots, T^*_{k_i})$ or $T^*_{d(k_i)} \geq z(\alpha(k_i))$, then we reject H_{0j}, $j = d(k_i), \ldots, k_i$; otherwise, stop testing. When testing stops at, say, the mth step, identify the MED as $d(k_{m-1})$ or $k_m + 1$.

Notice that the p-value of a single test which is the smallest significance level leading to the rejection of its null hypothesis is usually reported for demonstrating the strength of the statistical evidence for the rejection. For the multiple test proposed in this paper, the p-value of the identified MED can be computed as the smallest significance level at which the dose level would be declared as the MED. Let $t^*_{d(k_i)}$ be the observed value of $T^*_{d(k_i)} = \max\{T^*_1, \ldots, T^*_{k_i}\}$ at the ith step. Compute

$$\begin{aligned} p^*(k_j) &= P\left\{ T^*_{(k_j)} \geq t^*_{d(k_j)} \middle| H_{0k_j} \right\} \\ &= P\left\{ \text{At least one } T^*_s \geq t^*_{d(k_j)},\ s = 1, \ldots, k_j \middle| H_{0k_j} \right\} \\ &= 1 - P\left\{ T^*_s < t^*_{d(k_j)},\ s = 1, \ldots, k_j \middle| H_{0k_j} \right\} \\ &\approx 1 - \left\{ \Phi(t^*_{d(k_j)}) \right\}^{k_j}, \end{aligned}$$

where $\Phi(\cdot)$ is the distribution function of a standard normal variable. The adjusted p-value (Wright, 1992) is then defined to be

$$p(k_i) = \max\left\{ p^*(k_1), \ldots, p^*(k_i) \right\}.$$

As an equivalent version of the step-down testing procedure mentioned in last paragraph, the MED can be identified at significance level α based on the adjusted p-value, $p(k_i)$, where the null hypotheses H_{0j}, $j = d(k_i), \ldots, ki$, are rejected at the ith step, if $p(k_i) < \alpha$. If the test stops at, say, the mth step, then the MED is identified to be $k_m + 1$ and the p-value of this conclusion is $p(k_{m-1})$, which provides a measure of the strength of evidence for the rejection of $H_{0k_{m-1}} : (\theta_0 = \theta_1 = \cdots = \theta_{k_{m-1}})$.

3. EXAMPLES

First consider the data set in Table 1 analyzed in House (1986), which corresponds to an experiment conducted to determine the lowest dose of sulfur dioxide (SO_2) with a significant increase in a specific airway resistance

Table 1. Changes[a] in sRaw (cm. H_2O/sec.) for Eleven Subjects Exposed to a Control and Three Concentration of SO_2 (ppm)

	Concentration of SO_2 (ppm)			
Subject	0.00	0.25	0.50	1.00
1	0.2	2.3	−0.8	4.0
2	6.2	12.7	13.1	9.0
3	0.3	−0.2	1.1	4.2
4	0.3	2.1	12.8	6.7
5	4.9	6.0	18.2	35.0
6	1.8	1.8	3.4	9.0
7	3.9	3.9	13.5	12.9
8	2.0	1.1	4.4	2.0
9	0.3	3.8	6.1	7.1
10	2.5	2.5	2.8	1.5
11	5.4	1.3	10.6	10.6

[a]10-minute exposure measurement minus pre-exposure measurement.

(sRaw). Each of the 11 subjects (blocks) participated in four randomly ordered 10-minute exposures, one for each dose and separated by at least 1 week. The four doses of SO_2 under study were 0.00, 0.25, 0.5 and 1 ppm. The change in sRaw from pre-exposure to after 10 minutes of exposure is observed. The summary statistics are obtained in the following:

$$T_1 = 6.5, \quad T_2 = 20, \quad T_3 = 24$$
$$\mu(T_1) = 5.5, \quad \mu(T_2) = 11, \quad \mu(T_3) = 16.5$$
$$\sigma^2(T_1) = 2.0, \quad \sigma^2(T_2) = 7.33, \quad \sigma^2(T_3) = 13.5$$

Notice that the largest statistic among the three $T_i^{*\prime}s$ is T_2^*, so $d(3) = 2$. The value of $p(3) = p^*(3) \approx 1 - \{\Phi(3.32)\}^3 \approx 0.001 (< 0.01)$ leads to a second-step comparison with $k_2 = 1$. Since $p^*(1) \approx 1 - \Phi(0.71) \approx 0.2389$, the step-down closed test identifies the MED to be 2. Although, under the significance level $\alpha = 0.01$, House's (1986) test also reaches the same conclusion that 0.5 ppm is the lowest dose of SO_2 which produces a significant increase in sRaw. However, by using the step-down closed test, we further obtain 0.001 as an approximated p-value for the conclusion.

The second data set in Table 2 reported in Simpson and Margolin (1986) was obtained from the three replicate (block) Ames test conducted by Ames et al. (1975) in which plates containing Salmonella bacteria of strain T_A98 were exposed to various doses of Acid Red 114, including 0,

Table 2. Revertant Colonies for Acid Red 114, T_A98, Hamster Liver Activation

	Dose (μg/ml)					
Replicate	0	100	333	1000	3333	10000
1	22	60	98	60	22	23
	23	59	78	82	44	21
	23	54	50	59	33	25
2	19	15	26	39	33	10
	17	25	17	44	26	8
	16	24	31	30	23	
3	23	27	28	41	28	16
	22	23	37	37	21	19
	14	21	35	43	30	13

100, 333, 1000, 3333 and 10000 μg/ml. The number of visible revertant colonies on each plate was observed. Notice that there are 3 plates for each dose level in every replicate, but only 2 plates are used for the last dose level in the second replicate. To investigate at which dose of Acid Red 114 the number of visible revertant colonies shows a significant increase from that at the zero-dose control, we compute the following statistics:

$$T_1 = 21.5, \quad T_2 = 47.5, \quad T_3 = 72.5, \quad T_4 = 44, \quad T_5 = 8$$

$$\mu(T_1) = 13.5, \ \mu(T_2) = 27, \ \mu(T_3) = 40.5, \ \mu(T_4) = 54, \ \mu(T_5) = 60$$

$$\sigma^2(T_1) = 15.6, \quad \sigma^2(T_2) = 44.875, \quad \sigma^2(T_3) = 87.44$$

$$\sigma^2(T_4) = 143.66, \quad \sigma^2(T_5) = 187.2$$

$$T_1^* = 2.03, \quad T_2^* = 3.06, \quad T_3^* = 3.42, \quad T_4^* = -0.83, \quad T_5^* = -3.80$$

First, let $k_1 = 5$. Notice that $d(5) = 3$ and $p(5) = p^*(5) \approx 1 - \{\Phi(3.42)\}^5 = 0.0015 (< 0.01)$ lead to a second-step comparison with $k_2 = 2$ and $d(2) = 2$. Since $p^*(2) \approx 1 - \{\Phi(3.06)\}^2 \approx 0.0022$, the adjusted p-value is obtained as $p(2) = \max\{p^*(5), p^*(2)\} = 0.0022 (< 0.01)$. Now, $p^*(1) \approx 1 - \Phi(2.03) = 0.0212$. Therefore, we reach the conclusion that the MED of Acid Red 114 is 333 μg/ml at which there is a significant increase of visible revertant colonies with an approximate p-value of 0.0022. However, we can also conclude that the MED is 100 μg/ml, but the associated p-value is about $p(1) = \max\{p^*(5), p^*(2), p^*(1)\} = 0.0212$.

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4. MONTE CARLO STUDY

A Monte Carlo study was conducted to examine the relative error rate and power performances of House's (H) test, Lim-Wolfe tests for both the peak-known (LW(p)) and peak-unknown (LW($\hat{p}$)) cases, and the step-down closed test (SDT) proposed in this paper for identifying the MED in a randomized block design with one observation per cell. The study was performed for comparing $k=3$ and 4 treatments with a control in $b=10$ blocks and for a variety of monotonic (ordered) and up-and-down (umbrella) dose–response relationship.

For each of these settings, appropriate normal and exponential deviates were generated by using the IMSL routines RNNOR and RNEXP, respectively. The normal distributions under consideration have the same variance 10 but different means θ_i, and the exponential distributions have various location parameters θ_i with a common scale parameter 1. The designated alternative configurations correspond to values of $\theta_{i0}=\theta_i-\theta_0$, $i=1,2,\ldots,k$, which include step and linear typed ordered treatment effects and umbrella patterned treatment effects. The family-wise error rate (FWE, the probability of incorrectly identifying a lower MED) and the power (the probability of correctly identifying the MED) are simulated. In each case, we used 10 000 replications in obtaining the various FWE and power estimators. To assess the power performances of the four tests over all the situations considered in the study, we also computed their average powers. The FWE and power estimates for the four tests are presented in Tables 3 and 4. Notice that, under the nominal level $\alpha=0.05$, the standard deviation of the estimated FWE is about $0.002(\approx \sqrt{(0.05)(0.95/10000)}$. Also notice that, when the true MED is 3, for example, if the identified MED ≤ 2, then the test makes the Type I error and contributes to the family-wise error rate. If, however, the true MED is 1, then the FWE is zero, since no Type I errors are involved. Therefore, the entry of estimated FWE = .000 is omitted for all procedures.

We observe from the simulation results that the FWE of the four testing procedures are not significantly higher than the nominal level 0.05. In fact, the SDT test even tends to be conservative in controlling its FWE for some configurations.

The power estimates in Tables 3 and 4 show that the H test (a special case of LW(p) test with $p=k$) has excellent power when treatment effects have a monotonic ordering. However, the power of the H test drops when there is a downturn in the dose–response relationship. For the umbrella pattern dose–response relationship with MED $\$ > \$$ 1 under study, the SDT test has, in general, higher power than does the H test. Therefore, on the average, the power performance of the SDT test is better than the H test.

Table 3. Estimated FWE and Power for $\alpha = 0.05$, $k = 3$ and $b = 10$

			FWE				Power			
θ_{10}	θ_{20}	θ_{30}	H	LW(p)	LW($\hat{p}$)	SDT	H	LW(p)	LW($\hat{p}$)	SDT
(a) Normal distribution										
0	0	3	0.049	0.049	0.047	0.023	0.827	0.827	0.782	0.930
0	3	3	0.053	0.053	0.052	0.048	0.818	0.818	0.408	0.849
3	3	3	—	—	—	—	0.862	0.862	0.273	0.731
0	2	3	0.051	0.051	0.047	0.036	0.569	0.569	0.391	0.535
1	2	3	—	—	—	—	0.247	0.247	0.193	0.155
0	3	2	0.053	0.053	0.045	0.049	0.725	0.870	0.425	0.854
0	3	0	0.042	0.052	0.023	0.047	0.237	0.851	0.781	0.856
2	3	2	—	—	—	—	0.596	0.619	0.288	0.486
2	3	0	—	—	—	—	0.379	0.624	0.385	0.492
Average power							0.584	0.699	0.436	0.654
(b) Exponential distribution										
0	0	3	0.048	0.048	0.046	0.026	0.614	0.614	0.536	0.754
0	3	3	0.055	0.055	0.048	0.041	0.599	0.599	0.324	0.624
3	3	3	—	—	—	—	0.618	0.618	0.226	0.441
0	2	3	0.048	0.048	0.040	0.025	0.396	0.339	0.396	0.247
1	2	3	—	—	—	—	0.198	0.113	0.198	0.144
0	3	2	0.056	0.058	0.042	0.044	0.490	0.714	0.350	0.619
0	3	0	0.035	0.052	0.022	0.037	0.150	0.676	0.533	0.617
2	3	2	—	—	—	—	0.423	0.457	0.206	0.296
2	3	0	—	—	—	—	0.253	0.441	0.239	0.292
Average power							0.416	0.508	0.334	0.448

It is not surprising to find that the peak-known Lim-Wolfe LW(p) test performs well for all the alternatives under consideration. However, when the true MED is not the first nonzero dose level, the SDT test even outperforms the LW(p) test. Although the average power of SDT test is slightly lower than that of the LW(p) test, the SDT test provides indeed a competitor to the LW(p) test for identifying the MED. Moreover, the power performance of the LW($\hat{p}$) test further indicates that the SDT test should be used if the peak of the umbrella pattern dose–response relationship is not certain.

In conclusion, the use of the proposed step-down closed test is recommended for identifying the MED in a randomized block design. The proposed test is very easy to implement relative to the competing House's or Lim-Wolfe tests, since it involves only the two-sample Mann–Whitney

Table 4. Estimated FWE and Power for $\alpha = 0.05$, $k = 4$ and $b = 10$

				FWE				Power			
θ_{10}	θ_{20}	θ_{30}	θ_{40}	H	LW(p)	LW($\hat{p}$)	SDT	H	LW(p)	LW($\hat{p}$)	SDT
(a) Normal distribution											
0	0	0	4	0.044	0.044	0.058	0.041	0.938	0.938	0.895	0.958
0	0	4	4	0.049	0.049	0.049	0.025	0.925	0.925	0.419	0.973
0	4	4	4	0.055	0.055	0.055	0.054	0.926	0.926	0.263	0.936
4	4	4	4	—	—	—	—	0.981	0.981	0.288	0.926
0	0	3	4	0.050	0.050	0.049	0.024	0.823	0.823	0.631	0.927
0	2	3	4	0.048	0.048	0.046	0.032	0.572	0.572	0.383	0.537
1	2	3	4	—	—	—	—	0.238	0.238	0.203	0.150
0	0	4	3	0.049	0.049	0.049	0.028	0.916	0.928	0.250	0.971
0	0	4	0	0.044	0.048	0.038	0.024	0.365	0.917	0.896	0.974
0	3	4	3	0.050	0.050	0.050	0.046	0.842	0.846	0.379	0.857
0	3	4	0	0.051	0.053	0.043	0.049	0.570	0.823	0.634	0.849
2	3	4	3	—	—	—	—	0.624	0.625	0.479	0.488
2	3	4	0	—	—	—	—	0.554	0.602	0.379	0.477
Average power								0.713	0.780	0.469	0.771
(b) Exponential distribution											
0	0	0	4	0.043	0.043	0.058	0.044	0.817	0.817	0.696	0.925
0	0	4	4	0.053	0.053	0.051	0.026	0.756	0.756	0.371	0.913
0	4	4	4	0.054	0.054	0.053	0.048	0.754	0.754	0.250	0.800
4	4	4	4	—	—	—	—	0.784	0.784	0.251	0.611
0	0	3	4	0.045	0.045	0.044	0.023	0.622	0.622	0.427	0.755
0	2	3	4	0.048	0.048	0.043	0.027	0.398	0.398	0.237	0.351
1	2	3	4	—	—	—	—	0.195	0.195	0.159	0.112
0	0	4	3	0.051	0.051	0.046	0.026	0.729	0.831	0.329	0.917
0	0	4	0	0.044	0.052	0.042	0.030	0.242	0.792	0.698	0.914
0	3	4	3	0.054	0.054	0.050	0.041	0.621	0.622	0.274	0.624
0	3	4	0	0.052	0.056	0.044	0.040	0.362	0.610	0.420	0.616
2	3	4	3	—	—	—	—	0.444	0.447	0.317	0.302
2	3	4	0	—	—	—	—	0.380	0.436	0.246	0.302
Average power								0.532	0.622	0.347	0.618

statistics and the necessary critical values can be found from a standard normal table. Meanwhile, when there is only one observation per cell, the proposed test controls the family-wise error rate well and has a better or, at least competitive power performance to the competing tests for most practical situations. In addition, the proposed test is applicable to the general randomized block design with multiple observations per cell, which is of

greater practical use. Finally, by using the proposed step-down test, the approximate *p*-value of the identified MED can be obtained which further provides a measure of strength of statistical evidence for the MED identification.

ACKNOWLEDGMENTS

The work of the first author was supported in part by National Science Council of Taiwan under the grant NSC-87-2121-M-008-006. The authors wish to thank Mr. T. S. Chen for his computing assistance.

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