DOUBLE BLIND STUDY OF HYDROXYZINE, PROMETHAZINE, SECOBARBITAL, AND A PLACEBO FOR PREANAESTHETIC MEDICATION*

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HYDROXYZINE (Atarax®, Vistaril®) has been under clinical trial to determine its efficacy for pre-anaesthetic medication on the basis of its purported neurosedative, antihistaminic, antispasmodic, anti-emetic, and anaesthetic potentiating properties¹⁻⁶ Laboratory studies have shown that the intravenous injection of hydroxyzine causes a transient fall in blood pressure, an increase in coronary blood flow, and suppression of epinephrine-induced ventricular arrhythmias⁷ The protective effect of hydroxyzine against arrhythmias is unreliable⁸ In clinical tests, the therapeutic sedative dose has virtually no antisialogogue effect,⁹ nor does it disturb the blood pressure even when circulatory stress of 60-degree head-up tilt is used¹⁰ No undesirable side effects have been reported clinically

Promethazine (Phenergan®) has been used widely for pre-anaesthetic medication during the past ten years,¹¹⁻¹⁶ particularly when it is desirable to provide an antihistaminic effect^{17,18} It is a potent sedative, as determined by the potentiation of thiopental anaesthesia,⁸ is a powerful antisialogogue on account of its marked anticholinergic properties,^{19,20} and it has a minimal effect on the circulatory response to tilt²¹ The only drawback to its routine use is the frequent complaint by patients of a "twitchy" feeling, which appears to be a common effect of phenothiazine derivatives^{22,23}

Secobarbital is a short-acting hypnotic sedative that has been used widely for pre-anaesthetic medication for many years It is recognized to be effective and has virtually no undesirable effects, except that occasionally an elderly patient becomes confused during the half-asleep state that is induced, which increases the alarm if the patient is in an unfamiliar environment This response is not uncommon with most of the barbiturate sedatives²²

This report describes a double-blind study in which hydroxyzine, secobarbital and a placebo (coded unknowns) were compared with promethazine (coded, but known) for pre-anaesthetic medication

METHODS

Four hundred identical capsules were prepared of which 100 contained 50 mg

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hydroxyzine (Vistaril®), 100 contained 50 mg promethazine (Phenergan®), 100 contained 100 mg secobarbital (Seconal®), and 100 contained a placebo, lactose, and 2-ml brown ampoules were prepared, 100 containing 25 mg/ml hydroxyzine, 100 containing 50 mg/ml secobarbital, and 100 containing a placebo, saline. Promethazine was provided in cartridges containing 25 mg and 50 mg.

A random-number table was used to assign the three drugs and the placebo to a list of 400 consecutive numbers. Envelopes containing a capsule for evening oral administration, and an ampoule of the same compound (or cartridge of promethazine) for morning intramuscular administration were labelled with the assigned number and sealed. The envelopes with the drugs were placed in the hospital pharmacy and were requisitioned in numerical sequence. A sealed copy of the drug code was kept by the pharmacist until the study was completed and all data were tabulated.

Each day following pre-anaesthetic rounds, adult patients who were scheduled for a major elective operation, who were judged to be fit for the contemplated surgical procedure, and for whom a general anaesthetic was considered appropriate, were assigned a consecutive coded drug number. Those patients who were to have intracranial or cardiopulmonary procedures, and those who were to have short operations, were excluded from the study. A capsule of the coded drug was always prescribed for oral administration at the time of retiring, and a *volume* of the drug not exceeding 2 ml was ordered for intramuscular injection one hour before the time of operation, along with 0.3 to 0.4 mg scopolamine. The volume of the coded drug prescribed was based upon the size, physique, and mental state of the patient. Although all the preparations used were in numbered envelopes, the nurse who administered promethazine in each case would be able to identify this drug because it was supplied in a cartridge instead of an ampoule, so only three of the four preparations were considered as unknowns. For each case that was studied, a questionnaire (see Fig. 1) was completed by a graduate nurse who was trained for this study and assigned to it full-time. She abstracted information from the patient's chart pre-operatively, asked the patient direct questions immediately prior to induction of anaesthesia, and questioned the anaesthesiologist immediately following induction of anaesthesia. All anaesthetics were supervised directly by the authors, who used a uniform induction procedure (gallamine with thiopental), and maintenance of anaesthesia was carried out in most cases with either nitrous oxide-halothane or nitrous oxide-methoxyflurane and controlled respiration in a non-rebreathing system. Post-operatively, the anaesthetic chart and the recovery room record were abstracted by the same nurse, she visited the patient 24 hours postoperatively to obtain pertinent information from the chart and to question the patient further, then the protocol was checked for completeness by one of the authors.

At the conclusion of the study, all the information on the protocol sheets of 373 of the patients (Fig. 1) was tabulated and transferred to IBM cards. The code was then revealed in order to analyze the data according to the compounds. All data were analyzed statistically employing the chi-square test and *p* values.²⁴

PREMEDICATION STUDY		NAME OF PATIENT	
PURPOSE OF ADMISSION		AGE	HEIGHT
OPERATION		DATE	WEIGHT
CODED DRUG h. 5	TIME H S CAPSULE GIVEN P M	TIME PRE INDUCTION	DOSE C C, I M
ASSESSMENT			
1 SLEEPING DRUG USUALLY TAKEN? _____			
2 PRE DRUG ASSESSMENT ☐ VERY NERVOUS ☐ NORMAL ☐ STABLE			
3 TIME OF ONSET OF SLEEP _____			
4 THYROTOXICITY PRESENT _____ PAST _____ DEGREE ☐ MILD ☐ SEVERE			
PRE INDUCTION QUESTIONS		ANAESTHETIST'S OWN IMPRESSION	
1 ARE YOU COMFORTABLE? ☐ YES ☐ NO		WAS THE PATIENT ☐ COMFORTABLE ☐ UNCOMFORTABLE	
2 ARE YOU WORRIED? ☐ YES ☐ NO		☐ WORRIED APPREHENSIVE ☐ UNTRoubLED	
3 ARE YOU TENSE? ☐ YES ☐ NO		☐ EXCITED ☐ RELAXED	
4 ARE YOU UNUSUALLY HAPPY? ☐ YES ☐ NO		☐ HAPPY EUPHORIC ☐ SERENE	
5 ARE YOU UNUSUALLY SLEEPY? ☐ YES ☐ NO		☐ DROWSY SLEEPY ☐ WIDE AWAKE	
6 IS YOUR STOMACH UPSET? ☐ YES ☐ NO		☐ TALKATIVE ☐ QUIET	
7 DID YOU VOMIT? ☐ YES ☐ NO		NAUSEATED ☐ YES ☐ NO	
8 DO YOU FEEL TIRED? ☐ YES ☐ NO		ABLE TO RAISE EYELIDS ☐ YES ☐ NO	
9 DO YOU SEE DOUBLE? ☐ YES ☐ NO		ABLE TO HAND GRIP FIRMLY ☐ YES ☐ NO	
10 ANY COMPLAINTS? ☐ YES ☐ NO			
ANAESTHETIST'S REPORT			
VITAL SIGNS	ADMISSION BLOOD PRESSURE _____ PULSE _____ RESPIRATION _____		
	PRE SEDATION BLOOD PRESSURE _____ PULSE _____ RESPIRATION _____		
	PRE INDUCTION BLOOD PRESSURE _____ PULSE _____ RESPIRATION _____ PUPIL SIZE _____		
TIDAL VOLUME	PRE SEDATION _____ ML PRE INDUCTION _____ ML		
CHARACTER OF INDUCTION	☐ SMOOTH ☐ SMOOTH BUT SLOW ☐ DIFFICULT ☐ STORMY ☐ EXCESSIVE SECRETION		
TIME IN MINUTES BETWEEN IM DRUG & INDUCTION	INDUCTION AGENT	AMOUNT OF INDUCTION AGENT	ANAESTHETIC TECHNIQUE
ANAESTHETIST'S ESTIMATION OF ADEQUACY OF PREMEDICATION ☐ ADEQUATE ☐ INADEQUATE ☐ EXCESSIVE			
POST OPERATION QUESTIONS			
WHAT DO YOU REMEMBER HAPPENING JUST PRIOR TO YOUR OPERATION?			
1 ☐ I M INJECTION			
2 ☐ TRIP TO OPERATING ROOM			
3 ☐ MOVEMENT TO OPERATING TABLE			
4 ☐ WAS INDUCTION ☐ PLEASANT ☐ UNPLEASANT ☐ INDIFFERENT OR UNKNOWN			
POST OPERATIVE REPORT			
1 ☐ AMNESIA			
2 ☐ URINARY RETENTION (DID THE PATIENT HAVE TO BE CATHETERIZED WITHIN 10 HRS. OF OPERATION? ☐ YES ☐ NO)			
3 ☐ SHIVERING			
4 ☐ HYPOTENSION ☐ AFTER INDUCTION ☐ POST INDUCTION			
5 ☐ NAUSEA AND VOMITING POST-OPERATIVE			
6 ☐ DELAY IN AWAKENING AFTER COMPLETION OF OPERATION (FROM RECOVERY ROOM NOTES) _____ MINUTES			
7 REMARKS _____			
*COMPARISON OF SECOBARBITAL HYDROXYZINE Promethazine & PLACEBO			
Allen B Dobkin M D		INITIALS _____	

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FIGURE 1 Protocol for compiling data and questionnaire

TABLE I
PATIENTS' ANSWERS TO DIRECT QUESTIONS

	Placebo, 91 pts (%)	Promethazine, 96 pts (%)	Hydroxyzine, 90 pts (%)	Secobarbital, 96 pts (%)
Discomfort	2	9	7	7
Apprehension	37	36	32	37
Excitement	33	35	25	24
Euphoria	5	2	5	4
Tiredness	41	54	51	41
Sleepiness	33	41	41	41
Nausea	7	10	4	6
Vomited	1	1	2	1
Diplopia	3	6	3	1
Complaints	22	14	17	28

TABLE II
ANAESTHESIOLOGIST'S IMPRESSION AS TO PATIENT'S STATE

	Placebo, 91 pts (%)	Promethazine, 96 pts (%)	Hydroxyzine, 90 pts (%)	Secobarbital, 96 pts (%)
Discomfort	8	8	5	6
Apprehension	38	42	27	35
Excitement	28	23	8	17
Euphoria	24	25	5	13
Sleepiness	39	57	60	59
Nausea	3	2	4	1
Talkativeness	6	12	8	9
Lid lag	1	3	1	7
Weakness	3	4	3	8

TABLE III
EFFECT OF PREMEDICATION ON VITAL SIGNS BEFORE INDUCTION

	Placebo, 91 pts (%)	Promethazine, 96 pts (%)	Hydroxyzine, 90 pts (%)	Secobarbital, 96 pts (%)
Hypotension (>20%)	6	10	11	12
Hypertension (>20%)	12	6	10	7
Tachycardia (>20%)	4	9	14	6
Bradycardia (>20%)	3	1	5	9

TABLE IV
EFFECT OF PREMEDICATION AND THIOPENTAL INDUCTION ON BLOOD PRESSURE
(>20% HYPOTENSION) DURING FIRST 20 MINUTES

	Placebo, 91 pts	Promethazine, 96 pts	Hydroxyzine, 90 pts	Secobarbital, 96 pts
Halothane	5/22	5/33	4/38	1/31
Methoxyflurane	16/63	15/59	10/43	17/57
Others	1/6	1/4	1/9	2/8

TABLE V
POSTOPERATIVE RESPONSES DURING FIRST 24 HOURS RELATED TO PREMEDICATION

	Placebo, 91 pts (%)	Promethazine, 96 pts (%)	Hydroxyzine, 90 pts (%)	Secobarbital, 96 pts (%)
Hypotension (>20%)	2	2	2	7
Nausea and vomiting	23	25	25	24
Urinary retention	2	7	4	2
Shivering	6	5	9	13
Delayed recovery (>30 min)	16	32	29	31
Amnesia	6	16	13	17
Reacting in O R	43	35	35	34

TABLE VI
INCIDENCE OF VOMITING 24 HOURS POSTOPERATIVELY

	Placebo (91 pts)			Promethazine (96 pts)			Hydroxyzine (90 pts)			Secobarbital (96 pts)		
	Cases	Vomited (no) (%)		Cases	Vomited (no) (%)		Cases	Vomited (no) (%)		Cases	Vomited (no) (%)	
Anaesthetic												
Halothane	22	7 32		33	5 15		38	9 24		31	7 22	
Methoxyflurane	63	14 22		59	17 29		43	12 28		57	16 28	
Others	6	— —		4	2 —		9	2 —		8	— —	

TABLE VII
INCIDENCE OF DELAY IN RECOVERY FROM ANAESTHESIA

		Placebo			Promethazine			Hydroxyzine			Secobarbital		
		Cases	Awakened (no) (%)		Cases	Awakened (no) (%)		Cases	Awakened (no) (%)		Cases	Awakened (no) (%)	
0 delay	Halothane	22	11 50		33	12 36		38	15 39		31	14 45	
	Methoxyflurane	63	25 40		59	21 36		43	12 28		57	14 24	
0-30 min delay	Halothane	22	7 32		33	13 39		38	17 45		31	11 35	
	Methoxyflurane	63	28 44		59	18 30		43	13 30		57	19 33	
>30 min delay	Halothane	22	5 23		33	8 24		38	6 16		31	6 19	
	Methoxyflurane	63	10 16		59	21 35		43	19 44		57	23 40	

RESULTS

Tables I to VII contain a summary of the pertinent data that were abstracted from completed protocols obtained on 373 patients. Ampoule breakage accounted for 27 deletions.

Statistical analysis of the data showed that the four treatment groups had equivalent distributions with respect to age, sex, dosage, and primary anaesthetic given, indicating satisfactory randomization.

Preinduction Questions (see Table I)

A value of chi-square equal to or greater than 6.0 indicated a statistically significant difference between the drugs at .05 probability level. The chi-square test showed that there was no significant difference between the drugs and the placebo in the development of worry, euphoria, upset stomach, vomiting, and diplopia. Fewer patients complained of discomfort with the placebo, and significantly fewer patients complained of tenseness or excitement with hydroxyzine and secobarbital ($p < .05$). Significantly more patients were tired or sleepy with promethazine, hydroxyzine, and secobarbital than with the placebo ($p < .01$) and most complaints (usually that the patient did not sleep well) were found with the placebo and with secobarbital ($p = .02$). Considering all the pre-anaesthetic questions each patient was asked, and relating the answers to the preoperative sedation, we may rank the patients' preference for hydroxyzine or promethazine as higher than for secobarbital or the placebo.

The anaesthesiologists' impressions (see Table II) in a similar analysis showed no significant differences in the incidence of discomfort or nausea. Fewer patients were apprehensive, excited, and euphoric with hydroxyzine than with the other agents used ($p < .001$), and apparent sleepiness occurred least often with the placebo ($p < .001$), while manifestations of agitation (apprehension, euphoria, talkativeness) were most common with promethazine ($p < .02$). Considering the over-all answers expressed by the anaesthesiologists, hydroxyzine and secobarbital would be ranked higher than promethazine and the placebo.

Combining the results of the answers by the patient and the anaesthesiologist, the sedatives may be ranked as follows: hydroxyzine, secobarbital, promethazine, placebo.

Effect of Premedication on Vital Signs before and after Induction of Anaesthesia (see Tables III and IV)

The number of patients showing an increase, a decrease, or no change in blood-pressure levels between pre-sedation and pre-induction was not statistically significant although mild hypotension occurred less frequently with the placebo. Tachycardia occurred more often with hydroxyzine, and bradycardia occurred more often with secobarbital, but in no case were these alterations alarming. Hypotension of greater than 20 per cent following induction of anaesthesia appeared to be quite unrelated to the pre-operative sedative used. That is to say, it appeared unlikely that any of the sedatives (including the placebo) affected the blood-pressure response to the induction of anaesthesia, and in none of the cases in this study did an alarming fall in blood pressure (> 30 per cent) occur immediately following the induction of anaesthesia.

Postoperative Report (see Tables V and VI)

Chi-square tests did not reveal any appreciable difference in postanaesthetic incidence of hypotension or nausea and vomiting in the first 24 hours that could be related to the premedicants. The groups were too small to relate the incidence of nausea and vomiting to the primary anaesthetic alone.

Amnesia occurred more frequently in the patients that received a drug for premedication than those that received the placebo ($p < .001$), urinary retention requiring catheterization occurred more often in the patients who received promethazine ($p < .05$), and postanaesthetic shivering occurred more often in the patients who received secobarbital ($p < .01$).

Incidence of Delay in Awakening after Termination of Anaesthesia

Fewer patients had zero delay in reacting in the operating room (i.e., were responsive to questions and instructions) that received premedicant drugs than those that received the placebo ($p < .01$). When the comparison was made with regard to recovery within 30 minutes of termination of the anaesthetic, this difference was striking ($p < .001$). When this effect was related to the primary anaesthetics used, there was no consistent difference in effect (See Table VII).

DISCUSSION

It is now an established practice for the clinician to take every measure possible to eliminate prejudice and bias from the evaluation of new therapeutic measures.^{25, 26} Although the double-blind technique is ideal when the primary effects of the drugs to be compared are very similar, it may not be a fool-proof device when each of the drugs has certain side effects that the astute clinician can recognize.^{23, 27} Nevertheless, if the study is well designed and carefully controlled, and if a proper balance is struck among the psychological and physiological factors that may be measured or evaluated subjectively and objectively, it is possible to approach the correct answer with somewhat more assurance than if one relies purely on clinical impressions.²⁸

The authors recognized beforehand that it was essential to ensure sedation to some degree in every patient, because this is one of our primary duties. On the basis of past experience, it was decided therefore that every patient in this study should receive scopolamine as the antisialogogue along with the placebo or any of the three sedatives, because scopolamine not only has some sedative properties of its own, but it also makes it difficult to identify the presence of other drugs which have predominantly hypnotic properties.^{27, 29} The obvious disadvantage to using this method is that it tends to "dilute" changes in effect that differentiate the drugs that are being tested and compared to an inert placebo. However, we took into account the knowledge that as many as 50 per cent of the patients might appear to be "sedated" with the placebo alone, and that the broad approach to evaluating several psychological factors both subjectively and objectively would give us enough information to differentiate the placebo-scopolamine effect from that produced by the combination of scopolamine and one of the three sedatives.

All the recorded factors were reviewed with respect to the main conditions one desires in a patient responding to a premedicant drug, such as general bodily comfort, sleepiness, and amnesia, the exclusion of excitement, euphoria, nausea, or other annoying complaints, the absence of gross changes in blood pressure and pulse rate before and after induction of anaesthesia, and the uncommon occurrence of unexpected delay in recovery from anaesthesia. It was evident that

the placebo was less effective than the three drugs that were tested although the over-all incidence of apprehension was disappointingly high. It was also evident that promethazine appeared to be less effective in reducing the incidence of apprehension, excitement, euphoria, and talkativeness than the other sedatives, even though the occurrence of sleepiness and tiredness were comparable. Except for a somewhat higher incidence of complaints by the patients who received secobarbital (usually related to inadequate overnight sleep), there was little choice between it and hydroxyzine. These findings are in essential agreement with the observations of Bizzarri and associates². In our study, no patient had an untoward response to any of the premedicants.

It is apparent that it will take a much more widely documented experience to determine whether hydroxyzine has in fact much greater efficacy than secobarbital or promethazine. As Modell has stated, "Do not fear about the good drugs, they will be recognized if they are placed in proper hands, will make themselves felt promptly, will be recognized for what they are, and they will survive. Remember there is no guarantee that a new drug is better than an old one, the chances are less than even, and if you throw the weight of your experience into the balance, the odds against it are still longer. Therefore, until the evidence is in, until after a drug's probationary period is over, I suggest that the value of experience be held in proper esteem and take precedence over shakily established claims and hurried use of new drugs."³⁰

SUMMARY AND CONCLUSIONS

A double-blind test was employed to compare the effect of three unknowns (hydroxyzine, secobarbital, and a placebo) with promethazine for pre-anaesthetic sedation on 373 adult patients who were being prepared for a major elective operation under general anaesthesia. Each patient was given a capsule the night before, by mouth, and one hour before the operation the same compound was given intramuscularly, with scopolamine, to ensure an adequate antisialogogue effect and to help in preventing the identification of the sedative compound. Data were collected on a special protocol which was completed for each patient by a nurse who was trained in this work. The protocol contained information recorded from the initial pre-anaesthetic visit, before induction of anaesthesia (answers to direct questions by the patient), following induction of anaesthesia (answers to questions by the anaesthesiologist), and changes in vital signs and symptoms immediately after anaesthesia and during the first 24 hours after the anaesthetic. Upon completion of the study, the data were tabulated and transferred to IBM cards. All data were then analyzed statistically by means of the chi-square test. The analysis revealed that the patients seemed to feel better with hydroxyzine than with promethazine, secobarbital, or the placebo, in that order, whereas with the anaesthesiologist the order of preference was hydroxyzine, secobarbital, promethazine, and placebo. When the results were combined, the order preferred by the anaesthesiologist appeared to be the more valid.

None of the sedatives appeared to have an appreciable effect on the blood pressure or pulse rate before or after induction of anaesthesia, nor did the pre-

medicant drugs appear to influence the incidence of postanaesthetic hypotension or nausea and vomiting. On the other hand, amnesia occurred more frequently in the patients who received drugs for sedation, and the incidence of slow recovery from anaesthesia was significantly higher among these as compared to the patients who received the placebo. The only other postoperative symptoms that might be related to the sedatives were the occurrence of shivering, which was highest among those patients who received secobarbital, and urinary retention (requiring catheterization), which occurred most often with those receiving promethazine.

Although the preferred order of the three sedatives and the placebo was statistically valid, the over-all differences were not great. Only by careful documentation of the effects in a far larger series of patients will it be possible perhaps to obtain an unequivocal answer.

RÉSUMÉ

Nous avons fait une étude à double-inconnu pour comparer les effets de trois substances inconnues (l'hydroxyzine, le sécobarbital et le placebo) avec la prométhazine en prémédication chez 373 adultes qui devaient subir une opération majeure sous anesthésie générale. La veille, chaque malade a pris par la bouche une capsule et, une heure avant l'opération, la même substance additionnée de scopolamine a été injectée dans le but de diminuer la sécrétion salivaire et d'empêcher l'identification de la substance sédatrice. Les données ont été recueillies sur une feuille de protocole spéciale pour chaque malade et inscrites par une feuille de protocole spéciale pour chaque malade et inscrites par une infirmière qualifiée pour ce travail. Ce protocole contient des renseignements recueillis à partir de la première visite préanesthésique, avant l'induction de l'anesthésie (les réponses aux questions posées par le malade), à la suite de l'induction de l'anesthésie (les réponses aux questions posées par les anesthésiologistes), les changements des signes vitaux et des symptômes immédiatement après l'anesthésie et durant les 24 premières heures après l'anesthésie. À la fin de l'étude, les données ont été accumulées et imprimées sur des cartes IBM. Toutes les données ont alors été analysées statistiquement en employant le test "chi square". L'analyse a révélé que les malades semblaient se sentir mieux avec l'hydroxyzine qu'avec la prométhazine, le sécobarbital et le placebo, dans cet ordre, alors que d'après le jugement de l'anesthésiste, l'ordre de préférence était l'hydroxyzine, le sécobarbital, la prométhazine et le placebo. Lorsque les résultats furent combinés, l'ordre préféré par l'anesthésiologiste semble être le plus valide.

Aucun des sédatifs ne semble produire un effet sensible sur la pression artérielle ou sur la vitesse du pouls avant ou après l'induction de l'anesthésie, il en est ainsi pour les médicaments donnés en prémédication, ils ne semblent pas avoir d'influence sur l'hypotension postanesthésique, les nausées et les vomissements. D'autre part, nous avons observé plus souvent de l'amnésie chez les malades qui avaient reçu la médication sédatrice, et les réveils tardifs se sont produits beaucoup plus fréquemment chez ces malades si on les compare à ceux qui ont reçu du placebo. Les seuls autres symptômes postopératoires qui peuvent se rattacher aux sédatifs sont le frisson qui a été plus fréquent chez les malades qui avaient

reçu du sécobarbital, et la rétention d'urine (nécessitant une sonde) qui est survenue la plupart du temps chez ceux qui avaient pris de la prométhazine.

Bien que l'on place les trois sédatifs et le placebo dans un ordre de préférence statistiquement valide, les différences générales n'étaient pas grandes. Pour avoir une réponse non équivoque, il faudrait une documentation soignée sur les effets de ces médicaments pour un groupe de malades beaucoup plus considérable.

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