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Pharmacokinetic-pharmacodynamic modeling of electroencephalographic effects of midazolam in eight Chinese men[1]

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ABSTRACT The effects of midazolam (Mid) on the electroencephalogram (EEG) were related to Mid concentrations in serum in 8 Chinese healthy male volunteers for the assessment of concentration-effect relationship. The total number of waves per second within the frequency range of 12—30 Hz (TNW_{12-30}) in the central-occipital (C_1-O_1) lead EEG obtained by aperiodic analysis was used as EEG effect of the drug.

The PK-PD parameters were calculated by PK-PD software using the sigmoid E_{max} model. They were: $T_{\frac{1}{2}ke_0}=1.3\pm0.9$ min^{-1}, $EC_{50}=254\pm54$ $\mu g\cdot L^{-1}$, $N=2.9\pm0.6$. E_0 and E_{max} were calculated from the observed values, being 3.4 ± 1.3 and 11.4 ± 2.2 TNW_{12-30}, respectively. Our results showed that the concentration-EEG effect relationship of Mid could be characterized in individual Chinese man using TNW_{12-30} as a measure of pharmacological response.

KEY WORDS midazolam; pharmacokinetics; pharmacodynamics; electroencephalography

The effects of benzodiazepines are usually quantified by using psychomotor tests or with subjective scores[1]. These are difficult to use in patients after anesthesia. The EEG may provide a continuous, sensitive, and reproducible method for quantifying the central effect of midazolam (Mid) without stimulating the patients[2,3].

The most frequently used EEG parameters are derived from fast Fourier transformation (FFT) analysis[4]. In contrast to FFT, the recently introduced technic of aperiodic analysis was based on the aperiodic nature of the EEG signal[5]. We have described the pharmacokinetics (PK) of Mid[6]. In this study, we characterize the concentration-EEG effect relationship of Mid by combined pharmacokinetic-pharmacodynamic modeling technic in 8 Chinese men.

MATERIALS AND METHODS

Volunteers In this study, 8 healthy men participated, aged 27 ± 4 a, weighing 61 ± 4.5 kg. None received benzodiazepines; All were refrained from alcohol, caffeine-containing beverages, and food since the midday prior to the investigation. The subjects were the same as those mentioned in previous paper[6].

Study design All experiments were undertaken at 16:00 in the same room. The subject lay on a bed. Two iv catheters were inserted: one for blood sampling, and the other for injection of Mid. Mid maleate (Roche) 15 mg dissolved in 20 ml of 0.9 % saline was injected in 2 min. Blood samples were taken at 0, 2, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 min after iv. Mid concentrations in serum were measured by reverse HPLC[6].

EEG recording Five AgCl electrodes were fixed on scalp for recording EEG. Electrode positions were frontal pole (Fp_1, Fp_2), Occipital (O_1, O_2), and central zero (C_z) according to the international 10—20 system. The EEG analog signal of four channels was first digitized at a sampling rate of 960 Hz through analog to digital converter and then stored in the Sun-

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386 computer for off-line analysis.

Baseline EEG was recorded for at least 5 min. The subjects kept their eyes closed during baseline recording. They fell asleep during iv and the effect of the drug was recorded until the subjects awoke. Digitized EEG data stored in computer were then backed up with floppy diskette for off-line analysis.

EEG analysis The aperiodic analysis[5] was performed with the software made by authors. The EEG data stored on floppy diskette were reshowed in computer screen and resampled for excluding blocks containing artifacts from analysis. Digitized data of sequential 2 s epochs of the EEG signal were then subjected to aperiodic analysis.

Aperiodic analysis split the complex EEG waveform into units of consecutive trough-peak-trough waves, determined corresponding wavelength and time duration of each wave per second. Various EEG drug effect parameters were then generated from the aperiodic analysis files, ie, total number of waves/s and total voltage/s in various frequency ranges 1 — 3, 4 — 7, 8 — 11, and 12 — 30 Hz. The parameters were smoothed by use of a moving average over 60 s. No other data editing was performed. From various EEG parameters derived from four channels, the total number in 12— 30 Hz (TNW_{12-30}) of the 3rd channel (O_1 —C_1) was selected as the descriptor of EEG effect.

A total of about fifty data points during 0 — 70 min after iv was used as the effect measure in the modeling procedure. EEG effect measure was taken more often while the concentration of Mid was changing rapidly, immediately after the iv.

Data analysis The TNW_{12-30} *vs* concentration showed a good correlation. To account for a possible delay between Mid concentration in serum and EEG effect, a hypothetical effect compartment was included in PK-PD modeling. The PK of Mid were described by a two-exponential equation for intravenous infusion.

$$C_t=\sum_{i=1}^{2}\frac{A_i}{\alpha_i}(1-e^{-\alpha_i t}) \quad t\leqslant TD \tag{1}$$

$$C_t=\sum_{i=1}^{2}\frac{A_i}{\alpha_i}(1-e^{-\alpha_i TD})\,e^{-\alpha_i(t-TD)} \quad t>TD \tag{2}$$

Where C_t was the serum concentration, t was the time from the start of iv, TD was the iv duration, and A_i, α_i were constants, n was number of concentration points. The hypothetical effect-site compartment concentration (C_e) could be described by analytical solution.

$$C_e=\sum_{i=1}^{2}\left(\frac{A_i}{\alpha_i K_{e0}}(1-e^{-K_{e0}t})-\frac{A_i}{\alpha_i(K_{e0}-\alpha_i)}(e^{-\alpha_i t}-e^{-K_{e0}t})\right) \quad t\leqslant TD \tag{3}$$

$$C_e=\sum_{i=1}^{2}\left[\frac{A_i}{\alpha_i(K_{e0}-\alpha_i)}(1-e^{-\alpha_i TD})(e^{-\alpha_i(t-TD)}-e^{-K_{e0}(t-TD)})\right]+AET\,e^{K_{e0}(t-TD)} \quad t>TD \tag{4}$$

Where K_{e0} was equilibration rate constant between serum concentration and effect; AET was the effect concentration at the end of iv. Sigmoid E_{max} model was used to relate the C_e with EEG effect.

$$E=E_0+\frac{E_{max}\cdot C_e^N}{C_e^N+EC_{50}^N} \tag{5}$$

Where E was the observed effect, E_0 was the observed average baseline EEG effect recorded at least 5 min before iv. E_{max} was the observed maximal effect subtracting E_0. C_e was the calculated hypothetical effect-site compartment concentration, EC_{50} was the "effect-site compartment concentration" causing half of the maximal effect, and N was the power of concentration determining the slope of the curve.

PK-PD software (made by authors) was used to estimate parameters as follows: First the PK parameters were estimated and then the K_{e0} and PD parameters were estimated in second step, with the observed E_{max} value fixed.

RESULTS

In all subjects there was a marked increase in TNW_{12-30} during the Mid injection, from a baseline of 3.4±1.3 to a maximum of 13.8±1.4 at 2—3 min after iv. Thereafter it gradually decreased. There was a decrease of number of waves in 8—11 Hz band during the injection and thereafter. But there was no consistent change in 1—3 Hz or 4—7 Hz band in eight Chinese men during or after iv Mid (Fig 1).

All subjects started to move from 60 to 120 min after the end of the injection. The TNW_{12-30} after 60 min was 5.9±0.9 and the average Mid concentration in serum at that time was 152±31 $\mu g\cdot L^{-1}$. Three hours after iv, the TNW_{12-30} returned to the baseline value in all subjects.

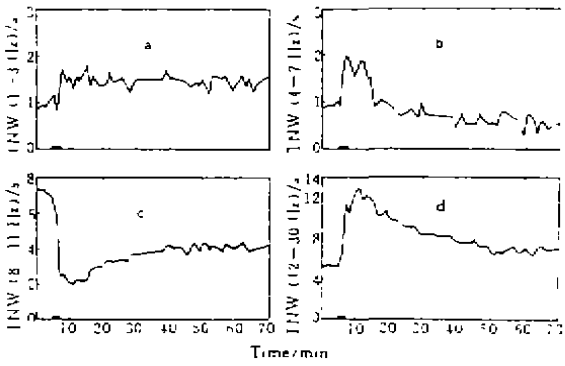

Fig 1. Time-course of the total number of waves/s (TNW) of central-occipital leads (C_1-O_1) in the frequency ranges 1—3 Hz (a), 4—7 Hz (b), 8—11 Hz (c), and 12—30 Hz (d) during the last 5 min of baseline registration, during and after a 2-min iv of midazolam (15 mg) in one man.

In PK-PD fitting, the estimated PK parameters used in equation (3) and (4) were obtained from the same subjects as was mentioned[6]. The small value of $T_{\frac{1}{2}ke0}$ (1.3±0.9 min) confirmed the rapid onset of Mid effect (Tab 1).

From pharmacodynamic curves of EEG effect *vs* C_e, we found that sigmoid curve described the EEG effect *vs* concentration relationship best (Fig 2).

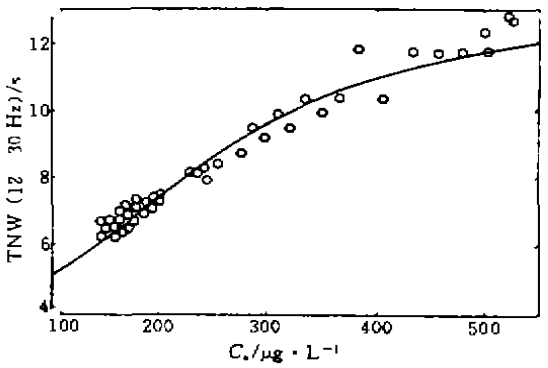

Fig 2. Relationship between the total number of waves/s in the 12—30 Hz frequency range (TNW_{12-30}) and the effect-site compartment concentration (C_e). The fitted line was estimated using a sigmoid E_{max} model.

DISCUSSION

EEG parameters derived from FFT or

Tab 1. Pharmacokinetic-pharmacodynamic analysis of the effect of iv midazolam 15 mg on EEG TNW_{12-30} in healthy Chinese.

Man	Observed E_0/ TNW_{12-30}	Observed E_{max}/ TNW_{12-30}	Parametric estimation				Nonparametric estimation	
			$T_{\frac{1}{2}ke0}$/ min	EC_{50}/ μg·L⁻¹	N	r	$T_{\frac{1}{2}ke0}$/ min	r
1	4.3	9.0	0.9	254.9	2.5	0.98	1.1	0.99
2	2.5	11.7	1.9	238.8	4.0	0.93	2.2	0.93
3	3.3	10.8	0.6	228.0	2.6	0.98	0.6	0.98
4	5.0	8.2	1.3	224.7	2.6	0.88	1.8	0.92
5	1.7	12.5	3.3	218.8	3.5	0.98	4.3	0.91
6	2.0	13.2	1.3	304.0	3.0	0.99	1.6	0.97
7	5.0	11.0	0.5	199.9	2.4	0.96	0.6	0.99
8	3.3	15.0	0.6	363.0	2.2	0.99	0.5	1.00
$\bar{x}$	3.4	11.4	1.3	253.9	2.9	0.96	1.6	0.96
±s	1.3	2.2	0.9	53.9	0.6	0.04	1.3	0.04

$T_{\frac{1}{2}ke0}$ = half-life of equilibration rate constant; EC_{50} = the effect-site compartment concentration causing half the maximum effect; N = power determining the slope of effect curve; E_0 = observed baseline effect; E_{max} = observed ceiling effect subtracting E_0; r = regression coefficient.

aperiodic analysis could be used to study the effect of Mid[4,7]. Koopmans *et al*[4] used the decrease in relative activity in the alpha range (7.5—13.4 Hz) by FFT analysis of the EEG as the measure of effect after po Mid 15 mg. Breimer *et al*[3] considered the total number of waves/s in the frequency range 12—30 Hz by aperiodic analysis was the best indicator of EEG effect in eight volunteers after iv Mid 15 mg. In our study, we compared the various EEG parameters, ie, total number of voltage/s, or total number of waves/s in different frequency bands. We found that total number in 12—30 Hz band best characterized the effect of Mid and the TNW_{12-30} was used here as the effect parameter in the pharmacokinetic-pharmacodynamic modeling. Two-compartment infusion equation was used in PK-PD modeling technique because the EEG effect was appeared during 2 min injection. PK parameters calculated by PK-PD software were similar to the value reported elsewhere[6]. In our study, TNW_{12-30} exhibited a maximal or ceiling effect, so the E_{max} value was constrained to be the value calculated from observed maximal effect and the PD parameters were estimated with E_{max} constrained.

The values of EC_{50} (17.0—110.4 $\mu g \cdot L^{-1}$) and $T_{\frac{1}{2}ke0}$ (0.01—1.73 h) reported by Koopmans *et al* differed markedly from present study. This was due to the different concentration ranges studied. The peak concentration in the study of Koopmans *et al* was about 45 $\mu g \cdot L^{-1}$ in which the subjects awoke in the presnt study. In the study of Buhrer *et al*[8], the EC_{50} value (94—385 $\mu g \cdot L^{-1}$) was of the same order of magnitude. The $T_{\frac{1}{2}ke0}$, (5.4 min) was larger than that found by this study, which could be explained as using different iv method (3-min iv with constant rate pump *vs* 2-min iv). Above all, the values of $T_{\frac{1}{2}ke0}$, EC_{50} and N were consistent with those reported by Breimer *et al*.

These results confirmed that TNW_{12-30} had the characteristics of ideal pharmacodynamic measure, being continuous, objective, sensitive and reproducible, and was an ideal EEG effect indicator.

In conclusion, we developed a PK-PD model using the TNW_{12-30} as the effect parameter. Its success showed an attractive new field potentially useful for continuously monitoring the degree of hypnosis.

REFERENCES

1 Dingemanse J, Danhof M, Breimer DD. Pharmacokinetic-pharmacodynamic modeling of CNS drug effect; An overview. Pharmacol Ther 1988; **38**: 1—52.

2 Mandema JW, Danhof M. Electroencephalogram effect messures snd relationships between pharmacokinetics and pharmacodnamics of centrally acting drugs. Clin Pharmacokinet 1992; **23**: 191—215.

3 Breimer LTM, Hennis PJ, Burm AGL, Danhof M, Bovill JG, Spierdijk J, *et al*. Quantification of the EEG effect of midazolam by aperiodic analysis in volunteers : Pharmacokinetic/pharmacodynamic modeling. Clin Pharmacokinet 1990; **18**: 245—53.

4 Koopmans R, Dingemanse J, Danhof M, Horsten GPM, van Boxtel CJ. Pharmacokinetic-pharmacodynamic modeling of midazolsm effects on the human central nervous system. Clin Pharmacol Ther 1988; **44**: 14—22.

5 Gregory TK, Pettus DC. An electroencephalogrsphic processing algorithm specially intended for anslysis of the cerebral activity. J Clin Monit 1986; **2**: 190—7.

6 Lu JF, Wu MF, Chen G, Xiang BR, An DK. Midazolam pharmacokinetics and electroencephalogrsphic changes in eight Chinese men. Acta Pharmacol Sin 1993; **14**: 485—8.

7 Buhrer M, Maitre PO, Hung O, Stanski DR. Pharmacodynamics of benzodiazepines I, Choosing an EEG parsmeter to measure the CNS effect of midazolam. Clin Pharmacol Ther 1990; **48**: 544—54.

8 Buhrer M, Maitre PO, Hung O, Stanski DR. Pharmacodynamics of bensodiazepines II; Pharmacodynamic modeling of the electroencephalographic effects of midszolsm and diazepsm. Clin Pharmacol Ther 1990; **48**: 555—67.

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八位中国男性咪达唑仑脑电效应的药物动力学

药效学模型

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摘要 本文分析了8位中国健康男性血清咪达唑仑浓度-脑电效应的定量关系，采用 12－30 Hz 之间的每秒总波数 (TNW_{12-30})作为脑电效应指标．由药物动力学-药效学软件所计算的药效学参数为：$T_{\frac{1}{2}keo}$ = 1.3±0.9 min^{-1}，EC_{50} = 254±54 $\mu g \cdot L^{-1}$，N = 2.9±0.6．实验证明了由脑电分析得出的参数 TNW_{12-30} 可用于浓度-效应关系的研究．

关键词 咪达唑仑；药物动力学；药效学；脑电描记术

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Microprocessor-programmed infusion of theophylline rapidly attained expected steady-state level in rabbit plasma[1]

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ABSTRACT A self-made microprocessor-programmed (two-compartmental model) infusion controller was connected with an infusion pump, which achieved an expected steady-state plasma concentration (C_{pss}) rapidly (5 $T_{\frac{1}{2}\alpha}$) and maintained the level. Theophylline was selected as an example, and its pharmacokinetic parameters of rabbits, expected C_{pss}, body weight (wt), and infusion time (t) were inputted. The programmed infusion rate (K_t) was determined by the following equation: $(K_t) = C_{pss} \cdot K_{10} \cdot V_c \cdot wt \{1 + [(K_{21} - \beta)/\beta] EXP(-K_{21} t)\}$ and the predicted value was calculated by the formula: $C_{(t)} = C_{pss} \times [1 - EXP(-\alpha t)]$. The needed concentration and total volume of drug were automatically shown on the screen. The drug was automatically infused after pumping, and the plasma concentration of theophylline was measured by colorimetric method. The results showed that the median absolute value of the performance error (MAVPE) was 8.3 %. Although $T_{\frac{1}{2}\beta}$ of theophylline was 6.08 h, the expected C_{pss} was attained in only 30 min (5 $T_{\frac{1}{2}\alpha}$) after start of infusion and then well maintained.

KEY WORDS theophylline; pharmacokinetics; computer-assisted drug therapy; drug administration schedule

Since 1981 computer-assisted continuous infusion system (CACI) has been gradually developing in clinical drug therapy. The microprocessor-controlled infusion is a convenient way to optimize application schemes in some area of drug treatment. In a CACI of a linear open (2 or 3)-compartment model, many investigators used a bolus loading dose so as to rapidly reach an expected C_{pss} and then maintained this level by the automated continuous infusion system[1,2]. Since some drugs could not be given in a bolus loading way, we

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