Acta Medica Okayama

Volume 52, *Issue* 3 1998 *Article* 3

JUNE 1998

Steady-state serum concentrations of carbamazepine and valproic acid in obese and lean patients with epilepsy.

Katsuya Suemaru[*] Hiromu Kawasaki[†] Kanako Yasuhara[‡]

Kazuhisa Yao[**] Katusushi Furuno[††] Yasuhiro Kawakami[‡‡]

Hiroaki Araki[§] Yutaka Gomita[¶] Eiji Oka[‖]

[*]Okayama University,

[†]Okayama University, kawasaki@pheasant.pharm.okayama-u.ac.jp

[‡]Okayama Univeristy,

[**]Okayama University,

[††]Okayama University,

[‡‡]Okayama University,

[§]Okayama University,

[¶]Okayama University,

[‖]Okayama University,

Steady-state serum concentrations of carbamazepine and valproic acid in obese and lean patients with epilepsy.*

Katsuya Suemaru, Hiromu Kawasaki, Kanako Yasuhara, Kazuhisa Yao, Katusushi Furuno, Yasuhiro Kawakami, Hiroaki Araki, Yutaka Gomita, and Eiji Oka

Abstract

Steady-state serum concentrations of carbamazepine (CBZ) and valproic acid (VPA) were investigated in normal weight (body mass index; BMI 20 to 25), lean (smaller than 20 BMI) and moderately obese subjects (greater than 25 BMI) who received either 400 mg/day of CBZ or 800 mg/day of VPA. The CBZ serum concentration in lean subjects was significantly higher than that in normal weight subjects. However, no significant differences in VPA serum concentration were found between the three groups. The CBZ serum concentration decreased with increases in total body weight, and the VPA serum concentration decreased with increases in ideal body weight. However, both serum concentrations were not correlated with BMI. These results suggest that VPA doses should be calculated using ideal body weight and that degree of obesity may affect CBZ serum concentration rather than VPA serum concentration.

KEYWORDS: carbamazepine, valproic acid, serum concentration, obesity, lean

---

*PMID: 9661740 [PubMed - indexed for MEDLINE]

ACTA MED OKAYAMA 1998; 52(3): 139-142

Steady-State Serum Concentrations of Carbamazepine and Valproic Acid in Obese and Lean Patients with Epilepsy

Katsuya SUEMARU[a], Hiromu KAWASAKI[a], Kanako YASUHARA[a], Kazuhisa YAO[a], Katsushi FURUNO[a], Yasuhiro KAWAKAMI[a], Hiroaki ARAKI[a], Yutaka GOMITA[a]* and Eiji OKA[b]

Departments of [a]Hospital Pharmacy and [b]Child Neurology, Okayama University Medical School, Okayama 700-8558, Japan

Steady-state serum concentrations of carbamazepine (CBZ) and valproic acid (VPA) were investigated in normal weight (body mass index; BMI 20 to 25), lean (smaller than 20 BMI) and moderately obese subjects (greater than 25 BMI) who received either 400 mg/day of CBZ or 800 mg/day of VPA. The CBZ serum concentration in lean subjects was significantly higher than that in normal weight subjects. However, no significant differences in VPA serum concentration were found between the three groups. The CBZ serum concentration decreased with increases in total body weight, and the VPA serum concentration decreased with increases in ideal body weight. However, both serum concentrations were not correlated with BMI. These results suggest that VPA doses should be calculated using ideal body weight and that degree of obesity may affect CBZ serum concentration rather than VPA serum concentration.

Key words: carbamazepine, valproic acid, serum concentration, obesity, lean

Drug pharmacokinetics are influenced by various factors, such as age, sex, body weight and obesity. Lipophilic drugs such as diazepam (1), phenytoin (2) and carbamazepine (3) have been shown to undergo a marked increase in the apparent volume of distribution and a significant prolongation of elimination half-life in obese patients. These findings suggest that the pharmacokinetics of antiepileptic drugs in an obese patient may be very different from those in a lean patient of the same total body weight.

Carbamazepine (CBZ), a lipophilic drug, and valproic acid (VPA), a hydrophilic drug, are antiepileptic drugs with a narrow therapeutic range, hence calculating dosage based on total body weight alone in obese patients may result in either significant toxicity or subtherapeutic serum concentration of these drugs. Therefore, therapeutic drug monitoring (TDM) provides useful information on the appropriate dosage adjustment for these drugs, and it is important to determine whether ideal or total body weight should be used to calculate loading and maintenance doses of antiepileptic drugs for obese patients. However, the steady-state pharmacokinetics of antiepileptic drugs in obese and lean epileptic patients are not yet clearly understood. Here, we report the effects of obesity and lean on steady-state serum concentrations of CBZ and VPA in patients with epilepsy.

Subjects and Methods

All subjects of the present study were epilepsy sufferers who were out-patients of the Department of Child Neurology, Okayama University Medical School. We collected TDM data from patients who met the following criteria: patients aged from 15 to 29 years, who had received either CBZ 400 mg/day or VPA 800 mg/day singularly twice a day for more than 4 weeks.

Venous blood samples were drawn into tubes (Meecus AG, Nippon Chemiphar Co., Tokyo, Japan) 2-3 h after the morning administration. After centrifugation, serum was separated and kept frozen at $-20^{\circ}C$ until assay. CBZ and VPA serum concentrations were determined by the fluorescence polarization immunoassay system (TDX, Abbott Laboratories Co., Tokyo, Japan).

Body mass index (BMI) is calculated as the ratio of weight/height^2 (kg/m^2). Ideal body weight is calculated as $22 \times$ height^2 (kg). An international classification of

* To whom correspondence should be addressed.

obesity based on arbitrary ranges of BMI was introduced by the World Health Organization in 1988: moderate obesity (25 to 29.9 BMI); severe obesity (30 to 39.9 BMI); and morbidly obese (greater than 40 BMI). In the present study, the subjects were divided into three groups according to their BMI; lean subjects (less than 20 BMI); normal weight subjects (20 to 25 BMI); and obese subjects (greater than 25 BMI).

Differences of drug serum concentrations in obese, lean and normal weight subjects were analyzed by Dunnett's test. Relationships among drug serum concentrations and subject characteristics were evaluated by Spearman's rank correlation analysis.

Results

The subjects receiving CBZ (400 mg/day) were 31 patients with partial epilepsy (13 females and 18 males), their average age was 21.9 years (range, 15–29 years). The subjects receiving VPA (800 mg/day) were 17 patients with generalized epilepsy (9 females and 8 males) whose mean age was 20.5 years (range, 15–29 years).

Tables 1 and 2 show the characteristics of normal weight, obese and lean subjects. The mean total body weights in obese and lean patients receiving CBZ and VPA were significantly higher and lower respectively ($P < 0.01$) than those in normal weight subjects. However, no significant differences in ideal body weight, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were found between the three groups.

Fig. 1 shows the correlation between the CBZ serum concentration and body weight or BMI. Total body weight was significantly ($P < 0.05$) correlated with a decrease in the CBZ serum concentration. However, BMI was not correlated with serum concentration. The CBZ serum concentration in obese subjects was not different from that in normal weight subjects. However,

Table 1 Carbamazepine (CBZ) serum concentrations and subject characteristics in normal weight, obese and lean patients with epilepsy

	Normal (16)	Obese (6)	Lean (9)
CBZ serum concentration (μg/ml)	7.7 ± 0.3	7.8 ± 0.4	8.9 ± 0.4*
BMI (kg/m^2)	21.9 ± 0.4	29.9 ± 1.8**	18.6 ± 0.4**
Total body weight (kg)	59.7 ± 1.7	79.5 ± 5.2**	47.8 ± 1.7**
Ideal body weight (kg)	60.2 ± 2.2	59.3 ± 2.1	56.7 ± 1.9
GOT (UI/L)	18.1 ± 1.5	19.2 ± 1.3	15.8 ± 1.0
GPT (UI/L)	17.6 ± 2.8	22.2 ± 2.3	15.8 ± 1.9

Subjects received CBZ (400 mg/day) twice a day for more than 4 weeks. Each value represents the mean ± SEM, *$P < 0.05$, **$P < 0.01$ compared with normal body weight subjects.
BMI: Body mass index; GOT: Glutamic oxaloacetic transaminase; GPT: Glutamic pyruvic transaminase.

Table 2 Valproic acid (VPA) serum concentrations and subject characteristics in normal weight, obese and lean patients with epilepsy

	Normal (6)	Obese (5)	Lean (6)
VPA serum concentration (μg/ml)	79.3 ± 2.5	79.3 ± 5.1	78.3 ± 6.6
BMI (kg/m^2)	21.4 ± 0.8	26.6 ± 0.8**	17.6 ± 0.6**
Total body weight (kg)	57.2 ± 1.5	75.4 ± 5.1**	47.5 ± 3.5**
Ideal body weight (kg)	59.1 ± 1.9	62.1 ± 3.1	58.7 ± 3.3
GOT (UI/L)	15.8 ± 2.8	19.0 ± 0.9	16.3 ± 1.0
GPT (UI/L)	12.3 ± 1.8	21.0 ± 6.5	10.8 ± 1.1

Subjects received VPA (800 mg/day) twice a day for more than 4 weeks. Each value represents the mean ± SEM, **$P < 0.01$ compared with normal body weight subjects.
BMI, GOT, GPT: See legend to Table 1.

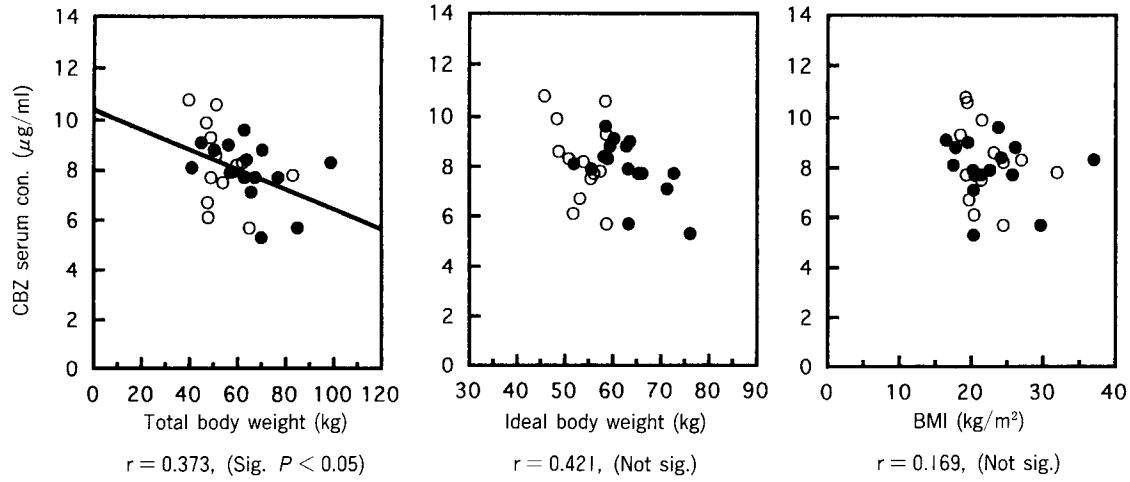

Fig. 1 Relation of total body weight, ideal body weight and body mass index (BMI) to carbamazepine (CBZ) serum concentration in patients with epilepsy. Subjects were given CBZ (400 mg/day) for more than 4 weeks. ●: Male subjects (n = 18); ○: Female subjects (n = 13). Con.: Concentration; Sig.: Significant.

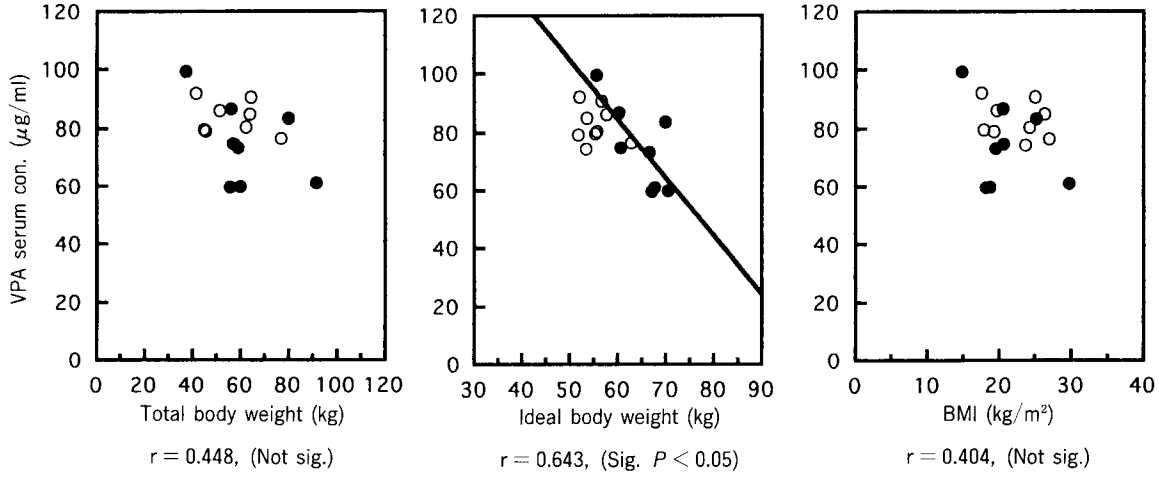

Fig. 2 Relation of total body weight, ideal body weight and body mass index (BMI) to valproic acid (VPA) serum concentration in patients with epilepsy. Subjects were given VPA (800 mg/day) for more than 4 weeks. ●: Male subjects (n = 8); ○: Female subjects (n = 9). Con., Sig.: See legend to Fig. 1.

the serum concentration in lean subjects was significantly higher ($P < 0.05$) than that in normal weight subjects (Table 1).

As shown in Fig. 2, ideal body weight was significantly correlated with a decrease in the VPA serum concentration ($r = 0.643$, $P < 0.05$), but which was not correlated with total body weight or BMI. No significant differences in VPA serum concentration were found between normal weight, obese and lean subjects (Table 2).

Discussion

In the present study, the range of CBZ serum concentration in epileptic patients who received 400 mg/day of CBZ was within 5–12 μg/ml, and that of VPA serum concentration in patients who received 800 mg/day of VPA was within 50–100 μg/ml. Thus, the CBZ and VPA serum concentrations were within optimal therapeu-

tic ranges (4).

Potential pharmacokinetic changes seen in obesity independent of other disease states have been reported to include changes in drug distribution, biotransformation and excretion (5, 6). It appears that lipophilic drugs, particularly, are influenced by a marked enlargement of distribution volume in obese subjects. Caraco *et al.* (3), reported on the pharmacokinetic parameters of a single administration of CBZ in severely overweight subjects (greater than 30 BMI) before and after a significant weight reduction, and observed that obese subjects have a larger distribution volume of CBZ, a markedly prolonged elimination half-life and a decreased clearance rate of CBZ.

In the present study, the steady-state serum concentrations of CBZ in lean patients was significantly higher than that in normal weight patients. This result of increased CBZ serum concentration in lean patients may be due to the fact that CBZ, a lipophilic drug, has a lower distribution volume of CBZ in lean patients than that in normal weight patients. However, the serum concentration in obese patients was not different from that in normal weight patients. This result may be due to the fact that obese patients in the present study included four subjects of moderate obesity (BMI 25 to 29.9), two subjects of severe obesity (BMI 30 to 39.9) and no subjects of morbid obesity (BMI greater than 40).

Hydrophilic drugs whose distribution is confined mainly to nonadipose tissues or body water, such as digoxin or antipyrine, show minimal changes in distribution volume regardless of degree of obesity (6, 7). In the present study, VPA, a hydrophilic drug, showed a significant correlation ($r = 0.643$, $P < 0.05$) between serum concentration and ideal body weight, and the VPA serum concentration was not affected by obesity and degree of leanness. These results suggest that VPA loading and maintenance doses should be calculated using ideal body weight.

The present study suggests that obesity and degree of leanness may affect steady-state CBZ serum concentration rather than VPA serum concentration. However, further examples and pharmacokinetic studies are necessary to produce clear evidence. Optimal therapy for obese and lean subjects who have epilepsy should be guided by careful monitoring of CBZ and VPA serum concentrations.

References

1. Abernethy DR, Greenblatt DJ, Harmatz JS and Shader RI: Alterations in drug distribution and clearance due to obesity. J Pharmacol Exp Ther (1981) **217**, 681-685.
2. Abernethy DR and Greenblatt DJ: Phenytoin disposition in obesity. Arch Neurol (1985) **42**, 468-471.
3. Caraco Y, Zyllber E, Berry EM and Levy M: Significant weight reduction in obese subjects enhances carbamazepine elimination. Clin Pharmacol Ther (1992) **51**, 501-506.
4. Tange SM, Grey VL and Senecal PE: Therapeutic drugs monitoring in pediatrics: A need for improvement. J Clin Pharmacol (1994) **34**, 200-214.
5. Cheymol G: Clinical pharmacokinetics of drugs in obesity. Clin Pharmacokinet (1993) **25**, 103-114.
6. Abernethy DR and Greenblatt DJ: Pharmacokinetics of drugs in obesity. Clin Pharmacokinet (1982) **7**, 108-124.
7. Morgan DJ and Bray KM: Lean body mass as a predictor of drug dosage. Clin Pharmacokinet (1994) **26**, 292-307.

Received September 10, 1997; accepted December 26, 1997.