Eur J Clin Pharmacol (1990) 38: 526–527

European Journal of Clinical Pharmacology
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Effect of posture on total phenytoin plasma concentration

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Received: August 11, 1989/Accepted in revised form: December 18, 1989

Key words: phenytoin; posture, pharmacokinetics, plasma levels

Standing for 35 min increases venous haematocrit, haemoglobin and the plasma protein level by 10.3%, 10.8%, and 20.8%, respectively [1]. Standing for 90 min raises serum total calcium from 9.68 $mg \cdot dl^{-1}$ to 10.02 $mg \cdot dl^{-1}$ [2]. Standing for 15 min increases plasma cholesterol by 10.4% and plasma triglycerides by 12.4% [3]. Standing for 30 to 40 min increases Vitamin B 12 and folate plasma levels by more than 10% [4]. The explanation for all these effects is that when a subject stands, fluid (up to 23% of plasma volume; [5]) leaves the circulation under hydrostatic pressure, particularly in the lower limbs [1, 6, 7], which swell [7]. This leads to an increase in the concentrations of such blood constituents as red cells, proteins and protein-bound substances (calcium, etc.), which do not readily pass through the capillary membrane. Reverting to the horizontal position reverses these changes.

Phenytoin is highly bound to plasma proteins (69 to 96%; [8]), so it is highly likely that standing would increase the total plasma phenytoin concentration. To test this hypothesis, an experiment was conducted.

The subjects were 7 epileptic inpatients treated with phenytoin and 4 healthy volunteers who took phenytoin for the experiment. There were 7 men and 4 women, mean (SD) age 49.2 (18.2) y (range 20–78 y); mean weight 61.7 (12.9) kg (range 39–83 kg). Informed consent was obtained. When the experiment started, the subjects were in the steady state and were taking a constant daily oral dose of phenytoin 100 to 300 mg (mean (SD) 231 (64.3) mg) given at 2 (08.00 h, 20.00 h), or at 3 (08.00 h, 12.00 h, and 18.00 h) in equal doses. Any concurrent medication remained constant during the two weeks preceding the experiment and during the two experimental days. The latter are called the "recumbent" and "erect" days.

On the "recumbent" day, the subjects lay down from 00.00 h and remained recumbent until 08.45 h, blood being collected at 08.00 h and 08.45 h. They were given the last dose of phenytoin and any concurrent medication at least 12 h prior to blood sampling. They fasted for the 12 h preceding and during blood sampling. The drug, which would normally have been given at 08.00 h, was given once blood sampling was over. On the "erect" day, the procedure was the same, except that the subjects, who were recumbent until 08.00 and during the first 08.00 h blood sampling, stood up immediately after the 08.00 h blood sampling and remained standing as still as possible, with the arms dangling, until 08.45 h, when the second sample was collected, with the subject still erect. For five subjects the "recumbent" day preceeded the "erect" day by 24 h, and for 6 subjects the order was reversed (random allocation).

Blood was collected as follows. Each morning on the two blood collection days, at 07.45 h an indwelling catheter was inserted into a superficial antecubital vein. It was removed once the last blood sample of the morning had been taken. Blood was collected from the catheter with a plastic syringe, after allowing blood to run freely

Table 1. Total plasma phenytoin level (mg/l) after:
a) 8 h recumbency (La) and recumbency for the following 45 min (La')
b) 8 h recumbency (Lb) and standing for the following 45 min (Stb')

Subject	La	La'	Lb	Stb'
1	11.6	11.7	11.2	11.1
2	8.5	9.5	8.7	9.1
3	2.2	2.2	2.3	2.5
4	15.9	13.7	15.7	16.9
5	3.1	3.0	3.4	3.4
6	9.3	9.9	9.9	11.3
7	26.7	25.8	26.2	28.6
8	3.2	3.0	2.8	2.9
9	2.8	2.6	2.7	2.5
10	7.6	7.3	6.1	6.5
11	16.2	15.9	12.5	15.0
Mean	9.74	9.51	9.23	9.98
(SEM)	(2.27)	(2.17)	(2.18)	(2.41)

Wilcoxon signed ranks test
La versus La': non significant
Lb versus Stb': $P < 0{,}02$

from the catheter for 10 s prior to sample collection. The syringe load was rapidly placed in a heparinized tube for total plasma phenytoin determination. A flexible obturator was inserted between blood sampling. To avoid modification of phenytoin total plasma levels due to venous compression [9, 10], blood was withdrawn with minimal venous occlusion. When recumbent, the subject held the arms beside the body, with the fists clenched; when standing, the arms were left dangling.

Total phenytoin plasma levels were determined in duplicate by the EMIT method (SYVA Corp., Palo Alto, Cal., USA; [11]) and the mean of the two values was taken. The coefficient of variation was 5%. Determinations were done blind with regard to posture.

The results are presented in Table 1.

Standing during for 45 min increased the total plasma phenytoin concentration by 8.13% (range −7.41% to +20.00%). If the increase were corrected by the 2.36% (range −13.84% to +11.76%) decrease (due to phenytoin elimination) observed in the subjects lying down for the same 45 min period, there was an average increase of 10% in the total plasma level due to the influence of standing for 45 min.

The results show that posture is one of the factors that can modify the total plasma phenytoin level. The results have implications for studies of total phenytoin pharmacokinetics and chronopharmacological research.

Acknowledgements. We thank the test subjects, the nurses and staff of the Centre Hospitalier Spécialisé Charles Perrens, in Bordeaux and Hôpital Garde-Rose in Libourne and R. Cooke for their help.

References

1. Hagan RD, Diaz FJ, Horvath SM (1978) Plasma volume changes with movement to supine and standing position. J Appl Physiol: Respir Environ Exercise Physiol 45: 414–418
2. Husdan H, Rapoport A, Locke S (1973) Influence of posture on the serum concentration of calcium. Metabolism 22: 787–797
3. Tan MH, Wilmshurst EG, Gleason RE, Soeldner JS (1973) Effect of posture on serum lipids. N Engl J Med 289: 416–419
4. Abalan F, Toulet V, Tignol J, Lacoste G, Brument C, Vuillemin L, Ducassou D, Couzigou P (1987) Folate, vitamin B 12 and posture. Br J Psychiat 151: 130
5. Fawcett JK, Wynn V (1960) Effects of posture on plasma volume and some blood constituents. J Clin Pathol 13: 304–310
6. Waterfield RL (1931) The effects of posture on the circulating blood volume. J Physiol (London) 72: 110–120
7. Waterfield RL (1931) The effect of posture on the volume of the leg. J Physiol (London) 72: 121–131
8. Hooper WD, Bochner F, Eadie MJ, Tyrer JH (1973) Plasma protein binding of diphenylhydantoin. Effects of sex hormones, renal and hepatic disease. Clin Pharmacol Ther 15: 276–282
9. Dent CE (1962) Some problems of hyperparathyroidism. Br Med J 2: 1419–1425
10. Page IH, Moinuddin M (1962) The effect of venous occlusion on serum cholesterol and total protein concentration-A warning. Circulation 25: 651–652
11. Schlottelius DD (1978) Homogenous immunoassay system (EMIT) for quantitation of antiepileptic drug in biological fluids. In: Pippenger CE, Penry JK, Kutt H (eds) Antiepileptic drugs: quantitative analysis and interpretation. Raven Press, New York, pp 95–108

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