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Intrapatient Variability of Serial Steady-State Plasma Tricyclic Antidepressant Concentrations

V. E. ZIEGLER, L. T. WYLIE, and JOHN T. BIGGS ˣ

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Abstract □ Nine or 10 serial steady-state plasma measurements of amitriptyline, desipramine, desmethyldoxepin, doxepin, imipramine, nortriptyline, or protriptyline were made in 23 depressed patients. Each patient was monitored for compliance by pill counts, and sampling time was controlled carefully to determine intrapatient variability of steady-state tricyclic levels on a day-to-day basis. The coefficients of variation during serial sampling of the various ingested drugs were: amitriptyline, 21%; desipramine, 26%; doxepin, 21%; imipramine, 14%; nortriptyline, 13%; and protriptyline, 17%. The therapeutic ranges for the tricyclic antidepressants are relatively wide, so coefficients of variation of these magnitudes indicate that the position of an individual patient in relation to the optimal therapeutic range can be reliably determined on a clinical basis.

Keyphrases □ Plasma drug levels—various tricyclic antidepressants, intrapatient variability at steady state □ Antidepressants, various—plasma drug levels, intrapatient variability at steady state

Although it has been over 10 years since Hammer *et al.* (1) first demonstrated a 36-fold difference between the lowest and highest steady-state levels of desipramine in patients ingesting equal amounts of the same drug, the use of plasma tricyclic antidepressant levels as a practical way to improve patient management is only slowly being accepted. Since the evidence that plasma drug levels more closely correspond to therapeutic response than oral dosage, there has been marked interest in the routine determination of plasma tricyclic antidepressant levels as a method of improving clinical response (2–8) and predicting toxicity (9).

Although therapeutic ranges have been suggested for most of the marketed tricyclic antidepressants, the interpretation of the results of plasma tricyclic determinations is often difficult. Differences in optimal plasma therapeutic ranges have been caused by varying purity of the standard drugs used, assay and blood collection methods, and the patient populations studied. In addition, day-to-day variation occurs in the steady-state level in individual patients. This variation is influenced not only by the reliability of the drug assay techniques but by biological variation within the individual.

The purpose of this study was to determine the variation for the entire procedure, controlling for such factors as is practical in a clinical setting.

EXPERIMENTAL

Plasma tricyclic antidepressant levels were assayed by GLC–mass fragmentography by a method described previously (10). This method is specific for each drug monitored and does not assay undescribed metabolites. Differences between duplicate samples are less than 10%.

To examine the biological and laboratory variability of steady-state plasma levels, outpatients undergoing treatment for depression on level doses of drug for at least 2 weeks were subjected to nine or 10 serial samplings over 3 weeks. Patient compliance was monitored by pill counts.

Table I—Tertiary and Secondary Amine Tricyclic Antidepressant Plasma Levels in Depressed Outpatients following Serial Plasma Sampling ($\bar{x} \pm SD$)

Patient	Daily Dosage, mg	Number of Samples	Tertiary Amine, ng/ml	Secondary Amine, ng/ml	Total Tricyclic, ng/ml
			Amitriptyline[a]		
1	100	9	58.6 ± 12.6	128.4 ± 36.1	187.0 ± 37.5
2	100	10	53.6 ± 8.3	24.4 ± 3.1	80.0 ± 8.1
3	100	9	37.8 ± 8.1	56.7 ± 2.2	94.4 ± 17.6
4	150	10	62.2 ± 17.7	91.8 ± 20.7	154.0 ± 22.4
			Doxepin[a]		
1	100	10	13.7 ± 3.1	15.7 ± 3.4	29.4 ± 5.3
2	100	10	9.2 ± 2.7	21.2 ± 1.2	30.2 ± 2.6
3	100	10	15.3 ± 6.2	23.1 ± 6.8	38.4 ± 12.6
4	100	9	145.8 ± 15.9	93.7 ± 14.6	239.4 ± 26.0
			Imipramine[a]		
1	150	10	79.7 ± 11.4	54.2 ± 8.4	133.9 ± 17.2
2	150	10	227.8 ± 25.7	162.9 ± 27.4	390.7 ± 43.9
3	200	10	78.3 ± 13.3	112.0 ± 17.5	190.3 ± 27.4
4	200	10	110.3 ± 10.4	111.4 ± 16.0	221.7 ± 18.2

[a] Compound ingested.

In all cases, samples were drawn at the same hour of the day, thus controlling for sampling time and dosage schedule on an individual basis. The samples were assayed in duplicate to determine the coefficient of variation for the entire procedure.

RESULTS AND DISCUSSION

Table I shows the number of patients ingesting each tertiary amine tricyclic antidepressant, the individual dosage, the number of samplings, the tertiary amine plasma level and its active secondary amine metabolite plasma level, and the total plasma tricyclic level. The mean plasma level ± *SD* is expressed in nanograms per milliliter.

For the tertiary amines, amitriptyline, doxepin, or imipramine, both the parent drug and the corresponding secondary amine desmethyl metabolites, nortriptyline, desmethyldoxepin, and desipramine, were measured. As expected, the plasma levels on similar dosages varied markedly from individual to individual. The coefficient of variation for total tricyclic was 21% for patients ingesting amitriptyline, 21% for doxepin, and 14% for imipramine. This variation includes both laboratory and biological variations, including drug compliance in the individual patient. Drug compliance by pill count was above 95% in all patients.

Table II presents data in the same manner for patients ingesting the secondary amine tricyclic antidepressants, desipramine, nortriptyline, and protriptyline. Plasma levels of patients on similar dosages again varied markedly. The coefficient of variation for desipramine was 26%; for nortriptyline, it was 13%; and for protriptyline, it was 17%. The optimal therapeutic ranges for the tricyclic antidepressants are relatively wide, 50–150 ng/ml for nortriptyline (2, 4, 6), which is the drug with the narrowest optimal therapeutic range. Therefore, a 13–26% coefficient of variation indicates that the position of an individual patient in relationship to the optimal therapeutic range can be determined reliably. This is also true for overdose patients who are toxic (9). Evidence from a study (9) of acute overdose patients indicates serious medical complications are more frequent when maximum total plasma tricyclic antidepressant levels are above 1000 ng/ml, with death occurring at considerably higher levels, yielding a therapeutic index of greater than 10.

Table II—Plasma Tricyclic Antidepressant Levels in Depressed Outpatients following Serial Plasma Sampling ($\bar{x} \pm SD$)

Patient	Daily Dosage, mg	Number of Samples	Level, ng/ml
		Desipramine[a]	
1	100	9	55.9 ± 15.5
2	100	10	62.4 ± 25.3
3	150	10	105.2 ± 21.9
4	200	10	217.7 ± 33.3
		Nortriptyline[a]	
1	100	10	125.6 ± 12.5
2	100	9	74.3 ± 12.5
3	100	10	65.1 ± 9.3
4	150	10	150.7 ± 19.2
		Protriptyline[a]	
1	20	9	111.6 ± 15.2
2	30	10	144.3 ± 29.4
3	40	10	164.2 ± 31.1

[a] Compound ingested.

In conclusion, the large interpatient variability of steady-state plasma tricyclic levels has been of interest to pharmacologists since its discovery. The clinician has now become aware of the usefulness of plasma tricyclic antidepressant levels. It is necessary to consider the assay methods employed and individual variations in steady-state plasma levels based on intraindividual biological variation for the practical interpretation of routine plasma tricyclic measurements. The coefficient of variation during steady state must be considered carefully when patients are at extremes of the optimal therapeutic range before dosage is adjusted; however, this variation is small enough to allow for control of patients within the optimal therapeutic ranges for the various tricyclic antidepressants.

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