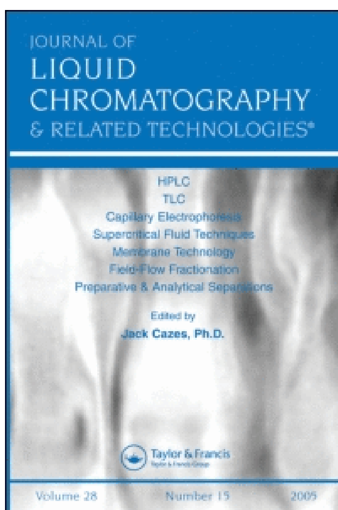
This article was downloaded by:
On: *24 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

Free Drug Monitoring by Liquid Chromatography and Implications for Therapeutic Drug Monitoring

E. Howard Taylor[a]; Bruce H. Ackerman[a]
[a] Departments of Pathology and Pharmacy Practice, University of Arkansas for Medical Sciences, Little Rock, Arkansas

To cite this Article Taylor, E. Howard and Ackerman, Bruce H.(1987) 'Free Drug Monitoring by Liquid Chromatography and Implications for Therapeutic Drug Monitoring', Journal of Liquid Chromatography & Related Technologies, 10: 2, 323 — 343
To link to this Article: DOI: 10.1080/01483918708066722
URL: http://dx.doi.org/10.1080/01483918708066722

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

JOURNAL OF LIQUID CHROMATOGRAPHY, 10(2&3), 323-343 (1987)

FREE DRUG MONITORING BY LIQUID CHROMATOGRAPHY AND IMPLICATIONS FOR THERAPEUTIC DRUG MONITORING

E. Howard Taylor and Bruce H. Ackerman
Departments of Pathology and Pharmacy Practice
University of Arkansas for Medical Sciences
Little Rock, Arkansas 72205

Downloaded At: 15:27 24 January 2011

ABSTRACT

Free (non-protein bound) drug monitoring is very complex but new advances in separation of protein bound from free drug by ultrafiltration can facilitate free concentration therapeutic drug monitoring. Free drug can be separated from protein-bound drug by means of ultrafiltration in which the free drug passes through the membrane filter while the protein bound drug is retained. The ultrafiltrate is then subjected to chromatographic analysis (HPLC). Limitations include a sufficient sample for these highly protein bound drugs and detector sensitivity at the low free drug concentrations. Free drug fractions that have been successfully analyzed by HPLC include disopyramide, phenytoin, carbamazepine, and propranolol. HPLC offers important advantages over immunoassays, since

Copyright © 1987 by Marcel Dekker, Inc.

chromatographic methods can also measure the amount of metabolite present. The detection of metabolites can be important, e.g. N-desisopropyl disopyramide which displaces disopyramide from its binding sites on alpha-one acid glycoprotein. The main controversies concerning free drug concentration monitoring have revolved around the time expenditure as well as clinical significance of changes in free fraction. Obtaining free and total drug concentrations of monitored drugs permits an assessment of the free fraction of drug and provides pharmacokinetic parameters for more accurate dose prediction and dose adjustment, in which HPLC can offer an attractive method of analysis.

Free drug concentration monitoring is controversial and is not indicated for all highly protein bound drugs (e.g., warfarin and the sulfonylureas). Candidates for free drug monitoring must have a relationship between pharmacologic effect and drug concentrations, or considerable variance in the free fraction of drug in serum. Potentially toxic drugs demonstrating poor correlations by linear and orthogonal regression of total drug concentrations versus free drug concentrations are ideal for such monitoring. For such drugs, nomograms developed to predict free drug concentrations are often unhelpful, particularly with seriously ill patients. Likewise highly protein bound drugs with metabolites capable of displacing parent drug may also unpredictably affect the free drug concentrations.

Downloaded At: 15:27 24 January 2011

INTRODUCTION

Drugs are distributed in the body as free molecules disolved in body water or as molecules bound to various tissue proteins including plasma proteins. The extent of drug binding to proteins is affected by the affinity constants to the various tissue proteins

and the concentrations of these drug binding proteins (1,2). The free fraction of drug in serum represents the percent unbound drug. Drugs greater than eighty percent bound to serum proteins may have significant changes in the "free fraction" due to disease, drug displacement, or altered serum protein concentrations (3,4). Drug displacement from protein binding sites results from concomitant drug therapy or competative binding by endogenous ligands (e.g., free fatty acids) with higher binding affinity (1,5,6). It is generally assumed that only free drug is pharmacologically active, capable of binding to affected tissues, and available for biotransformation (metabolism) and elimination (2,5). Though it may seem logical that the free drug concentration should be dependent on both the free fraction and the total drug concentration, this is not so (1,2,7). The total serum drug concentration used in therapeutic drug monitoring is actually dependent on the free drug concentration and the free drug concentration pharmacokinetic parameters should more accurately predict actual drug disposition (7-9).

Downloaded At: 15:27 24 January 2011

ANALYTICAL METHODS

Separation of free drug has proved extremely tedious by methods such as equilibrium dialysis in which free drug will diffuse into the buffer compartment (dialysate). In addition to being time consuming, equilibrium dialysis poses other problems such as: 1) variable in vitro experimental conditions (i.e., temperature, dialysis time, and buffer concentrations), 2) varying bound and unbound fractions compared to pre-dialysis equilibrium, 3) adsorption of highly ionized drugs to dialysis membrane. An excellent review of these complications is presented by Kwong (5).

Downloaded At: 15:27 24 January 2011

Ultrafiltration is becoming an increasingly popular method for separating protein bound from unbound drug concentrations due to its ease of use and low cost. Variables such as temperature (increasing temperature causes decreased protein binding), centrifugal forces (1000 to 2000 X g), time of centrifugation (approximately 10 minutes) need to be controlled. Adsorption of drug to the ultrafiltration membrane must

be measured. Ideally this is done with radioactively labeled drug; however, a more practical method is to measure the concentration of drug in an aqueous solution before and after ultrafiltration. We have successfully used this method to verify absence of ultrafiltration membrane binding with disopyramide (10).

The rate of filtration of free drug decreases as the serum viscosity increases, thus the volume of ultrafiltrate may be limited by clogging of the membrane by sera with high protein concentrations. The limitation of ultrafiltrate volume may be important for highly protein bound drugs in which a large volume is necessary to provide sufficient drug to be detected by HPLC.

In our laboratory, we use the Amicon Centrifree(R) filter (Amicon Corp., Danvers Ma. 01923) for the analysis of free phenytoin and free disopyramide. Neither of these drugs is adsorbed by the membrane filter (10,11). Separation is achieved by filtration of 500 uL of serum by centrifugation at 2000 X g for 10 minutes at 25° C. For the analysis of free disopyramide,

Downloaded At: 15:27 24 January 2011

100 uL of filtrate is combined with 25 uL of 40 ug/ml of internal standard, p-chlorodisopyramide. Internal standard is added following filtration to avoid any competition of internal standard with disopyramide for binding sites on the carrier protein (most commonly alpha-1 acid glycoprotein) thereby factitiously increasing the free fraction of drug. Disopyramide, its metabolite (N-desisopropyl disopyramide), and the internal standard can be separated with a mobile phase (5 mM Na_2HPO_4 pH 7.9, acetonitrile, and methanol,5:12:3 by volume) which we have successfully used for tricyclic antidepressant analysis (12) with a short (5 minute) run time. This analysis (Figure 1) was done on a Waters QA-1 analyzer with a 10 um cyanopropyl column, flow rate of 3.0 ml/min, 50 uL injection volume. Detection is by absorbance at 254 nm with a chart speed of 0.5 cm/min. With this method the coefficient of variation was 4.5 % at 0.67, 6.0 % at 1.70, and 2.9% at 5.53 ug/ml of free disopyramide, respectively. The minimum detection limits of free disopyramide is 0.2 ug/mL (Figure 1) with this method. The coefficient of

Downloaded At: 15:27 24 January 2011

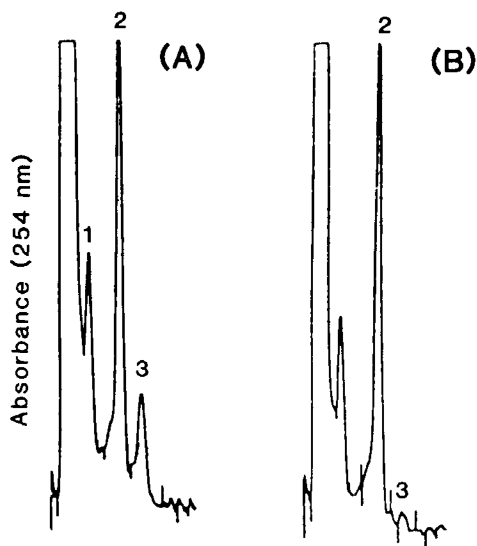


Figure 1: Separation by HPLC of n-Desisopropyl Disopyramide (1), Internal Standard, p-Chlorodisopyramide (2), and Disopyramide (3). Total run times is 5 minutes. (A) chromatogram for total drug assay (disopyramide concentration in patient serum is 1.30 ug/ml) and (B) free drug assay showing minimum detection limits without extraction (free disopyramide concentration is 0.21 ug.ml)

Downloaded At: 15:27 24 January 2011

variation at this low free drug concentration was 18.4% (n = 4) which we felt was acceptible for the majority of applications. Should lower limits of detection be necessary, extraction of the filtrate with chloroform and concentration can be employed (13).

The HPLC method of Kabra (14) for total phenytoin utilizing a chloroform extraction is sufficiently sen-

sitive to analyze free free phenytoin (if all of the reconstituted sample is injected). Due to the high protein binding (> 92%), any assay must be sufficiently sensitive to detect the small proportions of free drug present in the ultrafiltrate. Free carbamazepine has also been successfully analyzed by HPLC (15); values by an immunoassay method were consistently greater for free carbamazepine due to interferences with the 10,11 epoxide metabolite.

Downloaded At: 15:27 24 January 2011

The use of saliva to measure free drug has been advocated for carbamazepine, ethosuximide and phenytoin (16-23) and disopyramide (13). The rationale for saliva as the sampling method of choice is that saliva has much lower protein content (as an ultrafiltrate of blood) than serum and that there exists an equilibrium with serum free drug concentrations. Saliva varies as greatly as two pH units and this may contribute to variable saliva protein binding and compartmentalization into saliva. Thus, the choice of saliva instead of serum as a free drug monitoring sampling source is not reliable and is thus subject to error.

Propranolol has also been measured by HPLC (24) as well as its metabolite with fluorometric detection. Unbound propranolol and its metabolite had to be assayed on two separate runs due to the variation in excitation and emission characteristics of the parent drug and its metabolite. The detection of unbound metabolite may become important, since it shares binding sites with the parent drug, e.g. disopyramide (25) and its metabolite N-desisopropyl disopyramide, which also possesses some antiarrhythmic action. The analysis of both unbound parent drug and metabolite may offer a distinct advantage of HPLC over immunoassays which do not detect metabolites. Other candidates for

Downloaded At: 15:27 24 January 2011

Table 1

Drugs With Variable Protein Binding

Drug	Percent Bound
Phenytoin	75 to 93
Valproic Acid	70 to 90
Carbamazepine	70 to 80
Quinidine	50 to 95
Encainide	70 to 78
Lidocaine	45 to 80
Disopyramide	35 to 95

free drug monitoring include quinidine which is 80 - 90 % protein bound (see Table 1). The metabolite 3-OH quinidine has been proposed to have antiarrhythmic activity in man and the 2' oxoquinidine and O-desmethyl quinidine metabolites possess antiarrhythmic activity in animals, but their activity in man has not yet been determined (26).

Downloaded At: 15:27 24 January 2011

CHANGES IN SERUM PROTEIN CONCENTRATIONS

Age, sex, and disease states alter serum proteins and drug affinity. Serum albumin from elderly patients binds acidic drugs like phenytoin less avidly and elderly patients have higher concentrations of alpha-one acid glycoprotein, a serum protein binding (basic) cationic drugs (e.g., antidepressants, quinidine, disopyramide, and lidocaine). Males have slightly higher concentrations of alpha-one acid glycoprotein than do females, but these mean differences may result from the use by females of oral contraceptives (5,27).

Other diseases causing alpha-one acid glycoprotein rises include myocardial infarction (6), chronic

inflammatory disease, physical stress, burns, and malignancy (1). Many of these patients will have hypo-albuminemia as well. The lipoproteins in hyperlipidemia increase the total blood concentrations of cationic drugs. Apparent increases in total drug concentrations must be evaluated for free concentrations and signs of drug toxicity (2,5,28). Patients with diseases augmenting drug protein binding demonstrate poor correlations between therapeutic response and total blood drug concentrations.

Patients with thermal injuries (burns), malnutrition, the nephrotic syndrome, and rapidly progressive chronic liver disease are hypoalbuminemic. Chronic therapy with highly protein bound drugs, would be expected to increase serum free drug concentrations in hypoalbuminemic patients. This rise in free drug concentrations is transient because hepatic drug clearance is increased (2,28). The free drug concentration is dependent only on the dose, the dosing interval, and the clearance of the drug. Ultimately it is the total drug concentration which is dependent on

Downloaded At: 15:27 24 January 2011

the free drug concentration (7). Thus, with hypoalbuminemia hepatic clearance is increased.

CHANGES IN PROTEIN BINDING AND FREE DRUG CLEARANCE

Changes in serum protein concentrations of albumin, alpha-one acid glycoprotein, and lipoproteins alter the free fraction of drugs, their disposition, and their pharmacologic effects. Uremia decreases drug binding to albumin and likewise aspirin exposure decreases albumin binding (1,2,4,6,29-32). Elevated free fatty acids decrease valproate and phenytoin protein binding (5) and heparin exposure has been implicated to elevate free fatty acids through lipoprotein lipase activation (1,6). For others, the pharmacologic effects may fail to correlate well with total serum concentrations perhaps due to differences in free drug concentrations (1,2,33,34). This is apparently the case with the newer antidysrhythmic agents (34,35).

Free drug concentrations, as well as being pharmacologically active, are available for metabolism and excretion from the body. The biotransformation (meta-

Downloaded At: 15:27 24 January 2011

bolism) of drugs is a complex process described by simplified pharmacokinetic models which permit changes in protein binding. HPLC offers distinct advantages over immunological methods due to the ability of HPLC to simultaneously measure parent compound and metabolites. Displacement of parent drug from binding sites by metabolites thereby affects free drug clearance. Changes in hepatic clearance are partially dependent on the liver's capacity to extract free drug from blood (the extraction ratio). High extraction ratio drugs do not fit these models well, but most clinically used drugs may be referred to as low extraction drugs which fit these pharmacokinetic models well (36).

Drug displacement from binding proteins potentially can affect the free drug concentrations and ultimately the total serum concentrations being monitored. Drugs displaced from albumin may bind to alpha-one acid glycoprotein or vise versa (37). Increased free concentrations due to drug displacement will reflect the intrinsic distribution volume and

Downloaded At: 15:27 24 January 2011

smaller distribution volumes will have more significant changes. When protein bound drug is displaced, drug metabolism is increased and little change in the pharmacologic response occurs. Displacement of drug from serum proteins often lengthens the half-life in serum, while displacement from tissue proteins shortens the serum half-life (due to a decreased free concentration distribution volume).

Downloaded At: 15:27 24 January 2011

A significant drug interaction between phenytoin and valproic acid results in a decrease in the total phenytoin concentration and changes in tissue binding. The free fraction of 0.5 to 12 percent for phenytoin alone is increased to 12 to 23 percent with this combination (38,39). A similar problem occurs with patients treated with disopyramide where high production of the mono-alkylated metabolite will displace the parent compound and further complicate the pharmacokinetics of disopyramide (40).

CONCENTRATION DEPENDENT BINDING AND FREE DRUG CLEARANCE

Disopyramide and valproic acid demonstrate serum concentration dependent saturable protein binding in

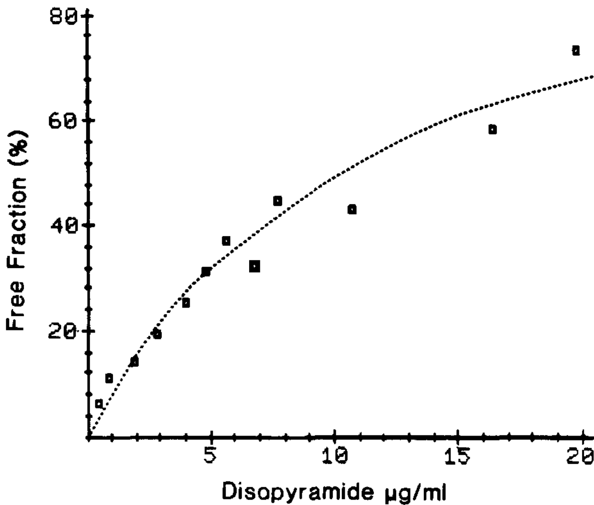


Figure 2: Concentration dependent protein binding of disopyramide, pooled sera was spiked with varying concentrations of disopyramide.

Downloaded At: 15:27 24 January 2011

which increased doses result in non-proportional total serum concentrations (Figure 2). Because the intrinsic distribution volume more accurately predicts needed dose adjustments, some have advocated free serum concentration monitoring of patients (41). Over the normal therapeutic range of disopyramide the free fraction ranges from 22 to 54 percent of total disopyramide (42). Correlations of free to total drug concentrations are complicated by normal variance in alpha-one acid glycoprotein which almost exclusively binds

disopyramide (43). Changes in pH and the degree of congestive heart failure also did not correlate with changes in disopyramide disposition (44,45) and this is reasonable since the free drug distribution volume remains unchanged (45). Because the free fraction of drug changes over the dosing interval for these two drugs, clearance is non-linear and thus the elimination rate constant is serum concentration dependent. An apparent disappearance constant can be determined from free phenytoin concentrations and may be applicable to disopyramide dosing as well (46). The ultimate goal of free drug monitoring is to utilize pharmacokinetic data based on free drug concentrations to adjust patient doses.

Downloaded At: 15:27 24 January 2011

REFERENCES

1. Levy, R.H., Moreland, T.A., Rationale for Monitoring Free Drug Levels, Clin. Pharmacokinet. 9(supl 1): 1 (1984)

2. Greenblatt, D.J., Sellers, E.M., Koch-Weser, J., Importance of Protein Binding for the Interpretation of Serum or Plasma Drug Concentrations, J. Clin. Pharm. 22: 259 (1982)

3. Rimmer, E.M., Buss, D.C., Routlege, P.A., Richens, A., Monitoring Free Plasma Concentrations of

Phenytoin--A Reply, Brit. J. Clin. Pharm. 18: 972 (1984)

4. Reidenberg, M.M., Odar-Cederloef, I., von Bahr, C., Olof Borgaa, M.L., Sjoeqvist, F., Protein Binding of Diphenylhydantoin and Desmethylimipramine in Plasma from Patients with Poor Renal Function, N. Eng. J. Med. 285: 264 (1974)

5. Kwong, T.C., Free Drug Measurements: Methodology and Clinical Significance, Clin. Chim. Acta, 151: 193 (1985)

6. Woosley, R.L., Siddoway, L.A., Thompson, K., Cerkus, I., Roden, D.M., Potential Applications of Free Drug Level Monitoring in Cardiovascular Therapy, Clin. Pharmacokinet. 9(Suppl. 1): 79 (1984)

7. Levy, R.H., Schmidt, D., Utility of Free Level Monitoring of Antiepileptic Drugs, Epilepsia 26: 199 (1985)

8. Riva, R., Albani, F., Ambrosetto, G., Contin, M., Cortelli, P., Perucca, E., Baruzzi, A., Diurnal Fluctuations in Free and Total Steady-state Plasma Levels of Carbamazepine and Correlation with Intermittent Side Effects, Epilepsia 25: 476 (1984)

9. Loescher, W., A Comparative Study of the Protein Binding of Anticonvulsant Drugs in Serum of Dog and Man, J. Pharmacol. and Exper. Ther. 208: 429 (1978)

10. Taylor, E.H., Nelson, D., Taylor, R.D., and Pappas, A.A., Rapid Sample Preparation and High Performance Liquid Chromatographic Determination of Total and Unbound Serum Disopyramide, Ther. Drug Monit. 8: 219 (1986)

11. Peterson, G.M., McLean, S., von Witt, R.J., Millingen, K.S., Audit fo a Monitoring Service for

Downloaded At: 15:27 24 January 2011

Free Phenytoin, Brit. J. Clin. Pharmacol. 19: 693 (1985)

12. Taylor, E.H., and Gadsden, Sr., R.H. Determination of Tricyclic and Tetracyclic Antidepressants by Liquid Chromatography, in: Selected Methods of Emergency Toxicology, vol 2, eds: Frings, C.S., and Faulkner, W.R., AACC Press, Washington, D.C., 1986 (In Press)

13. Lima, J.L., Liquid Chromatographic Analysis of Disopyramide and its Mono-dealkylated Metabolite, Clin. Chem. 25: 405 (1979)

14. Kabra, P.M., Gotelli, G., Stanfill, R., and Marton, L.J., Simultaneous Measurement of Phenobarbital, Diphenylhydantoin, and Primadone in Blood by High -Pressure Liquid Chromatography, Clin. Chem. 22: 824 (1976)

15. Contin, M., Riva, R., Albani, F., Perucca, E., Baruzzi, A., Determination of Total and Free Plasma Carbamazepine Concentrations by Enzyme Multiplied Immunoassay: Interference with the 10,11-Epoxide Metabolite, Ther. Drug Monit.7: 46 (1985)

16. Gerson, B., Essentials of Therapeutic Drug Monitoring, Igaku-Shoin Medical Publishers, New York, 1983, pp 22-23

17. McAuliffe, J.J., Sherwin, A.L., Leppik, I.E., Fayle, S.A., Pippenger, C.E., Salivary Levels of Anticonvulsants: A Practical Approach to Drug Monitoring, Neurol. 27: 409 (1977)

18. Reynolds, F., Ziroyanis, P.N., Jones, N.F., Smith, S.E., Salivary Phenytoin Concentrations in Epilepsy and in Chronic Renal Failure, Lancet (Aug 21, 1976): 384

19. Knott, C., Reynolds, F., The Place of Saliva in Antiepileptic Drug Monitoring, Ther. Drug Monit. 6: 35 (1984)

Downloaded At: 15:27 24 January 2011

20. Parnas, J., Flachs, H., Gram, L., Wuertz-Jorgensen, A., Secretion of Antiepileptic Drugs in Sweat, Acta Neurol. Scand. 58 197 (1978)

21. Paxton, J.W., Donald, R.A., Concentrations and Kinetics of Carbamazepine in Whole Saliva, Parotid Saliva, Serum Ultrafiltrate, and Serum, Clin. Pharm. and Ther. 28 695 (1980)

22. Bachmann, K., Forney, R.B., Voeller, K., Monitoring Phenytoin in Salivary and Plasma Ultrafiltrates of Pediatric Patients, Ther.Drug Monit. 5: 325 (1983)

23. Cramer, J.A., Mattson, R.H., and Bennett, D.M., Utilisation of Free Valproic Acid Determinations, Clin. Pharmacokinet. 9(suppl 1): 94 (1984)

24. Ray, K., Trawick, W.G., Mullins, R.E., Assay fo Total and Free Propranolol in Plasma by Liquid Chromatography with Fluometric Detection, Clin. Chem. 31: 131 (1985)

25. Chiang, W-T., von Bahr, C., Calissendorff, B., Dahlquist, R., Emilsson, H., Magnusson, A., Schenck-Gustafsson, K., Kinetics and Dynamics of Disopyramide and its Dealkylated Metabolite in Healthy Subjects, Clin. Pharm. Ther. 38: 37 (1985)

26. Evans, W.E., Oellerich, M., eds. Therapeutic Drug Monitoring Clinical Guide, Abbott Labs. North Chicago, Illinois, 1984; pp. 82-83.

27. Teitz, N.W., ed., Clinical Guide to Laboratory Tests, W.B. Saunders, Co., Philadelphia, PA, 1983; pg. 6.

28. Gugler, R., Azarnoff, D.L., Drug Protein Binding and the Nephrotic Syndrome, Clin. Pharmacokinet. 1: 25 (1976)

Downloaded At: 15:27 24 January 2011

29. Reidenberg, M.M., The Binding of Drugs to Plasma Proteins from Patients with Poor Renal Function, Clin. Pharmacokinet. 1: 121 (1976)

30. Odar-Cederlof, I., Plasma Protein Binding of Phenytoin and Warfarin in Patients Undergoing Renal Transplantation, Clin. Pharmacokinet. 2: 147 (1977)

31. Reidenberg, M.M., Drayer, D.E., Alteration of Drug-Protein Binding in Renal Disease, Clin. Pharmacokinet. 9(suppl 1): 18 (1984)

32. Fraser, D.G., Ludden, T.M., Evens, R.P., Sutherland, E.W., Displacement of Phenytoin from Plasma Binding Sites by Salicylate, Clin. Pharm. Ther. 27: 165 (1980)

33. Brandt, J., Dam, M., Valproate Sodium (Deprakine) A New Antiepileptic Drug, Epilepsia 20: 187 (1979)

34. Follath, F., Ganzinger, U., Schuetz, E., Reliability of Antiarrhythmic Drug Plasma Concentration Monitoring, Clin. Pharmacokinet. 8: 63 (1983)

35. Gillis, A.M., Kates, R.E., Clinical Pharmacokinetics of the Newer Antiarrhythmic Agents, Clin. Pharmacokinet. 9: 375 (1984)

36. Rowland, M., Leitch, D., Fleming, G., Smith, B., Protein Binding and Hepatic Clearance: Discrimination Between Models of Hepatic Clearance with Diazepam, a Drug of High Intrinsic Clearance, in the isolated Perfused Rat Liver Preparation, J. Pharmacokinet. Biopharm. 12: 129 (1984)

37. MacKichan, J.J., Pharmacokinetic Consequences of Drug Displacement from Blood and Tissue Proteins, Clin. Pharmacokinet. 9(suppl. 1): 32 (1984)

Downloaded At: 15:27 24 January 2011

38. Dahlqvist, R., Borgaa, O., Rane, A., Walsh, Z., Sjoeqvist, F., Decreased Plasma Protein Binding of Phenytoin in Patients on Valproic Acid, Brit. J. Clin. Pharmacol. 8: 547 (1979)

39. Friel, P.N., Leal, K.W., Wilensky, A.J., Valproic Acid--Phenytoin Interaction, Ther. Drug Monit. 1: 243 (1979)

40. Hinderling, P.H., Garrett, E.R., Pharmacokinetics of the Antiarrhythmic Disopyramide in Healthy Humans, J. Pharmacokinet. Biopharm. 4: 199 (1976)

41. Meffin, P.J., Robert, E.W., Winkle, R.A., Harapat, S., Peters, F.A., Harrison, D.C., Role of Concentration-Dependent Plasma Protein Binding in Disopyramide Disposition, J. Pharmacokinet. Biopharm. 7: 29 (1979)

42. Shaw, L.M., Altman, R., Thompson, B.C., Fields, L., Effect of Several Variables on the In Vitro Binding of Disopyramide to Serum Proteins, Clin. Pharmacokinet. 9(suppl. 1): 98 (1984)

43. Lima, J.J., Boudoulas, H., Blanford, M., Concentration-Dependence of Disopyramide Binding to Plasma Protein and Its Influence on Kinetics and Dynamics, J. Pharmacol. Exper. Ther. 219: 741 (1981)

44. Cunningham, J.L., Shen, D.D., Shudo, I., Azarnoff, D.L., The Effects of Urine pH and Plasma Protein Binding on the Renal Clearance of Disopyramide, Clin. Pharmacokinet. 2: 373 (1977)

45. Lima, J.J., Haughey, D.B., Leier, C.V., Disopyramide Pharmacokinetics and Bioavailability Following the Simultaneous Administration of Disopyramide and 14C-Disopyramide, J. Pharmacokinet. Biopharm. 12: 289 (1984)

Downloaded At: 15:27 24 January 2011