An. R. Acad. Nac. Farm., 2004, 70: 663-679

Artículo original

Pharmacokinetics and individualized Drug Therapy *

LENNART K. PAALZOW
Académico Correspondiente de la Real Academia Nacional de Farmacia en Suecia

ABSTRACT

This paper describes different aspects concerning the application of pharmacokinetics for individualized drug therapy. Pharmacokinetic sciences have developed rapidly during the last three decades, but its use in clinical practice is still lagging behind. The clinical use is often called therapeutic drug monitoring (TDM). By measuring one single drug plasma concentration and by applying prior knowledge of the population pharmacokinetic characteristics of a specific drug we can perform a Bayesian estimates of the pharmacokinetic parameters in the individual patient. Hereby, we can calculate the optimal dose and dosing interval for individual patient. Examples of Bayesian dose predictions and its therapeutic outcomes are given.

Key words: Pharmacokinetics.— Therapeutic drug monitoring (TDM).

RESUMEN

Farmacocinética y Terapéutica individualizada de Drogas

El presente artículo constituye una disertación sobre los diferentes aspectos relativos a los estudios farmacocinéticos. La farmacocinética abarca el estudio de la evolución de los niveles de fármacos presentes en los distintos fluidos biológicos, lo que explica los efectos terapéuticos y tóxicos de los mismos. Existen dife-

* Discurso pronunciado en su toma de posesión como Académico Correspondiente de la Real Academia Nacional de Farmacia, en fecha 7 de febrero de 2002.

rentes modelos matemáticos que describen el comportamiento y las concentraciones de estos medicamentos. Así cuando los medicamentos son administrados, su concentración en los fluidos biológicos cambia con el tiempo, dando una curva de perfil característico. La práctica clínica de la farmacocinética recibe la denominación de monitorización terapéutica de fármacos (TDM). La monotorización de fármacos se realiza determinando las concentraciones de un fármaco en plasma así como su intervalo de dosificación, mediante cuantificación de los niveles del mismo en plasma de pacientes individualizados. También se consideran los fármacos para los que es más adecuada su monitorización clínica y se describen los métodos estadísticos disponibles y adecuados para la descripción del comportamiento de un fármaco según los niveles de concentración medidos.

Palabras clave: Farmacocinética.— Monitorización terapéutica de fármacos (TDM).

INTRODUCTION

Pharmacokinetics is usually described as a science that describes what happens to a drug in the body. It is a study of the time course of drug and metabolite levels in different fluids, tissues and excreta of the body and the mathematical relationships required to interpret such data (1). The international development of pharmacokinetics as a separate science has been very rapid during the last three decades, but of course even before this period there were published a number of seminal research that laid the foundation to this discipline.

Personally, I am very pleased to know that professor Torsten Teorell, who was professor of physiology at our University, is considered as the father of pharmacokinetics. Already in the summer 1937, he wrote two famous articles (2, 3), which from the beginning nobody really understood and most experts in Sweden considered almost as rubbish and these papers were consequently forgotten. It took almost 30 years before researcher, especially in U.S.A., realized the importance of theses two articles and from around 1965 and onwards pharmacokinetics started to develop rapidly. These papers of Teorell are today considered as two of the most important articles in this area and they are considered as the origins of pharmacokinetics. We also have to remember that the development in pharmacokinetics was due to the rapid development of new analytical techniques like gas chromatography, liquid chromatography, high-pressure liquid chromato-

graphy and mass-spectrometry. These techniques have given us sensitive and specific methods that are able to measure drug and metabolite concentrations in extremely low concentrations.

When plasma concentrations obtained after given dose of a drug are measured, plasma is used as a reference tissue to describe what happens to a drug in the body and since its concentrations change over time it gives every drug its own characteristic time profile (Figure 1). You can say that the characteristic shape of each plasma concentration-time curve is an identity of the drug. It is also well established that a drug produces its therapeutic effect within a certain range of plasma concentration, its therapeutic window or target therapeutic drug concentration (Figure 1). To describe the plasma concentration-time curve mathematically we use certain pharmacokinetic parameters and the most important ones are clearance, volume of distribution, absorption rate constant and bioavailability (4). Once these parameters are known we can calculate the plasma concentration time profile after single or repeated doses.

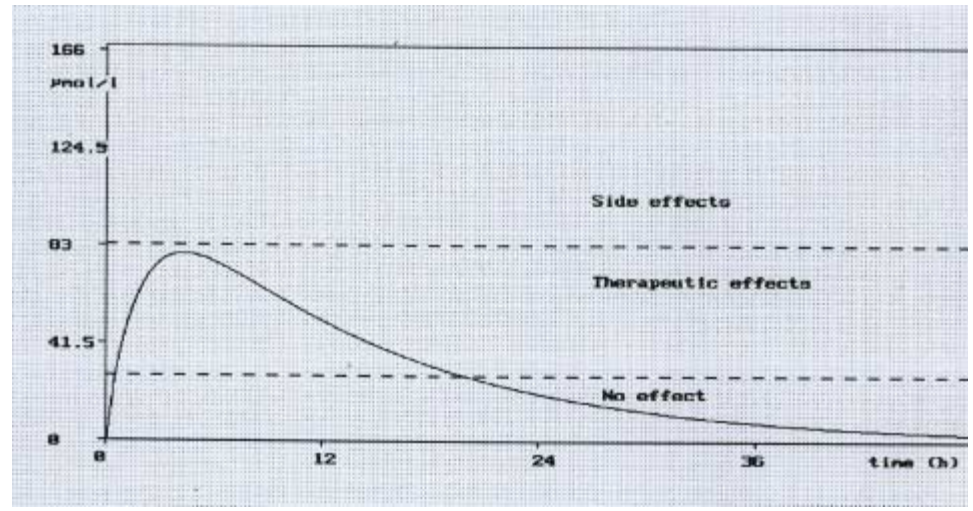

FIGURE 1. *Plasma concentration-time profile of a drug with its therapeutic window.*

DRUG DOSING TODAY

When the physician has decided to prescribe a specific drug she or he has to recommend a certain dose and dosing interval. Usually the doctor chooses the average dose found in the physician desk reference. Then she or he changes the dose by trial and error. In certain cases, although not very common, the prescribed dose is based on the gender, bodyweight and age. For certain drug excreted by the renal route, the kidney function is taken into consideration when chosen the dose.

The most common way of adjusting or prescribing the dose is based on how the patient reacts on the given drug and acordingly changed next time the patient meets the physician. In some few instances the dose is selected based on laboratory finding and finally for some drugs it is based on the measurements of drug concentration in the blood or plasma.

There are estimations reported that for certain drugs only about half of the patients get the correct dose and the 50% of the patients doses (5). However, by measuring the blood concentration and the use of the knowledge we have in pharmacokinetics we have today the possibility to decide about the dose and individual patient should take in order to get an optimal therapeutic effect. So the question is: Should we give the same dose to all individuals or after the specific need of the individual patient?

During recent years it has been an ongoing discussion that in the future the dose of a drug should be selected based on the genetic constitution of the patient. Examples of inherited variability in pharmacokinetics have so far been almost exclusively restricted to drug metabolism. By performing phenotyping or genotyping we have been able to characterize rare phenotypes. Despite its appeal, metabolite phenotyping is not widely employed in clinical practice while genotyping holds the promise of providing a more direct approach toward predicting metabolic phenotypes. However, we have to remember that pharmacokinetics parameters like volume of distribution, renal excretion and absorption most probably are not under genetic control and additionally, the behavior of a drug in the body are influenced by a number of physiological factors like drug binding, blood

flow, distribution characteristics etc. and not to forget environmental and patho physiological factors.

THERAPEUTIC DRUG MONITORING (TDM)

As mentioned above the pharmacokinetic science has developed tremendously but its use in clinical practice has been limited, although it is used widely during drug development by the drug industry. The usage of pharmacokinetics in clinical practice can be called TDM, therapeutic drug monitoring, which means: To monitor drug dose and dosing interval by measuring the plasma concentration of the drug in the individual patient. But in order to use plasma concentration for selecting the dose and dosing interval there has to been a relationship between concentration and therapeutic effects like for instance the sigmoidal relationships shown in Figure 2 (6). It may also be inferred that if a substance should become a drug, it has to be a relationship between dose and effect and if such relationship exists there is also certainly a relationship between drug concentration and effect, even if it in some circumstances can become somewhat more complex than the relationship shown in Figure 2.

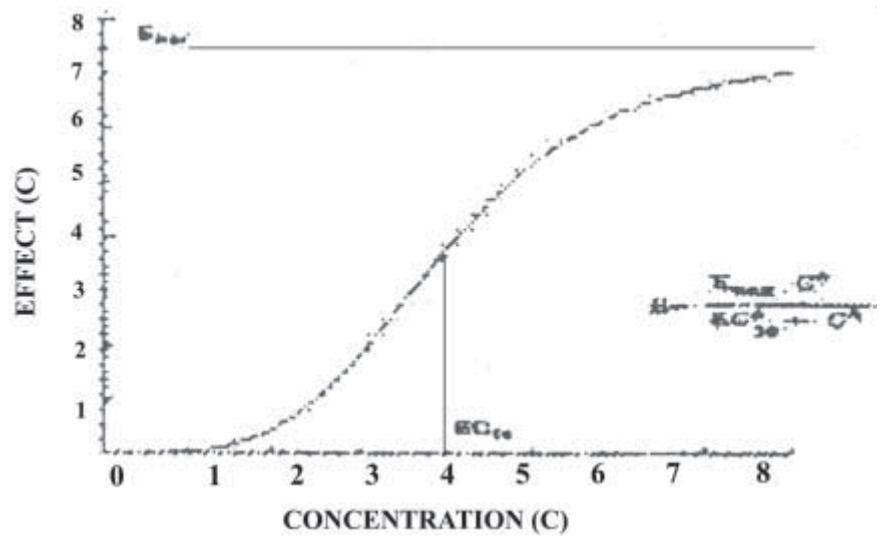

FIGURE 2. *The sigmoidal relationship between drug concentration and therapeutic effects according to a sigmoidal Emax equation.*

CLINICAL INDICATIONS FOR THERAPEUTIC DRUG MONITORING

When should we monitor drug doses by TDM? In the following I will give you some examples when TDM are indicated:

- Sometimes it is difficult to judge if lack of therapeutic effect is due to wrong choice of drug or that other factors could be the reason to e.g. absence of effects.
- For many drugs it takes time before we can see any effects. For drugs against e.g psychosis or cancer it may take weeks before we can say anything about the outcome of the prescribed drug.
- By measuring the plasma concentration we can figure out if the patient has taken the drug or not.
- For many drugs there is a large variability between patients in the uptake, distribution and elimination of the drug in the body, and by measuring plasma concentration we could individualize the dose.
- TDM should be used for drugs where it is a narrow concentration range between too low concentration giving no effect and concentration that are too high and consequently gives side effects.
- Liver and kidney functions are important for the elimination of drugs and we have to take their functions in consideration if they did not function normally.
- Sometimes it is difficult to judge if the patient does not respond to therapy, if this depends on the drug or the illness.
- Quite often we give several drugs simultaneously and in certain cases could they interact with each other.
- Genetic factors as mentioned above.

DRUGS SUITABLE FOR TDM

From what I have said you may get the impression that all drugs should be monitored by plasma concentration measurements. That

is not true. Many drugs have such a wide margin between good effects and side effects so if you do not observe an effect; it is just to increase the dose until you observe an effect. If you then do not get a therapeutic effect you may have to change drug.

Suitable drugs for TDM are of course drugs that are going to be used by the patients for a long time and where it is important that you find the correct dose and dosing interval in order to get the best therapeutic effect with a minimum of side effects. I will give you some examples of classes of drugs we have been working with in Uppsala.

Immunosuppressant drugs have to be taken in order to avoid organ rejections after transplantation, psychoactive drugs used to treat e.g. psychosis, antiepileptics, cardioactive glycosides and blood factors for hemophilia are examples of drugs used for long times, in certain cases for the whole life. Other examples are antibiotics and tuberculostatic drugs, where it is critical for the treatment that the correct concentration in the body is achieved otherwise the bacteria may become resistant. Anticancer drugs are a group of drugs that are used under the philosophy that it should be given in as large doses as possible, with the limitation that the patient can manage the serious side effects. There are still much to do with these drugs in order to improve the cancer therapy and I think that TDM is one way to optimize cancer treatment.

THERAPEUTIC DRUG MONITORING TODAY

There are performed a lot of drug chemical analyses at the hospitals all over the world. In Sweden there is analysed about 600.000 blood samples per year in a population of about 8 million. The question is of course how these measurements is interpreted. In Sweden, I may say, most medical doctors look upon the values just to find out if they fall within by the manufacturer recommended concentration range, without any, I may say, deeper consideration. If the value falls within the range, the prescribed dose is correct (Figure 3).

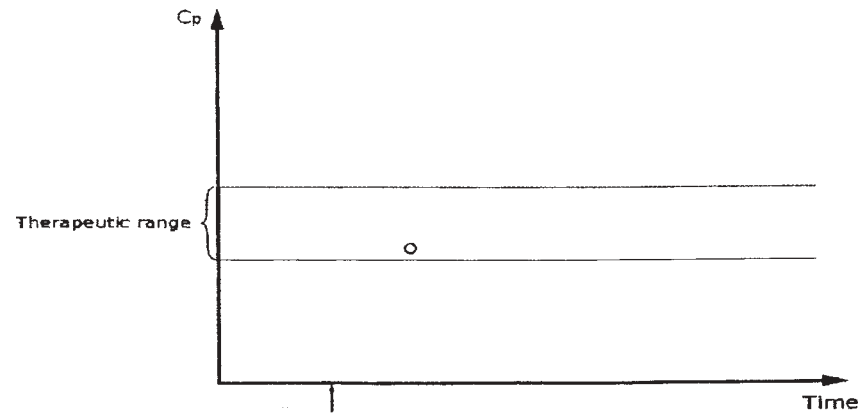

FIGURE 3. *Plasma concentration measurement indicating a value within the therapeutic concentration range.*

I will give you one example of how one concentration value could give limited or as in this case wrong information. As shown in Fig. 4 the obtained plasma concentration value could indicate that the selected dose and dosing interval are correctly chosen. However, without taking into account the dosing interval and the number of doses taken by the patient measured plasma concentration value can indicate that the prescribed dose is going to produce serious side effect and a much lower dose should be prescribed.

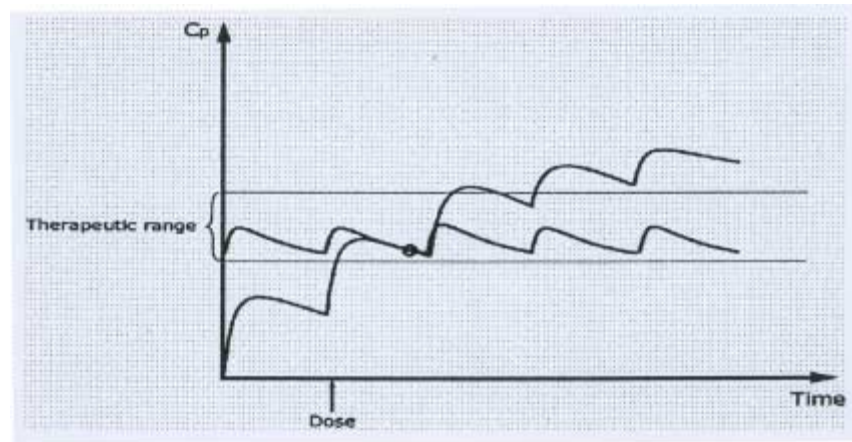

FIGURE 4. *The plasma concentration measurement in Fig. 3 may indicate that the selected dose and dosing interval are correct or indicating that the dose is too high leading to side effects if continued.*

EXAMPLES OF BAYESIAN DOSE PREDICTIONS

Today, there are computerized statistical techniques available to help us to perform the correct interpretations of measured plasma concentration values, although they are not used very much. The most reliable one is based on the statistical theory called Bayesian techniques after the English statistician Bayes. As shown in equation 1 the Bayesian analysis (Maximum likelihood estimates) takes into consideration, apart from the measured plasma concentration, what is known about the pharmacokinetic parameters in the population under investigation and its statistical variability.

$$\text{Bayes} = \text{Sum}\left[\frac{(\text{Cobs} - \text{Cpred})^2}{\text{S.D. ana}^2} + \frac{(\text{Ppop} - \text{Ppred})^2}{\text{S.D. pop}^2} + 1n\ (\text{S.D. pred})^2\right]$$

Cobs=	Measured plasma concentration for a specific individual
Cpred=	Predicted plasma concentration for a specific individual
Ppop=	Pharmacokinetics population paremeter value
Ppred=	Predicted pharmacokinetics parameter value for the individual
S.D. pop=	Standard deviation of the population value
S.D ana=	Standard deviation of the chemical analysis

By this technique, first introduced by Sheiner et al. (7), you can calculate the pharmacokinetic parameters in the individual patient with only one plasma concentration value available. Once you have calculated the pharmacokinetic parameter of the individual patient you can easily calculate the dose and dosing interval the patient should use in order to get desired plasma concentrations. I will give you some examples and the first one is shown in Fig. 5.

If this patient behaved as the normal average patient the recommended dosing should give a plasma concentration-time profile as the upper curve. A Bayesian estimate gave however the lower curve with trough values lower then the 250 ng/mL needed for the drug to have an effect in this individual. Obviously this patient needs a higher dose in order to get an effect of the drug.

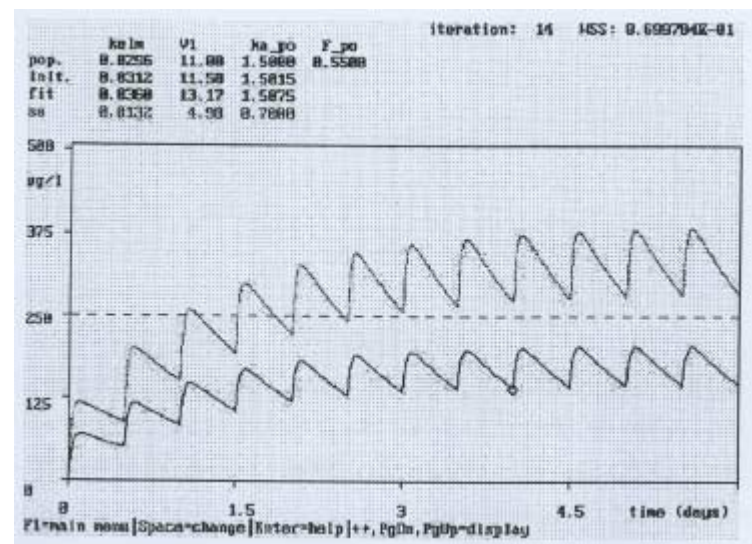

FIGURE 5. *A Bayesian prediction of drug dosing in a patient based on one plasma concentration value and knowledge of population pharmacokinetics values (lower curve) compared to plasma concentration-time profile for the actual population.*

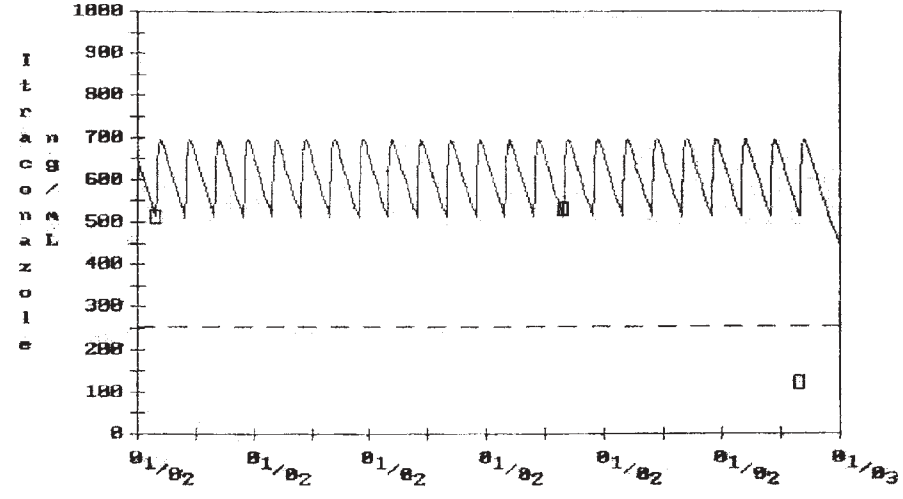

FIGURE 6. *Suspected non-compliance to prescribed drug dosing. The first two plasma concentration measurements show trough values above the minimum 500 ng/mL, while the third one was only 120 ng/mL.*

Figure 6 shows a seven year old boy treated against a fungus infection by the drug itraconazol and as you can see everything

looks fine when two blood samples were taken and the concentrations were measured; the trough level should exceed 500 ng/mL for this infection.

Suddenly, however, the last blood sample was very low and you start to wonder what has happen. The first question is of course to ask the patient if he really has been taken the drug. During the interviews with the parents it was evident that the mother usually had been supervising the medication, but during the last weeks the boy had been trusted to manage his own medication. He assured that he had been taken the drug, but the measured low concentration got him to confess that he has not been taken the drug for two weeks and an Bayesian estimate fitted very well to this kind of non compliance as shown in Fig. 7.

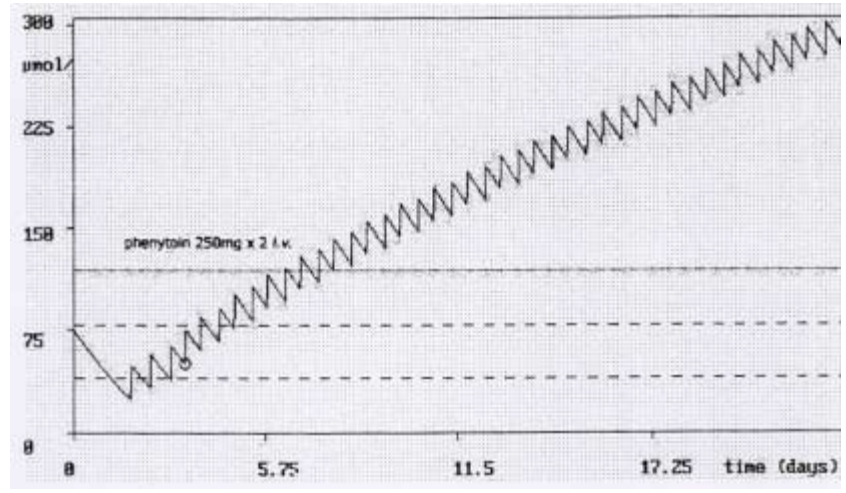

FIGURE 7. *A Bayesian estimate of drug dosing taking into consideration that the last 8 doses in Fig. 6 have not been taken by the patient.*

Phenytoin, as you know, is widely used as an antiepilectic drug, but it is difficult to find the correct dose, because it is very easy to saturate the enzymes for its elimination. Just a small increase in dose can lead to serious side effects and a too small dose does not protect against seizures. In Fig. 8 is shown a patient where the measured plasma concentration looks fine, but in reality, if the patient continues with the prescribed dose 250 mg two times daily it will lead to serious side effects.

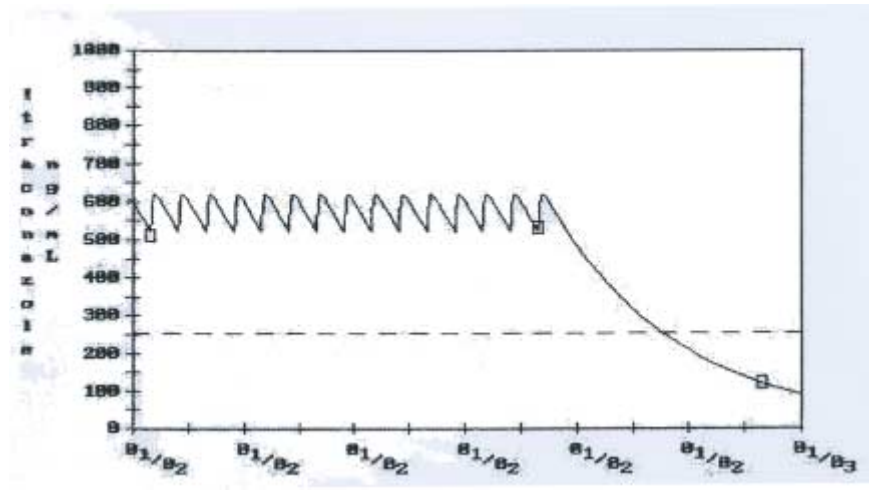

FIGURE 8. *Patient treated with standard dose of phenytoin against epilepsy (250 mgx2). Because of saturation of the metabolism, this drug dosing will lead to toxic levels if continued.*

A Bayesian estimate showed that this patient instead should have a dose of 150 mg. two times daily in order to keep the concentration within the therapeutic concentrations (Fig. 9).

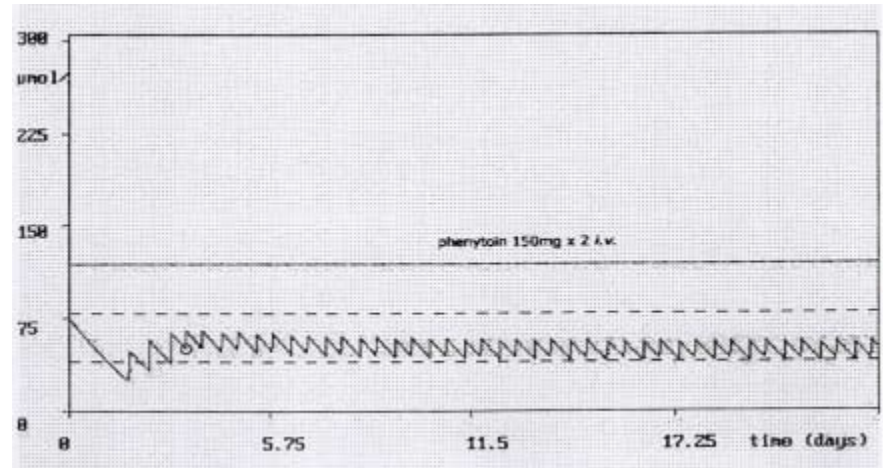

FIGURE 9. *The patient in Fig. 8 given the individually calculated dosing of 150 mgx2 yields a plasma concentration-time profile within the therapeutic window.*

In a study we recently have performed in Uppsala it was shown that in 39 new patients treated with phenytoin only about 5% got a prescribed dose that gave therapeutic plasma concentrations, while about 47% either got too high or too low plasma concentrations. With a Bayesian individualization program for phenytoin dosing it was furthermore shown that it was possible to predict the correct dose in 95% of patients treated with phenytoin. These examples demonstrate the difficulties of individualization drug dosing without performing correct interpretations of measured plasma concentration values.

As mentioned before, for immunosuppressant drugs it is very important to keep the drug concentrations within certain limits. If you get too high concentrations you can have toxic effect of the drug and the transplanted organ will be affected and if you get too low concentration the body may reject the organ. In order to avoid this, a number of blood samples are usually taken repeatedly in each patient, almost every day, during the first weeks after the surgery. In figure 10 is shown a patient that had much lower plasma concentrations than expected in his population and if he had behaved as expected, this patient should have had a plasma concentration-time curve like the upper one, but instead he had low plasma concentration values as shown in the figure.

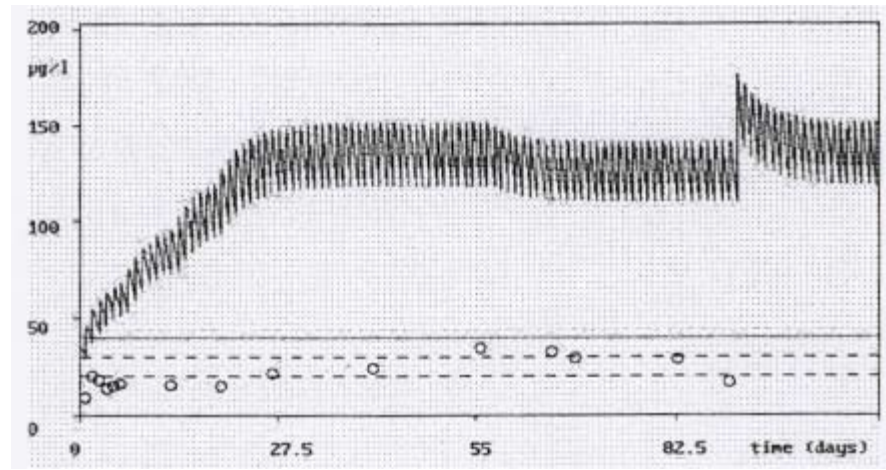

FIGURE 10. *Kidney-transplanted patient treated with the immunosuppressant drug sirolimus. Several drug analyses and dose adjustments performed. The upper curve shows the blood concentration-time profile if this patient had behaved kinetically as expected in his population.*

However, as shown in Fig. 11, a Bayesian estimates using only two or three samples in the beginning could predict the dosing for the following three months without blood sampling. All the subsequent blood samples could have been avoid if Bayesian technique had been utilized and by that saved hospital money and distress for the patient. It has to be inferred, however, that it may also be other factors than drug blood concentration values that have to be taken into consideration at the same time when performing blood sampling.

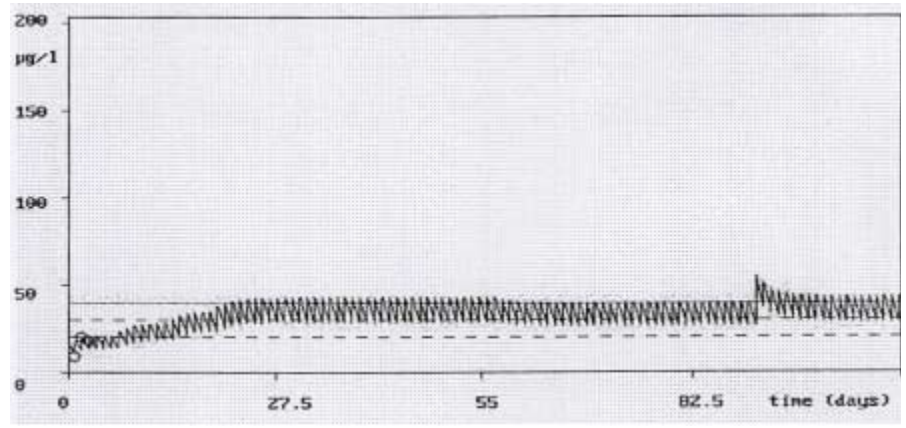

FIGURE 11. *The patient in Fig. 10 with individualized drug dose predictions based only on a Bayesian estimate using the first three blood concentration measurements.*

Neuroleptic drugs used to treat psychosis are used during long time periods. It is an interesting class of drugs since there is a distinct concentration range within which you have a therapeutic effect. The concentration effect-relationship is however complex for several of these drugs (8). With increasing concentration the effect against psychosis increases reaching a maximum and than the effect start to decline with further increase in concentration, a type of curve that we can call Bell-shaped. In order to get maximum therapeutic effects you have to keep the concentration within a certain limited range and therapeutic drug monitoring using Bayesian dose adaptation can facilitate this.

An example of these drugs, perphenazin is administered as an intramuscular depot injection with the aim of delivering the drug for a whole month. The problem with these depot preparations is that

it will take almost half a year before you know if the prescribed dose will end with a plasma concentration within the desired concentration range. In Fig. 12 is shown a woman who got 2 ml injected every second week and the first sample taken during the first dose was within the therapeutic range, but a Bayesian estimate showed that if the patient continues with this dosing scheme it will lead too high plasma concentrations that will be evident three months later.

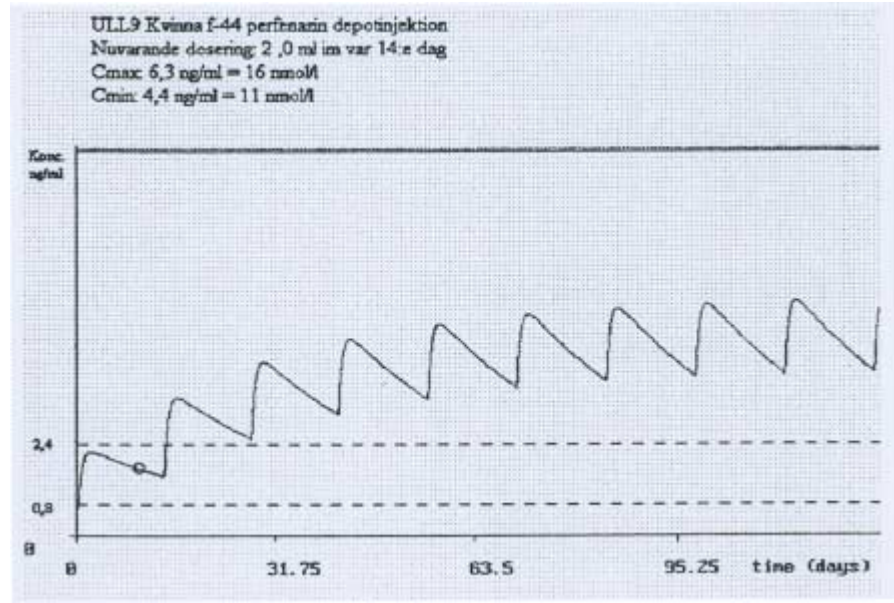

FIGURE 12. *A patient treated with perphenazin depot injections (2mL every second week) and a plasma concentration value taken during the first dose being within the therapeutic drug concentrations. However, this drug dosing will lead to drug levels above the therapeutically recommended.*

As illustrated in Fig. 13, this patient should only be given 0,5 mL every second week in order to keep the plasma concentrations within the therapeutic range.

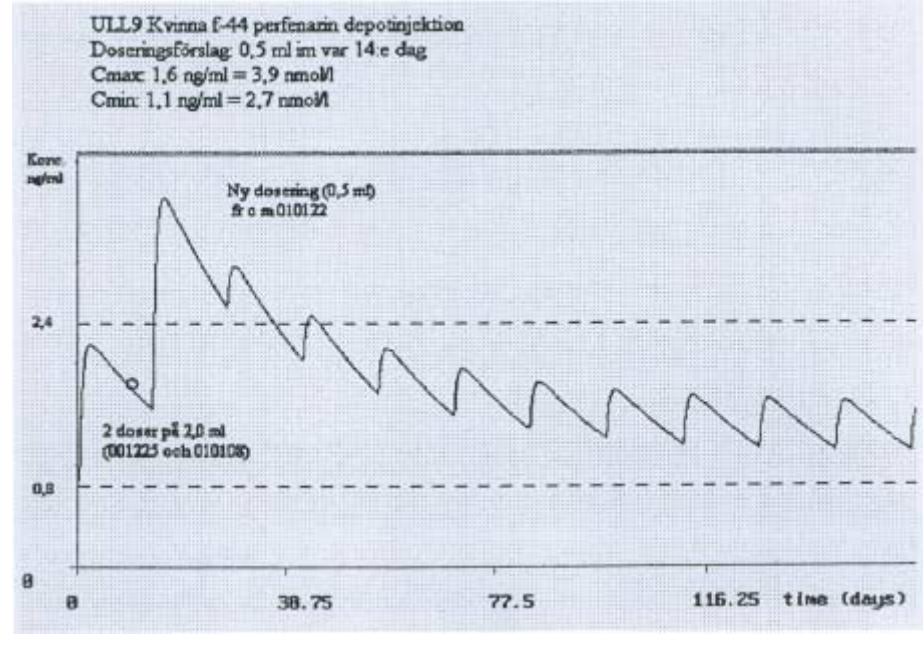

FIGURE 13. *A Bayesian estimate of the patient in Fig. 12 predicts that the patient should be given a dose of 0.5 mL perphenazin every second week.*

CONCLUSION

In my presentation I have given you some examples on how pharmacokinetics could be applied in clinical practice in order to optimize drug therapy. Bayesian estimates based on previous knowledge of the pharmacokinetics in a specific patient population and a single plasma concentration value is a technique that gives the possibility to estimate the desired drug dosing in an individual patient. There is still much research to do before we have reached the goals of individualizing drug dosing and I personally think that pharmacists and especially clinical pharmacists can do a lot in order to reach this goal.

REFERENCES

(1) GIBALDI, M.; PERRIER, D. (1975) In Pharmacokinetics, Marcel Dekker Inc, New York.
(2) TEORELL, T. (1937) Kinetics of distribution of substances administered to the body I. The extravascular modes of administration. *Arch. Int. Pharmacodyn.* 57: 205.
(3) TEORELL, T. (1937) Kinetics of distribution of substances administered to the body I. The extravascular modes of administration. *Arch. Int. Pharmacodyn.* 57: 226.
(4) ROWLAND, M.; TOZER, T.N. (1995) In Clinical Pharmacokinetics, Concepts and applications 3rd ed. Williams & Wilkens, Baltimore.
(5) EVANS, W.E., SCHENTAG, J.J.; JUSKO, W.J. (1992) In Applied Pharmacokinetics. Principles of Therapeutic Drug Monitoring 3rd ed. Applied Therapeutics, Inc., Vancouver.
(6) PAALZOW, L. (1990) Pharmacodynamics, pp. 333-358. In: Taylor, J.B. ed. Comprehensive Medical Chemistry, Vol. 5, Biopharmaceutics. Pergamon Press, Oxford.
(7) SHEINER, L.B.; ROSENBERG, B.; MELMON, K.L. (1972) Modelling of individual pharmacokinetics for computer aided drug dosage. *Comp. Biochem. Res*. 5: 441-459.
(8) PAALZOW, L.K.; PAALZOW, G.H.M.; TFELT-HANSEN, P. (1985) Variability in Bioavailability: Cencentration versus Effect. In Rowland, M,; Sheiner, L.B.; Steimer, J-L. (eds): Variability in Drug Therapy, Description, Estimation, and Control. Raven Press, New York.