sMATTerings
Midwest Association for Toxicology and Therapeutic Drug Monitoring

Volume 10 Issue 2 October 2004

President's Korner

Greetings fellow MATT members!

The annual MATT meeting is quickly approaching on May 19th and 20th. I encourage all of you to come and experience Kansas City. After living here for three years, I can honestly say you won't regret visiting the true Midwest, the geographical center of the USA. The plaza where the meeting will be held boasts world class restaurants, clubs, music, shopping, and of course, the world's finest steaks! A balanced mix of clinical and forensic toxicology awaits you in KC. Please mark your calendar now and plan to enjoy a time of education and social networking.

At this time, I would like to extend a very special "Thank You" to Dr. Adam Negrusz from the entire Executive Board for his hard work and dedication in what was a very successful and impressive meeting in Chicago.

I look forward to seeing all of you in May.

Barbara

In This Issue

We're always prompt … no matter how long it takes! The newsletter is on it's way.

There has been some shuffling around on the Executive Board as well as a new Treasurer so welcome aboard to Karen Leonard.

The Annual Meeting held in conjunction with the Society of Hair Testing was an excellent event and a big THANK YOU to the organizers, Dr. Christine Moore and Dr. Adam Negrusz. A special Thank You to Adam for all of his efforts on behalf of M.A.T.T.

On a completely unrelated note, I came across an article in the October 2004 Issue of R & D Magazine on a new and emerging field called Nanotechnology. It deals, in part, with delivering targeted medical therapies at the molecular level and has some very exciting potential. However, the thing that really caught my attention was the research going on at the University of Calgary in Alberta, Canada. They are working on an Electronic Mosquito(e-Mosquito) which is a semi-invasive, automated microsystem for bloodwork and delivery of medication.

The Canadian researchers expect that this technology will become available within the next five to 10 years. Wow!

Preliminary information on the Spring Meeting in Kansas City is available so we hope to see you there.

"Goin' to Kansas City Kansas City here I come!"

There when it *sMATTers* most!

Fred

MATT is an association focused on advancing the scientific, clinical, professional, and educational aspects of Toxicology and TDM. MATT provides a network for interested individuals in the Midwest.

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sMATTerings Meeting Calendar

American Academy of Forensic Sciences Annual Meeting
February 21-26, 2005
New Orleans, LA

Society of Toxicology's 44th Annual Meeting
New Orleans, Louisiana, is the host-city for the Society of Toxicology's 44th Annual Meeting. Scientific Sessions will be held at the Ernest Morial Convention Center during the week of March 6–10, 2005.
For additional information contact Nichelle Sankey at SOT Headquarters (703) 438-3115 or E-mail:nichelle@toxicology.org

37th Annual Oak Ridge Conference
Pushing the Technology Envelope II: An Exploration of the Future of Clinical Laboratory Testing
April 14-15, 2005
Baltimore, MD

9th International Congress of Therapeutic Drug Monitoring and Clinical Toxicology
April 23-28, 2005
Louisville, KT
For more information:
Tel 613-531-8166, Fax 613-531-0626 or visit the meeting website: **http://www.iatdmct.org/congress**

2005 MATT Annual Meeting
May 19 - 20, 2005
Kansas City, MO

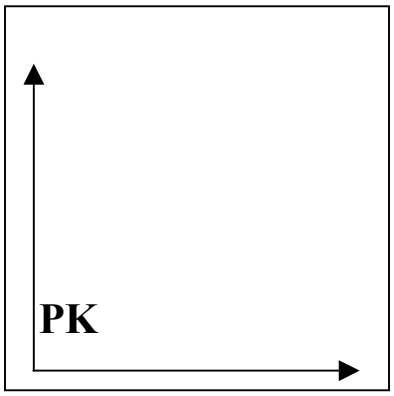
XIX International Congress of Clinical Chemistry and the AACC 2005 Annual Meeting
July 24-28, 2005
Orlando, FL
Email: info@aacc.org

Annual Report of the MATT Treasury for 2004 and Financial Update for 2005

1/01/2004	
Starting Balance:	
Checking Account	$ 15,167.17
Certificate Account	Discontinued in 2002 Rolled into Checking
Total Starting Balance	$ 15,167.17
Expenses:	
Web site:	$ 112.50
SMATTerings	$ 288.35
Annual Meeting	$ 27,916.00
Income:	
Membership Dues	$ 1,240.00
Interest on Checking(3yrs)	$ 139.22
Annual Meeting	$ 30,311.90
Total Income:	$ 31,691.12
Total Starting Balance	$ 15,167.17
Total Expenses	$ 28,316.85
Total Income	$ 31,691.12
Total Ending Balance	$ 18,541.44

This is the last report from my tenure of Treasurer. The balance of checking and certificate monies at the start of my term (8/01/2001) was $12,633.65 and the ending balance is $18,541.44. This represents a 47 % growth in the three years. The state of the treasury could not be possible without restraint from the three presidents and good sound fiscal judgement on their part. The treasury is in good shape for the future and we are all expecting great strides in the years ahead.
Thank you for the opportunity to serve.

Tim Caragher



Pharmacokinetics Korner

By John M. Wilson

PK Primer – Sometimes the muse rests and serendipity provides no relief. For whatever the reason, this issue's PK column has been more difficult to generate than previous. Faced with a receding deadline, rather than look forward, my instinct has been to look back. The last three years have seen an effort toward TDM Renaissance with three Baltimore symposia sponsored by the AACC TOX/TDM Division and MATT. These presentations attempted to focus our attention on the future of TDM, on topics like Pharmacogenomics, Antiretroviral therapy, Immunosuppression, FDA Practices and Policies, and a variety of newly approved medications for which monitoring makes excellent sense. Certainly the challenge has been established. But do we have the tools to meet this challenge? Are the practices of the past sufficient to meet the needs of the future? I suspect some review is in order, at least an inventory of our assets, so that the next steps can be measured and successful.

Essential TDM means analytical measurement and interpretation. Once a target drug is identified analysis is an art form. We must study the project, invest, conduct careful experiments, assess the results, modify and correct, finalize and then support the new approach. We must spread the word, accept criticism, expect new directions, and reevaluate our efforts. Many of the technologies of the past, GC, LC, and GC/MS, will serve us well for many of the new pharmaceuticals in the initial stages when the number of test requests is small. For other assays we may need to upgrade to LC/MS. For those successful strategies the market will grow and new test requests will be spawned. Industry will notice and contribute, but not for every drug. We can expect some market driven selectivity.

When assays are in place we must be prepared to interpret, that is, to understand the meaning of the data. We will need basic information about each drug and to place this in the context of a basic understanding of pharmacokinetics, biologic variability, pharmacology and toxicology. How well we can predict from our analytical data will be the test of utility for TDM. The pharmaceutical industry must provide pharmacokinetic and toxicological data under regulatory requirement about each drug. What is not provided will come out of subsequent studies in the field. Will we be ready to understand, to provide context and mature direction? To assure that we are let's review some of the basic tenets. I promised myself I would write this piece without resorting to equations. This restriction will compel us to understand relationships between variables and assist us in making predictive interpretations in even the most frantic situation.

Steady-state – Steady-state is achieved when the rate at which drug enters the body is equal to the rate at which it leaves. Metabolism represents a form of leaving the body in that the drug is transformed into another entity. Most of our predictive assumptions work best if we can assume steady-state conditions. When a drug is given intravenously at a constant rate the amount and concentration of drug in the body will come to a stable value and remain the same as long as we continue to give the drug at the same rate. Most of the time drug is given by mouth at regular intervals, and, over a dosing interval, concentrations will increase, reach a peak, and then decline. In this context steady-state means the concentration at equivalent times after each dose will be the same. Each concentration is repeatable. This stability is desirable in that it protects the patient from concentrations that are ineffective or that produce toxicity. Knowing the time required to achieve steady state can be important. We can avoid unnecessary drug concentration measurements and dosage changes. Time-to-steady-state is dependent on the various rate processes a drug will experience, such as, absorption, distribution and elimination. The slowest process will define the time to steady-state. This is generally elimination. Drug elimination half-life has come to be a useful indicator of time to steady-state and 4-5 half-lives is a reasonable predictor. More about half-life later, but if a drug has a 24 hour half-life then it will take regular drug administration over 4 to 5 days to achieve repeating body concentrations.

Volume of Distribution – The volume of distribution,Vd, of a drug is the ratio of the amount of drug in the body and the concentration of drug that we can measure. What the actual value is will depend on what we measure (blood, serum, plasma, red blood cells) and when we measure it. Vd is predominantly a binding phenomena. It is binding that controls the extent of final distribution. It is the affinity for tissues that affects the magnitude of the volume term. When a drug is very lipophilic it will have a tendency to leave the blood and reside in tissue space. When a drug is polar it will find a better home in the plasma or interstitial fluid. The presence of binding proteins can sequester the drug in the plasma/serum fraction and binding proteins in tissue space will increase the residence in those tissues. Former drugs will have a small Vd and drugs of the latter type can have very large Vds. Even though Vd has units of L or L/kg, it can be misleading to try to identify the location of drug by the magnitude of the measured Vd. Very lipophilic drugs can have volumes of distribution that greatly exceed physiological volumes. Digoxin has a volume of distribution of 500 liters in many patients, while the total body water for the average male human is around 42 L. When we measure drug is important because distribution is a kinetic process. It begins when the drug is administered and proceeds according to biological rates controlled by the lipophilicity of the drug and binding affinities in both the blood and tissues. A drug given intravenously will initially reside only in the vasculature and will also require time to distribute to the tissues. A lipophilic drug may ultimately reside mostly in the tissues. A drug given orally will reside in absorption sites and require time to enter the body and be subject to distribution forces. A drug given i.v. will have high initial blood concentrations which decline rapidly with distribution. Eventually an equilibrium between the tissues and the vasculature will be established. A drug given orally will have a low initial concentration, increase to a peak concentration and then decline. Because drug elimination begins immediately upon entering the body, we generally only know how much drug is present immediately after we give it, unless we can keep track of drug elimination. A drug concentration drawn prior to distribution will reflect more the volume of the vasculature. Following distribution drug is said to be at equilibrium and the volume of distribution will be different than during distribution.

Now that we've established that the Vd that we measure is dependent on a variety of factors, it is apparent that there are different volumes of distribution and you might encounter references to the volume of the central compartment, V_{area}, or V_{beta} depending on the form of drug administration and conditions at the time of blood draw(s) as well as how the result is calculated. Which is the preferred reference value? In general, it is the Volume of distribution at steady-state, Vd_{ss}, the ratio of the amount of drug in the body to the concentration in serum or blood at equilibrium and steady-state.

Clearance – Of the commonly referenced pharmacokinetic parameters, the one that is least understood is clearance. It is reasonable to think of clearance as an elimination term in contrast to Vd, which is a residence term. Clearance describes a change in location of drug to out of the body, such as removal from the vasculature into the bladder, or a change in the form of the drug, as exemplified by metabolism. Units of clearance are units of flow, ml/min or L/hr. The strict definition is the volume of blood completely cleared of drug per unit of time. You will see references in the literature to blood clearance curves which in reality reflect both distribution and elimination. While Vd appears to change according to when or how a drug is measured, Clearance is thought to be a constant. There are caveats to this because we know that clearance can be concentration dependent, but this requires an extreme condition as when a drug is present in very large amounts and saturates the ability of the body to metabolize it. We also know that clearance is age-related. You don't expect renal elimination to be the same for an 80 year old as for a 20 year old. These are important exceptions, but, for most drugs, in most situations, we can view clearance as an old reliable, unchanging in the face of time and amount. It may help to think of clearance as a relationship similar to the way we think of Vd. **We can think of clearance as the ratio of elimination rate and drug concentration**. If clearance is a constant it would appear that at high concentration the elimination rate must be higher than at low concentrations.

Clearance is useful in the sense that it only describes elimination. If steady-state is that condition where the rate of drug administered is equal to the elimination rate then we can describe the concentration at steady state as the ratio of the rate of administration and clearance. Thus if we know the clearance it is easy to calculate the amount of drug to give to achieve a given serum concentration. Just as Vd is dependent on binding, so is clearance. Drug that is protein bound in the blood is not readily metabolized. The binding protein restricts the drug from the active site of the metabolizing enzyme. For renal elimination the protein that binds drug will restrict the filtration of the bound portion. Therefore drugs that are highly protein bound will be cleared more slowly than drugs that are essentially unbound. The other physical characteristics that influence clearance are the flow rate of blood to clearing organs and the concentration or activity of metabolizing enzymes.

Half-life – You may be wondering why I have saved the discussion of drug half-life until the very end. The reason is that to understand half-life we must have a firm grasp of the relationships that define volume of distribution and clearance. The common definition of half-life is the time required for drug to decrease by half of its concentration. Once again, time has something to do with the interpretation of half-life. We know that a drug declines in concentration for two reasons, it is being distributed away from the measuring volume or it is being eliminated. In the earliest part of drug decline both distribution and elimination contribute. At a later part, after equilibrium with the tissues has been established, drug decline describes only elimination. A measured half-life can depend on the time of the measurement. Distribution

half-lives tend to be shorter than elimination half-lives so the time to equilibrium can be approximated by 4-5 distribution half-lives.

For our purpose it is best to regard half-life as a composite term, one that is affected by both Vd and clearance. Because it combines both processes, half-life is useful for estimating the time frame in which the processes occur. We know that it requires four to five half-lives to achieve steady-state conditions. Changes in dose will seek reproducibility according to the magnitude of the half-life.

By now you should be asking, but what is the relationship between the three terms? You can think of half-life as obtained by multiplying the term 0.693 by the ratio of Vd and clearance. This relationship states that lipophilic drugs will have large volumes of distribution and long half-lives. Drugs that are rapidly eliminated, that have high clearances, will have short half-lives. A low clearance for a lipophilic drug will only increase its half-life more.

And where did 0.693 come from? 0.693 is derived from the natural log of two, the ratio of drug concentrations that produce the time of the half-life.

Protein Binding – Finally, it is worthwhile to talk a bit about phenomena that will have effects on the parameters that we have discussed. Volume of distribution is affected by binding in both tissues and in the blood and by weight or size. The first factor is more important in that there is more variability from drug to drug. Size is important because the tissues exist in an environment saturated with water. The amount of water can effectively dilute or concentrate drug levels. The greatest differences come with aging, but there can also be gender differences.

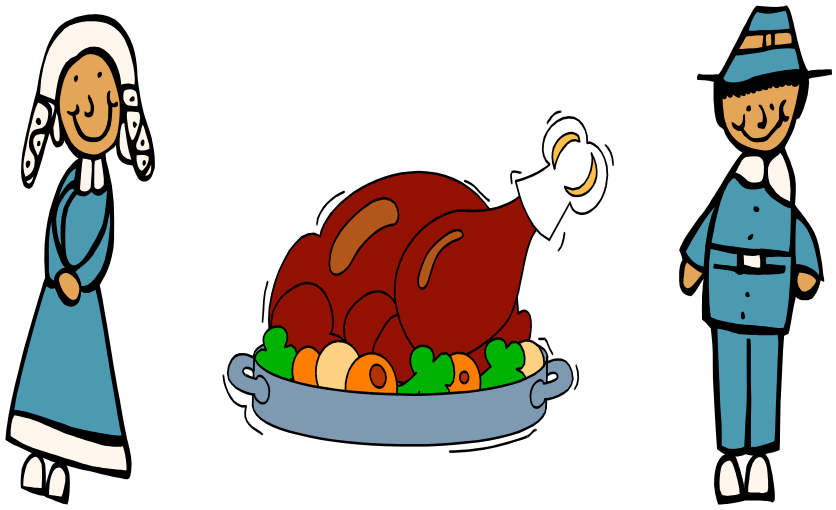
Changes in the quantity of blood flow will affect clearance. This can happen in disease, by the action of drugs or in stressful situations. Sometimes the change in blood flow is just temporary, as in a diversion of blood in stress, and it is soon restored. Transient changes like this don't have great importance for dosage prediction. Changes in binding directly affects clearance for drugs that are slowly metabolized and enzyme concentrations are controlled by genetic and environmental factors. The chemical structure of the drug provides the opportunity for metabolism by enzymes with different capabilities determined by genetic differences. Characterization of a genetic polymorphism can help to reduce the imprecision of predictions but disease and the effect of drugs can confound even the most rigorously characterized genotype. Hepatic and renal injury will decrease clearance. Some drugs can inhibit metabolism of other drugs. Other drugs can increase the metabolism of co-administered drugs.

Drugs and disease can also influence protein binding. The extent to which a drug is bound to serum proteins is important because of its effect on clearance and volume of distribution. Protein binding is affected by the amount of binding protein, the number of binding sites on the protein and the affinity for those sites. Just as sequestering the drug to protein containing fluids will affect volume of distribution, binding will restrict access of the drug to the pharmacological site of action. The size of the binding protein will not allow the attached drug to interact at the receptor site. This hypothesis is the basis for the assumption that only unbound drug is active drug.

Does that mean it is more important to measure unbound drug concentrations than total drug concentrations? Yes. But, we live in a practical world, and it is not as easy to measure unbound drug. First, unbound drug concentrations are lower; separation of bound and unbound

involves an additional methodological step so measurements tend to be less accurate, less precise, more costly, and more time consuming. It is pretty well established that measuring unbound drug concentrations offers advantages for drugs that are highly protein bound (> 80 %). Here a small change in the percent bound can cause a reciprocal increase in unbound concentration. Some have advocated only measuring unbound drug where it is appropriate. The unbound concentration can be related to a therapeutic window for unbound drug and the dose adjusted accordingly. I think it is important to report both total and unbound drug. It is the ratio of unbound to total that produces the percentage unbound drug. It is this percentage that will directly affect clearance and volume of distribution in many instances. If it is known that the percentage of unbound drug has changed from 10 to 15 % for an individual, then one can estimate the effect on clearance to be an increase of 50 % and, in some instances the effect on volume of distribution will be an increase of 50 %. In this example one would expect no change in the elimination half-life and no change in the time to steady-state. There are a number of conditions that must exist for this to be true in fact, but the health care provider, armed with these relationships can recognize their applicability and use simple mathematics to make rapid assessments.

It is axiomatic that pharmacokinetics is complex and difficult to employ in clinical settings. But if complexities can be reduced to simple relationships and if these relationships can be broadly applied, then pharmacokinetic data can be employed to solve problems in the real world and avoid costly errors. I hope that the foregoing simplifications will aid you in understanding and communicating the value of pharmacokinetics for the next generation of pharmaceuticals.



2005 ANNUAL MEETING

MARRIOTT KANSAS CITY COUNTRY CLUB PLAZA
KANSAS CITY, MISSOURI, USA

MAY 19 - 20, 2005

Registration Information

The 2005 MATT meeting will be held at the Marriott Kansas City Country Club Plaza at 4445 Main Street, Kansas City, Missouri.

The basic meeting registration includes scientific sessions, continental breakfast and luncheon on Thursday and Friday, all coffee breaks and a wine and cheese party on Thursday night. Individual day registration is available. Accompanying persons may purchase tickets for breaks and meals.

Prices are noted on the registration form. On-site registration will require a late fee.

Reservations by attendees must be received on or before Wednesday, April 27, 2005.

Hotel Registration and Transportation

Registration for the rooms should be made directly with the hotel on or before April 27, 2005. Room prices are $109 for single and $109 double. The hotel overlooks the Country Club Plaza, Kansas City's premiere shopping, dining and entertainment district. Parking options are available at the hotel for $7.00 / day. Hotel guests will have the parking added to their bill and individuals not utilizing a the hotel are charged by the parking garage attendant.

The hotel has a fully equipped health club with treadmills, stair steppers, stationary bikes and Nautilus weight stations. All rooms include coffee makers, hairdryers, irons, voice mail and video check-out.

The number to call for room reservations is 800-810-3708 or 816-531-3000. Be sure and let them know you are with MATT to receive the $109 room rate.

Rental Cars are available at the airport or the KCI shuttle can be used for transportation from the airport to the Marriott. The cost of the shuttle is $25 round trip or $15 one way. The shuttles run every 30 minutes and tickets can be purchased at baggage claim. The number for KCI shuttle is 816-243-5000.

Preliminary Program

The scientific sessions will include two days with one day for clinical toxicology and one day for forensic toxicology. Many speakers and vendors have already agreed to participate in MATT 2005. The complete list of speakers and scientific sessions will be published in the Spring 2005 issue of sMatterings. The meeting will go from 8:30 a.m. to 5:00 p.m. each day.

Entertainment on the Plaza

Over 120 stores fill the architecturally classic fourteen-block district and create the experience that makes "The Plaza" one of the Midwest's premiere destinations. There are approximately 30 distinctive restaurants and outdoor cafes that offer an extraordinary range in dinning option from elegant to casual including scones to scallops and KC barbecue to world famous steaks.

For more information please contact:

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2005 MATT Annual Meeting

MARRIOTT KANSAS CITY COUNTRY CLUB PLAZA
KANSAS CITY, MISSOURI, USA

MAY 19 - 20, 2005

Registration Form: The deadline for registration is April 27th 2005

Name:_____
Last First

Title:_____Agency:_____

Name to Appear on Badge _____

Address:_____

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	MATT MEMBER	Non-MEMBER	TOTAL ENCLOSED
Basic Meeting Registration: Includes scientific sessions, continental breakfast, breaks, and lunch Thursday and Friday	$ 120	$ 145	$_____
Daily Registration: ***Please circle day Thursday Friday***	*$ 65*	*$ 85*	$_____
Additional Meal Tickets: : Includes continental breakfast, lunch, and breaks	$ 40	# of tickets ____	$_____
Late Fee:	$ 20		$_____
Membership Renewal for 2005:	$ 25		$_____

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MATT Members:

Check made payable to **MATT**
Drawn on USA bank or Money Order. Must be paid in US dollars

MATT Tax ID# 31-1454533 **Total Amount: $ _____**

MAIL: Barbara Rowland
LabOne – Toxicology
10101 Renner Blvd.
Lenexa, KS 66219

Membership Application/Renewal Form

Full member renewal = $25
Lifetime Member = $250

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Professional interests, comments, or suggestions _____

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