

*Chicago ... Chicago ... ya tada da da, da da da da*



I'm just getting in the mood for the upcoming meeting, and I'm excited about the prospect of a joint meeting. Hope you are too!

In this issue we have a fundamental look at alternative testing in saliva by Christine Moore and an in-depth look at a single drug, gabapentin, by John Wilson.

Just a little reminder – **Registration deadline for the Meeting is April 15<sup>th</sup>, 2004!** Hope you all can make it to the meeting.

*Chicago ... Chicago ....* 

There when it *sMATTERs* most!

Fred

## President's Korner

Greetings, I hope all of you had a good holiday season and are ready for spring – I know I am!! Speaking of spring, the 2004 annual MATT meeting is right around the corner – May 23-25 - at the Sheraton Chicago Northwest Hotel in Arlington Heights, IL. Details and meeting registration forms are available on the MATT website, [www.midwesttox.org](http://www.midwesttox.org). I just spoke with the meeting hosts, Christine Moore and Adam Negrusz, at the American Academy Meeting last week in Dallas, and they both assured me that the meeting docket is full. We are having entertainment at the reception [no, it's not Adam doing a stand-up comedy or dance routine – darn.], and we have ample vendor sponsorship this year. Don't forget that this is a joint meeting with the Society of Hair Testing, which provides an excellent opportunity for those of us that are uninformed to learn more about this type of analytical testing.

According to Chris Goodall membership renewals are slowly coming in, however, MATT's biggest weakness is still loss of members. Please encourage your colleagues to join and emphasize the importance of the interaction between clinical and forensic toxicology. Drugs that are commonly encountered in a clinical lab are becoming more and more prevalent in the forensic lab – such as many of the old and new anti-epileptics. I, for one, have utilized my clinical toxicology colleagues (John Wilson for one) to help me interpret concentrations in this class of drugs in my forensic cases. The point being that I met ALL of my "clinical toxicology" colleagues through MATT. The clinical toxicologists usually do not attend SOFT or AAFS - they usually attend AACC, and the forensic toxicologists usually do not attend AACC – so...MATT is the place that brings us all together.

Even though the membership fee has been increased to \$25.00 per year – this is still very inexpensive compared to AAFS (\$145.00) and SOFT (\$50.00). MATT also offers meetings that are short and within driving distance to most of the states in the MATT

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*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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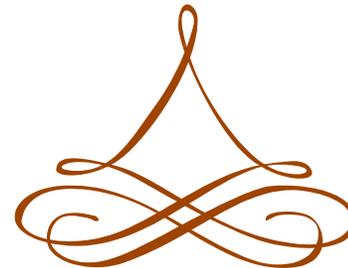
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region. If you have any suggestions about how to enlist new members to MATT or convince old members to re-join, please do not hesitate to contact myself or any of the MATT officers, and again, please encourage your colleagues to join. Kansas is the site for the 2005 MATT meeting, and I have asked SAT if they would consider a joint meeting with us in Kansas. We have no meeting sites beyond 2005 so think about hosting a meeting in your midwest town and bring your proposal to this year's meeting or submit it to one of the MATT officers.

Have a wonderful spring and don't forget you should have renewed your MATT membership by now. In the mean time, please promote MATT as much as you can. The success of this organization depends upon the members, every one of us. See you in May!

Submitted by: *Laureen J. Marinetti, M.S., Ph.D.,*  
 MATT President 2003/2004



## MATT Membership Meeting Minutes 2003    May 9, 2003 1:00 pm

Chris Goodall opened the meeting which started with a review of the 2002 meeting minutes. The minutes were reviewed and accepted with no comments from any MATT members present. The current meeting is progressing smoothly and financially, it is expected to break even. Watch for the updated MATT budget in an upcoming newsletter. The balance as of 5/5/03 is \$14,366.00. The fall 2002 newsletter was distributed to 110 members with no returns at a total cost of \$92.40. The possibility was discussed about MATT offering the newsletter via e-mail at last year's meeting. This option needs further exploration and will be revisited at a later time. Also, as proposed at last year's meeting, corporate sponsorship will be a future membership option for sponsors. Christine Moore will draft the guidelines to present to the Executive Board. The guidelines will outline the benefits and obligations of the corporate sponsorship. An ad hoc committee consisting of Adam Negrucz, Barbara Rowland, and Christine Moore was created called the Charter Award Committee. This committee will draft guidelines for this award which is designed to encourage student participation in the meeting such as best poster or platform presentation. Meeting guidelines will reflect that an honorarium of no more than \$ 500.00 dollars will be offered to guest presenters at future MATT meetings. Additional monies would have to be approved by the board. This would be in place of reimbursed expenses. The current MATT membership is down to approximately 60 members from 88. The membership chair will coordinate a membership drive and also update

the membership list and possibly put the list on the MATT website if it can be password protected and it is not cost prohibitive. Please tell all of your colleagues who are not yet members of MATT that they should join. For the 2004 membership it was approved by the membership to raise the membership dues to \$25.00. The membership also approved the new bylaws as written with no suggestions for changes.

The new slate of officers were presented by the nominating committee and approved. They are: President – Laureen Marinetti, Vice President – Barbara Rowland, Secretary – Don Frederick, and Treasurer – Tim Caragher.

MATT is currently accepting proposals for 2006 and beyond for future meeting sites. The 2004 meeting will be in Arlington Heights, IL, and hosted by Christine Moore and Adam Negrucz. This will be a joint meeting with the Society of Hair Testing. Barbara Rowland has offered to host a MATT meeting in Kansas City for 2006. Visit the MATT website for current meeting information [www.midwesttox.org](http://www.midwesttox.org) and let one of the MATT officers know if you have ideas or suggestions. Chris Goodall was presented with a token of appreciation for all her hard work as MATT president. The 2003 annual MATT general membership meeting concluded at 1:20 pm. See you in Arlington Heights in 2004 where we can all learn more about the wonderful world of hair testing in addition to all the excellent clinical and forensic toxicology information.

Submitted by Laureen Marinetti

# Drug Analysis using Laboratory Based Oral Fluid Testing

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## ***Introduction***

Within the drug testing system, urine has traditionally been used as the biological specimen for analysis. However, there are numerous products available which are designed to render a urine drug test inaccurate (gluteraldehyde, oxidants, nitrites etc.), as well as simple dilution of the specimen by the donor with tap or toilet water. Unless a collection is observed, the possibility of a diluted, adulterated, or substituted urine specimen is increased. While laboratories are able to test for some of these adulterants, obviously further testing increases overall costs.

As a result, interest in an alternative specimen for testing has increased. Advancing technology has allowed laboratories to measure lower amounts of drugs in biological specimens, allowing drug testing programs to incorporate the unique benefits offered by alternative biological fluids at a comparable cost.

When drugs are ingested, smoked, or injected, they travel through the body and, over time, convert into drug metabolites which are subsequently excreted from the body. The highest concentrations of these drugs and metabolites is in the urine, but they are also present in measurable quantities in blood, saliva, sweat, tears, hair, and even finger and toenails. Improved instrumentation has allowed laboratories to measure drugs in these “alternative” matrices.

***Due to its ease of collection, oral fluid has emerged as the specimen of choice to replace urine in many applications of testing for drugs of abuse.***

## ***Advantages of Oral Fluid Testing***

### **1. Collection**

Saliva is easy to collect, handle, transport, and store. Since the collection is observed, the chance of adulteration or substitution of the sample is minimized. The entire collection process is rapid, taking perhaps 2-3 minutes.

Applications specifically based on ease of collection include:

- a) Criminal justice, parole, and probation testing where often observed urine collection is required. There is no same sex observation requirement using saliva, and the dignity of the donor is preserved.
- b) Drug court where a high number of specimens are often required to be collected, handled, and shipped in a short space of time.
- c) Staffing agencies requiring a rapid specimen collection for pre-employment purposes.

### **2. Adulteration**

Since collection is observed, there is a limited opportunity for the donor to adulterate or substitute the sample. It is difficult to hold in the mouth anything which may affect the test for any length of time, particularly if engaged in conversation when filling out drug testing forms, providing personal information, and interacting with the collector.

In contrast to urine, the drug concentration in saliva is unaffected by liquid intake.

### 3. Window of detection

For most drugs, the detection time after use, using urine as the specimen, is approximately 2-4 days. (*Note: An exception is marijuana where in some cases chronic marijuana smokers can be detected up to 2-3 weeks after last use.*)

For oral fluid, the detection window is generally shorter, although for some drugs it can approach 2 days, overlapping the urine window. The advantage of this is that very recent drug use can be detected by employing saliva as the test specimen. Since saliva is thought to reflect blood levels at a given time point, the presence of a parent drug (for example cocaine) can be interpreted as an indication of being “under the influence” of cocaine at that specific time. It is generally not possible to interpret a urine test result as being “under the influence” of a drug, and this critical information would be lost using urine as the test specimen.

Applications specifically based on the ability of saliva to show a person to be “under the influence” of a drug include:

- a) Probation and parole settings where using illegal drugs is a violation of parole.
- b) “Reasonable suspicion”, “For cause”, or “Post accident” testing when there is an incident or a suspicious activity in the workplace which may be due to drug use.
- c) Methadone maintenance and pain management centers requiring a rapid answer as to whether the individual recently ingested the prescription drug.

### 4. Profile of drugs

The profile of drugs analyzed using saliva is somewhat wider and considerably more useful than those in the standard urine panel.

- *Opiates*: Recent data has shown a very high prevalence of 6-acetylmorphine (a metabolite of heroin) in saliva specimens testing positively for morphine. The selection of oral fluid as the test specimen increases the opportunity of identifying heroin users. Under the urine program, 6-AM is not even tested for unless over 2000 ng/ml of morphine are present, severely reducing the number of heroin users identified by urinalysis.
- *Marijuana*: Marijuana metabolites take 3-6 hours after smoking to be detectable in urine. However, the active compound, tetrahydrocannabinol (THC), will be present almost immediately in saliva, likely due to its presence in the mouth following marijuana smoking, therefore, very recent use can be identified.
- *Cocaine*: In urine testing only a metabolite, benzoylecgonine, is detectable using the SAMHSA guidelines. A positive urine finding gives no information on the state of the individual donor. In contrast, for oral fluid analysis, both parent cocaine and benzoylecgonine are identified. The presence of cocaine in the sample can be interpreted as very recent use of cocaine and possibly “under the influence” of the drug. The detection of benzoylecgonine lengthens the window of detection for cocaine use in saliva.
- *Amphetamines*: Under proposed guidelines for both urine and oral fluid, the inclusion of Ecstasy and its metabolite will be allowed in the amphetamine panel.

### 5. Cost savings:

The major cost saving in converting from urinalysis to oral fluid testing is in the collection:

- No special facilities or conditions are needed (for example “blueing” agent in toilet water).
- The cost of specimen transport and storage is significantly reduced.
- There are no added costs to determine “adulteration” of the specimen.

- In workplace settings there is a significant reduction in time wasted traveling to and from the collection site since collections can be performed anywhere.

### *Disadvantages of Oral Fluid Testing*

Of course nothing is perfect and there are disadvantages to using oral fluid as a test specimen.

#### **a) Collection Devices:**

There are several variations in collection devices, and it has been reported that the method of collection influences the test result. Some devices consist of a pad attached to a stick (like a popsicle) which is placed into the mouth for a given time (e.g. Intercept™). The saliva absorbs onto the pad and is then placed into a buffer for transport to the laboratory. The problem with this is that it is not known exactly how much oral fluid was actually collected so there is a potential for erroneous results, most likely false negatives based on insufficient sample volume. Cut-off concentrations based on such a device are not relevant or applicable to other types of collectors.

Other devices (e.g. Quantisal™) have a blue volume indicator on the collector showing when 1 mL has been collected. This is an improvement over the Intercept™ collection system, however, both of these devices are then placed into a buffer for transportation, and it is difficult to determine precisely how much drug is eluted from the pad into the buffer.

Some manufacturers are now requiring donors to “spit in a cup” which is often not too pretty to observe...

#### **b) Specimen Volume**

A problem related to the type of device is the collection of adequate volume for screening and confirmation, particularly if more than one drug confirmation is required. Generally, a much lower volume of saliva than urine is provided by a donor. This brings up the issues of re-testing of the specimen (in the event of a batch failure) and “split-sample” testing (when another laboratory is required to confirm the first result). An adequate volume of specimen is critical for a valid test. In some collection devices, drugs may absorb onto the collection pad and it is not clear how much drug is removed from the pad by the buffer.

Some “on-site” screening tests require the collection of an additional specimen to be sent to the laboratory for confirmation, but the same issues regarding collection devices are valid.

#### **c) Federal Workplace Testing**

The Division of Workplace Programs within the Substance Abuse and Mental Health Service Administration (SAMHSA) has yet to approve any alternative specimens for federal workplace testing, but saliva, hair and sweat are currently under consideration for approval in workplace programs. Guidelines have been drafted and are in the process of implementation. However, certified laboratories are currently offering oral fluid testing and carrying out its analysis under good laboratory practice conditions, including chain-of-custody, quality control, batch review, and formal reporting requirements. There are accrediting agencies specifically inspecting oral fluid procedures so that the quality of the result is ensured.

## **Summary**

*Oral fluid* offers a simple, dignified, observed collection. It provides a relatively short history of drug use, therefore, is an excellent specimen choice for “**reasonable suspicion**”, “**post-accident**”, or “**for cause**” testing where identification of the parent drug shows that the donor was “under the influence” of

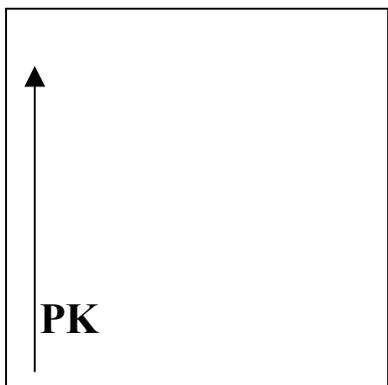
the drug at the time the sample was taken. It is particularly useful for the identification of heroin users and those under the influence of marijuana.

As oral fluid testing becomes more popular, the costs associated with its analysis are approaching those of urine, providing an excellent opportunity for drug testing programs to benefit from the analysis of alternate specimens.

Matrix	Advantages	Disadvantages
<b>URINE</b>	<ol style="list-style-type: none"> <li>1) Most widely tested specimen</li> <li>2) Drugs are generally in high concentration</li> <li>3) Adequate volume for testing and re-testing by a second laboratory</li> <li>4) Federal standard cut-offs, testing protocols and laboratory procedures exist</li> </ol>	<ol style="list-style-type: none"> <li>1) Easy to adulterate</li> <li>2) Collection not observed</li> <li>3) More costly for shipping and storage</li> <li>4) No relationship between drug concentration and impairment</li> </ol>
<b>SALIVA</b>	<ol style="list-style-type: none"> <li>1) Easy to collect</li> <li>2) Difficult to adulterate since collection is observed</li> <li>3) Presence of parent drug shows "under the influence"</li> <li>4) Useful for the detection of recent drug use</li> <li>5) Useful for the identification of heroin users</li> </ol>	<ol style="list-style-type: none"> <li>1) Short drug history</li> <li>2) Marijuana levels are low, and likely due to THC in the mouth following smoking</li> <li>3) Specimen volume may be device dependent and is generally low</li> <li>4) No standard cut-offs, testing or collection protocols, or laboratory procedures (yet !)</li> </ol>

#### Standard Drug Confirmation Panel

Urine Profile	Oral Fluid Profile
<b>Cocaine:</b> Benzoyllecgonine	<b>Cocaine:</b> Cocaine <b>and</b> benzoyllecgonine
<b>Opiates:</b> <ul style="list-style-type: none"> <li>• Codeine</li> <li>• Morphine</li> </ul> (Note: Over 2000 ng/ml morphine then requires further testing for 6-acetylmorphine)	<b>Opiates:</b> <ul style="list-style-type: none"> <li>• codeine</li> <li>• morphine</li> <li>• 6-acetylmorphine (heroin metabolite)</li> <li>• hydrocodone</li> <li>• hydromorphone</li> <li>• oxycodone</li> </ul>
<b>Amphetamines:</b> <ul style="list-style-type: none"> <li>• methamphetamine</li> <li>• amphetamine</li> </ul>	<b>Amphetamines:</b> <ul style="list-style-type: none"> <li>• methamphetamine</li> <li>• amphetamine</li> <li>• MDMA (Ecstasy)</li> <li>• MDA</li> </ul>
<b>Marijuana:</b> Carboxy-THC	<b>Marijuana:</b> THC
<b>Phencyclidine</b>	<b><i>Phencyclidine</i></b>



# Pharmacokinetics Korner

By John M. Wilson

## Monitor Gabapentin?

This is a piece I have intended to do for some time but never put pen to paper (or fingers to keyboard to be more precise), but now I am resolved. The thought originates from a challenge from Dr. Stefan Schwabe from the Robert Wood Johnson Pharmaceutical Research Group and a speaker at the 2002 AACC TDM Renaissance Forum in Baltimore. The discussion touched on the failure of the *in vitro* diagnostics industry to introduce products that permit monitoring of drugs that have been introduced in the last ten years and focused on those drugs for which new methods were appropriate. Gabapentin was on the list and Dr. Schwabe's question was to the effect, "Can anyone here tell me why its valuable to monitor Gabapentin?" As might be expected in such a setting there was no reply. On the following day I made an initial and meager attempt to provide a response, and now, more than a year later, I would like to elaborate on that attempt.

Gabapentin (Neurontin® Parke-Davis, a Pfizer company) is a drug that has been approved by the FDA since 1993 for the adjunctive treatment of epilepsy, specifically partial seizures in adult and pediatric patients (age 3-12). While its approval for epilepsy indicates it should be used in addition to other anti-epileptic agents, it is also approved as a stand-alone medication for the management of post-herpetic pain.<sup>1</sup> In fact, Gabapentin is used for many manifestations of pain and in psychiatry, in addition to antidepressants and antipsychotics, as a mood modifier. Off-label use of Gabapentin may well exceed approved usage.<sup>2</sup>

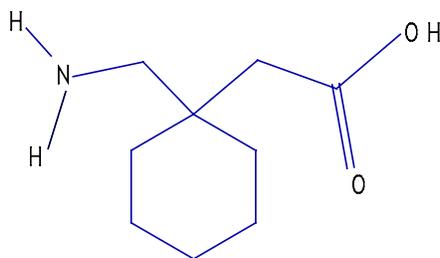


Fig. 1 Chemical Structure of Gabapentin

When you consider reasons for monitoring a drug, several criteria come to mind, one being that the drug is commonly used for conditions that are severe. No one would argue that epilepsy is not a severe illness requiring careful therapeutic decisions. Proper choice of drug, or drugs, reasoned development of drug regimens, and disciplined compliance are essential aspects of seizure prevention. The practice of monitoring reinforces these issues. When multiple drugs are administered, monitoring assists in interpreting drug-drug interactions. Knowledge of serum concentrations and pharmacokinetic insight aid in the generation of optimal dosing strategies and permit the individualization of therapy. Just the act and routine of monitoring communicates to the patient that regular and

consistent dosage compliance is important to their therapy. There also is little doubt that Gabapentin is widely used with sales of 1.2 billion dollars in 2000. The issue becomes ‘Can we use it better?’

Some drugs are monitored to avoid toxicity and adverse events. There are many considerations that suggest that Gabapentin may not warrant the same degree of concern that we exhibit toward a drug like Digoxin or Theophylline. The lethal dose of Gabapentin is very high. Parke-Davis reports that they weren’t able to achieve lethal concentrations in animal models and they gave oral doses up to 8000 mg/kg. Human overdoses have been as high as 49 grams with recovery.<sup>1</sup> The threshold for efficacy may be relatively low. Authors report that serum concentrations above 2 mcg/mL can produce therapeutic benefit.<sup>3</sup> Increasing the dose beyond that may have limited advantage. The PDR reports no difference in relief of post herpetic pain when dose is increased from 1800 mg/day to 2400 mg/day. Addition of Gabapentin to the regimen of refractory epileptic patients taking multiple antiepileptic medications showed some improvement in controlling seizure frequency varying from about 8 to 17 %. Again, it appears that the value of increasing the dose to achieve an enhanced affect may be limited, though when a limited number of studies were evaluated together it does appear that an improvement can be seen.

Gabapentin is an amino acid and thus its biochemistry resembles normal constituents of the body. It is rapidly absorbed and is not metabolized or extensively bound to proteins. Elimination is entirely by renal means. It, therefore, is not affected by diseases of the liver, genetic polymorphisms or by drugs that can influence drug metabolism. Every indication is that the therapeutic range is broad, and the product information indicates specifically that, “It is not necessary to monitor gabapentin plasma concentrations to optimize Neurontin® therapy.”

But consider the following: increasing the dose does demonstrate an increase in adverse affects, and it should be no surprise that the adverse affects were CNS and gastrointestinal, namely somnolence, dizziness, ataxia, fatigue, confusion, and nausea. Granted, these are conditions in which one is uncomfortable but generally not threatened. For other anti-epileptic medications, general deficits in fine motor skills, cognition, restrictions on driving autos, and concerns about school performance have been expressed. The concern should be no less when Gabapentin is taken for pain relief or depression. Clearly it would seem that taking the minimal dose would be advantageous from an efficacy, safety, and an economic point of view. Having a therapeutic target that would define an adequate trial and avoid breakthrough seizures would seem desirable.

Another prominent reason for monitoring anti-epileptic drugs is that they tend to interact with one another when combined. Phenytoin, Phenobarbital, and Carbamazepine can induce hepatic metabolism and Valproic Acid can inhibit drug metabolism. Gabapentin does not appear to influence the metabolism of any other drugs, and since it is not metabolized, there are few drugs likely to influence Gabapentin concentrations. To influence Gabapentin levels it is necessary to influence either the rate or extent of absorption or the rate of elimination. I think the case for monitoring Gabapentin best rests with this consideration. If we grant that it is inadvisable to allow Gabapentin concentrations to become so high as to produce sleep or reduce cognitive function or uneconomic to take more drug than is necessary, then we should be concerned that Gabapentin bioavailability is poor and that it has demonstrated saturable absorption. At low doses (< 900 mg/day) the fraction of the dose that is absorbed is 0.6, that is, 40% of what we administer is not absorbed at all. For 1200 mg/day, bioavailability falls below 50%. Doubling the dose to 2400 mg/day further reduces bioavailability to about a third. When we calculate the actual amount of drug absorbed with each dose (see Table 1.), we see that when we quadruple the dose from 1200 to 4800 mg we should see only an increase in serum concentration of 2.3.

Table 1.

Dose(mg/d)	F	Amt. Abs.(mg/d)
900	0.60	540
1200	0.47	564
2400	0.34	816
3600	0.33	1188
4800	0.27	1296

In addition a number of drugs appear to influence absorption. Naproxen appears to increase absorption as much as 15% when given in low doses. Morphine appears to increase Gabapentin absorption by 44% and Hydrocodone has demonstrated a 14% increase.<sup>1</sup> Co-ingested antacids decreased Gabapentin bioavailability by 20%. I would suggest that this could be the tip of the iceberg and that a very significant mechanism is at play. More research would be helpful, but it will involve measuring concentrations.

The problem becomes even more significant when elimination is considered. Though changes in hepatic function do not affect serum concentrations of Gabapentin, changes in renal function will. Blum et al.<sup>4</sup> studied the effect of impaired renal function on Gabapentin renal clearance. In a single 400 mg dose study involving 60 patients, they documented a significant relationship between Gabapentin renal clearance and creatinine clearance ( $Cl_{GR} = 0.78 \cdot Cl_{CR} - 0.24$ ,  $r=0.97$ ). Based on a normal dose of 1200 mg/d, the authors recommend that patients with  $Cl_{CR}$  between 30-59 receive a 50% dose reduction (2 fold), patients with  $Cl_{CR}$  of 15-29 see a 75% reduction (3-fold), and patients with  $Cl_{CR}$  of less than 15 almost a 10-fold reduction (300 mg every other day). Given the relationship above we can calculate Gabapentin renal clearance for any Creatinine clearance and use it to calculate  $C_{SS\ avg}$ . For an oral dose, the average serum concentration at steady-state,  $C_{SS\ avg}$ , will depend on the bioavailability  $F$ , the dose  $D$ , and dosing frequency  $\tau$ , and the clearance, which in this case is Gabapentin renal clearance,  $Cl_{GR}$ .

$$C_{ss\ avg} = \frac{FD}{Cl_{GR}\tau} \quad (1)$$

We can also estimate the biological half-life using the expression

$$T_{1/2} = \frac{0.693V_d}{Cl_{GR}} \quad (2)$$

where  $V_d$  is the volume of distribution. The literature gives a value of  $58 \pm 6$  L for Gabapentin volume but this should not be used in pediatric populations as the  $V_d$  should be considerably less. It is also suspect in the obese and cachectic patient as well as the physically dehydrated. A more reliable estimate is probably 0.8 L/kg.

With these parameters it is possible to compute the following table:

Table 2

$Cl_{CR}$ (mL/min)	$Cl_{GR}$ (mL/min)	$Cl_{GR}$ (L/Hr)	$T_{1/2}$ (Hrs)	$C_{SS\ avg}$ ( $\mu$ g/mL)
120	93.4	5.6	7.2	4.2
60	46.6	2.8	14.4	8.4
30	23.2	1.4	28.9	10.8
15	11.5	0.7	58.3	10.9

Figure 2 graphically presents how the average steady-state concentration will change with dose and renal function. At any given dose, changes in renal function will have an inverse effect on serum concentration. The magnitude of the effect is considerable. Our target concentrations are probably around 10 mcg/mL, because the trough concentrations will be less than the  $C_{SS\ avg}$ . A patient on a relatively small dose of 1200 mg/d with normal renal function would expect to have an average steady-state concentration of 4  $\mu$ g/mL. Giving the same dose to a patient with impaired renal function,  $Cl_{CR}$  of 15 mL/min, would give a concentration of 34  $\mu$ g/mL. By tracing horizontally to the line described by a creatinine clearance of 15 ml/min, it can be seen that the dose necessary to achieve the same concentrations would be about 100 mg/day. That assumes that bioavailability does not exceed 0.6 at low doses. A bioavailability of 0.8 would increase steady-state concentrations an additional 33%. Co-medication with Naproxen or an opiate might increase absorption still further.

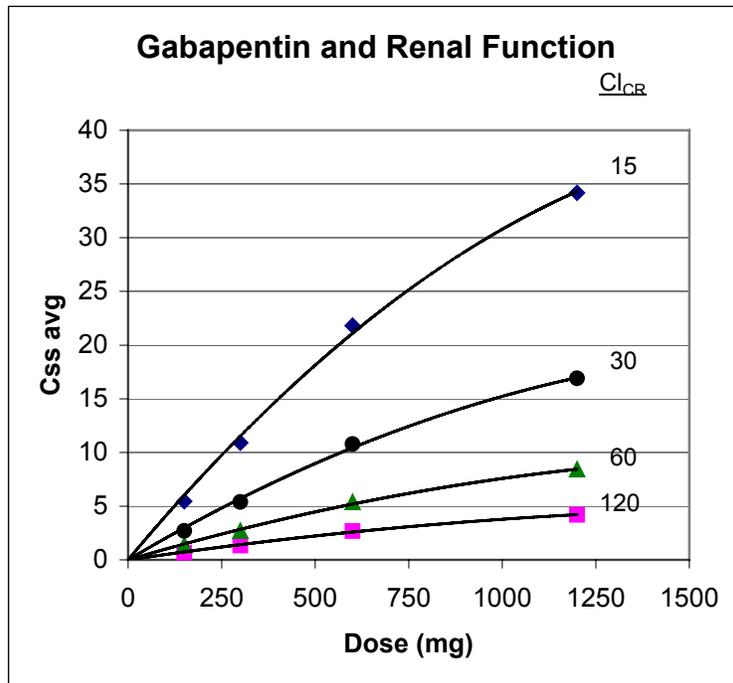


Fig. 2 The Relationship of Dose, Creatinine Clearance ( $Cl_{CR}$ ) and the Average Gabapentin Concentration at Steady-state ( $C_{SS\ avg}$ )

Another way to look at it would be to simulate the concentrations assuming a 1 compartment oral model with multiple doses (see Figure 2). Here the lower concentrations are those that would be obtained if the recommendations of Blum were followed for a patient with a half-life of 6 hours ( $Cl_{CR}= 144$  mL/min,  $Cl_{GR}=112$  mL/min ) and a half-life of 48 hours ( $Cl_{CR}= 18$  mL/min,  $Cl_{GR}= 14$  mL/min ). Note that since the clearances in this figure are higher than the previous figure and table, the  $C_{SS\ avg}$  is lower. The higher concentrations would be obtained if this patient were given the standard dose (1200 mg/d). Note that at 12 days the renal patient is just approaching steady-state.

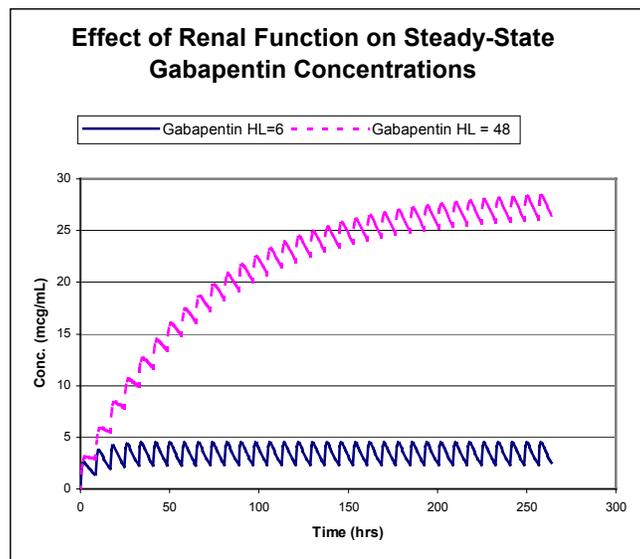


Fig. 3 Multidose Steady State Gabapentin Concentrations with a Dose of 400 mg TID for a patient with an elimination half-life of 6 hrs and 48 hrs.

There is little doubt that significant portions of the population cannot receive the standard dose or see substantial elevation of serum concentrations. It's important to keep in mind that physicians are being asked to

titrate to effect, and it would not be uncommon to see patients receive doses of 2400 mg/d or higher for pain if vestiges of pain continued.

Renal patients incur an additional problem. The qualities that make Gabapentin an attractive adjunctive therapy, no protein binding and metabolic interactions, make it extremely susceptible to dialysis. Wong et al<sup>5</sup> studied the effect of dialysis on Gabapentin clearance in anurics and found that a four-hour dialysis period required a replacement of approximately 50% of the preceding dose. The Gabapentin half-lives for these patients ranged from 50 to 336 hours.

Aging will also decrease renal function, though the decrease will not be readily manifested by a serum creatinine concentration. The unpredictability of  $Cl_{GR}$  in this group should make monitoring an important element of therapy. To quote from the product description in the PDR, “.. the risk of toxic reactions to this drug may be greater in patients with impaired renal function.” Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in those patients. It is very important that the method for estimating  $Cl_{CR}$  factor in age. I would note that our laboratory has a policy of appending the following statement to all Gabapentin concentrations greater than 20 mcg/mL, **“Gabapentin is not metabolized and depends on renal mechanisms for elimination. Changes in renal function, aging, and dialysis may necessitate dosage adjustment.”**

I think we can make a substantial case for monitoring Gabapentin for select populations such as the elderly, pediatrics, and the renally impaired. Certainly, there is a basis when symptoms of toxicity warrant, either when doses are pushed aggressively, when co-medications have been shown to affect absorption, or in cachectic or obese individuals, where the volume of distribution estimates may be unreliable. One other significant value in monitoring is that Gabapentin is itself an excellent diagnostic agent for the evaluation of renal function. Changes in renal function should prompt increases or decreases in steady-state serum concentrations proportional to the change in renal function. Accurate drug concentrations are probably less prone to interferences than the measurement of serum or urine creatinine.

A number of these points are illustrated in the following recent abbreviated case study: Patient Y is a 46 year old, morbidly obese female with a history of obstructive sleep apnea, diabetes, and chronic pain syndrome. She presented with “decreased mental state, lethargy, weakness... abdominal pain, lightheadedness” and was described as “obtunded and unable to maintain airway” and “cannot provide significant history.” Pertinent medications were Gabapentin (1600 mg/d), Effexor, and Vicodin. Her previous history “showed no evidence of diabetic renal disease.” Her admission serum creatinine was 5.4 mg/dL and BUN was 54 mg/dL. Toxicological studies were initiated. No toxic substances were noted but upon review of the history the laboratory performed a serum Gabapentin measurement on the serum received with the urine for toxicological analysis and a concentration of 100 mcg/mL was obtained. Summary: acute renal failure precipitating high concentrations of sedating medications.

While there is drama attached to an emergency room visit, I can tell you from experience that taking too much Gabapentin is an everyday experience. We looked at all the Gabapentin concentrations over a 1-year period and graphed the concentration against the corresponding serum creatinine value. The results are in Fig.4. In all, we looked at 374 serum levels. 191 (51%) were in the therapeutic range (2-10 µg/mL), 46 (12%) were subtherapeutic, and 137 (37%) exceeded the therapeutic range. 32 values were more than twice the therapeutic range (9%) and, of these, all but 5 had creatinines that exceeded the therapeutic range. Of the 191 values in the therapeutic range, only 17 (9%) had creatinines greater than 2.0 mg/dL. 88 patients (24%) had creatinine values greater than 2.0 mg/dL and only 25 of these (28%) had Gabapentin concentrations within the therapeutic range.

I draw the following conclusions from this data: 1) a significant number of patients receiving Gabapentin exhibit very high levels and that this is due to poor renal function, 2) patients with poor renal function were unlikely to have drug concentrations within the therapeutic range, 3) those patients within the therapeutic range tended to have normal renal function, and finally, 4) assuming the desirability of

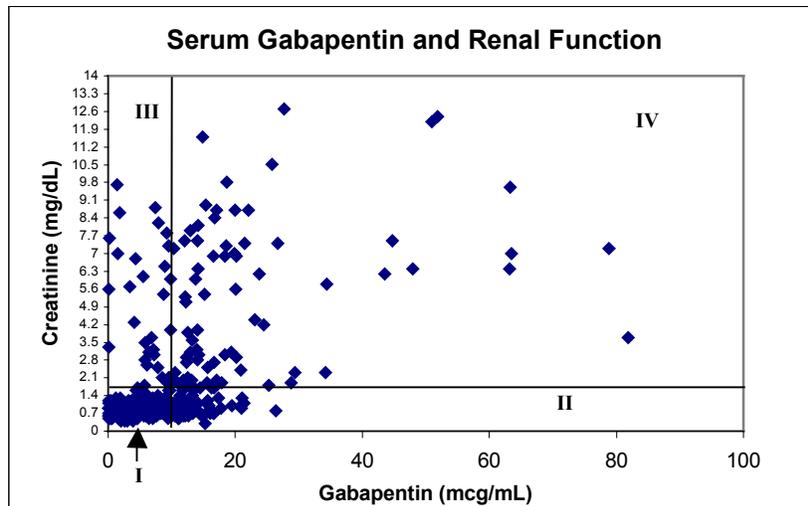


Fig. 4 Serum Gabapentin Concentrations and their associated Serum Creatinine Concentration [Region I defined by the upper limit of the Creatinine Adult Reference Range (1.5mg/dL) and the Therapeutic Range of Gabapentin (10  $\mu$ g/mL), Region II Abnormal Gabapentin Concentrations with Normal Renal Function, Region III Therapeutic Gabapentin Concentrations and Diminished Renal Function, and Region IV Supertherapeutic Gabapentin Concentrations and Diminished Renal Function]

therapeutic drug levels, many patients are not maintained on optimal regimens. Given that this is a group of monitored patients, I don't think that it is a stretch to suggest that patients who are not monitored would exhibit even worse statistics. **The fact that algorithms to adjust the dose of Gabapentin for renal function exist does not mean that they will be consistently used in clinical practice.**

I have long felt that the force that drives TDM is the interest of the physician in the well being of his patient. If he feels that monitoring drug levels is helpful, he will support the practice. When we see significant use of TDM for a drug in which the pharmaceutical industry has challenged the need for monitoring, I think we have to question the assumptions underlying their judgment. I urge laboratorians to support their clinical staff by developing the means to measure Gabapentin. I urge the *in vitro* diagnostics industry to recognize that the market for monitoring this drug is emerging and that their efforts will be profitable both for them and the patient population as well. Finally, I urge that if you have comments, opinions, or anecdotes regarding Gabapentin monitoring, to bring them forth and our editor may be able to combine them into a Reader's Forum.

*I acknowledge the effort and determination of David Alter, MD in the assembly and interpretation of the Gabapentin/Creatinine data*

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2. Suit Alleges Promotions of Drug Skirted U.S. Law, Matthias Rath, MD, [http://www.dr-rath-research.org/news/news\\_default\\_fullpage.php?document\\_id=383](http://www.dr-rath-research.org/news/news_default_fullpage.php?document_id=383)
3. Gabapentin: A Review of its Pharmacological Properties and Clinical Potential in Epilepsy. Goa KL, Sorkin EM. *Drugs* 46:409-427, 1993.
4. Pharmacokinetics of Gabapentin in Subjects with Various Degrees of Renal Function. Blum RA, Comstock TJ, Sica DA, Schultz RW, Keller E, Reetze P, Bockbrader H, Tuerck D, Busch JA, Reece PA, Sedman AJ. *Clin Pharmacol Therap*, 56:154-159, 1994.
5. Disposition of Gabapentin in Anuric Subjects on Hemodialysis. Wong MO, Eldon MA, Keane WF, Turck D, Bockbrader HN, Underwood BA, Sedman AJ, Halstenson CE. *J Clin Pharmacol* 35:622-626, 1995.

# ***sMATTERings Meeting Calendar***

## **AACC 2004 Annual Meeting and Clinical Lab Expo**

The 2004 Annual Meeting will be held in Los Angeles, California, July 25-29, 2004.

For further information:

email: [info@aacc.org](mailto:info@aacc.org) web: [www.aacc.org](http://www.aacc.org)

## **2004 FBI Laboratory Forensic Toxicology Symposium & Joint Meeting of the Society of Forensic Toxicologists (SOFT) and The International Society of Forensic Toxicologists (TIAFT)**

JW Marriott Hotel on Pennsylvania Avenue in Washington DC August 28-September 3, 2004

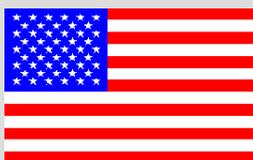
Topics will include: postmortem toxicology, behavioral toxicology, clinical and environmental toxicology, forensic urine drug testing, alternative matrices, and analytical methods. Contact Marc A. LeBeau at the Federal Bureau of Investigation, FBI Laboratory by phone 703-632-7408, fax 703-632-7411, or email [mlebeau@fbi.gov](mailto:mlebeau@fbi.gov). Visit [www.soft-tox.org](http://www.soft-tox.org) and [www.tiaft.org](http://www.tiaft.org) for more information.

## **Southwestern Association of Forensic Scientists 2004 Conference**

Southwestern Association of Forensic Scientists 2004 Training Conference and Meeting will be held October 11-15, 2004 in Oklahoma City, Oklahoma. Contact: Brandy Reese, Oklahoma State Bureau of Investigation, 2132 N. E. 36th Street, Oklahoma City, OK 73111 Tel: (405) 425-3857 Fax: (405) 427-5614. For further information visit: [www.swafs.us](http://www.swafs.us).

## **Society of Toxicology**

The 2004 Annual Meeting will be held in Baltimore, Maryland, March 21-25, 2004. Contact SOT at: [sothq@toxicology.org](mailto:sothq@toxicology.org)





# 2004 ANNUAL MEETING

SHERATON CHICAGO NORTHWEST  
ARLINGTON HEIGHTS, ILLINOIS, USA

MAY 23-25, 2004

<p><b>Location:</b> We are excited and honored to be able to host the 2004 Annual Meeting of MATT. The meeting will be held at the luxurious Sheraton Chicago Northwest Hotel, Arlington Heights, IL only 25 miles from downtown Chicago. The hotel features</p> <ul style="list-style-type: none"><li>•indoor swimming pool</li><li>•fitness room</li><li>•high speed internet access</li><li>•business center</li></ul> <p><b>Rates:</b> The room rate is \$ 109 per night.</p> <p>You can register by telephone at <b>1-888-627-8093</b>. You must identify yourself as attending the MATT/SoHT Conference. Or, register directly on-line at <a href="http://www.sheraton.com">www.sheraton.com</a></p> <p>Go to “<b>Meeting Sites</b>” then “<b>Attend a Meeting</b>”</p> <p>Use meeting code <b>2285</b> to obtain these special rates. The deadline for room rates is April 15<sup>th</sup> 2004</p> <p><b>Weather:</b> The weather in May is beautiful with an average high of 22°C and an average low of 10°C</p>	<p><b>Airport and Transportation:</b> You will likely be flying into Chicago O’Hare International airport, located approximately 15 miles from the hotel. Rental car and taxicabs are available at O’Hare, but we recommend you use one of the two limousine services listed below.</p> <p>Upon collection of your luggage call:</p> <p><b>My Chauffeur Limousine</b> at <b>1-800-244-6200</b> Reservations are <i>recommended</i> and can be made on-line at: <a href="http://www.americanlimousine.com">www.americanlimousine.com</a></p> <p>Click on “Reservations” and fill in the information The rate is approximately \$ 20</p> <p>Or call <b>Universal Taxi 1-888-344-TAXI</b> The rate is approximately \$ 25</p> <p><b>Hotel Shuttle:</b> The hotel operates a shuttle bus service in a 5-mile radius of the hotel, including Woodfield Mall and the local Metra train station which operates daily service to downtown Chicago.</p> <p><b>2004 Meeting Contacts:</b> Adam Negrusz <a href="mailto:anegrusz@uic.edu">anegrusz@uic.edu</a> Christine Moore <a href="mailto:cmmuk@yahoo.com">cmmuk@yahoo.com</a></p> <p><b>Hotel Contact:</b> Kristie Owens <a href="mailto:kowens@sheratonchicagonw.com">kowens@sheratonchicagonw.com</a></p>
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## 2004 MATT/SoHT Annual Conference



REGISTER EARLY !!!!! That's the message from the MATT organizers for the 2004 meeting. Space is limited for this exciting meeting since it is a joint conference with the Society of Hair Testing. As we go to press, a total of 80 attendees from the 2 groups can only be accommodated, so it is essential that you register well in advance of the meeting dates. A registration form is included with this issue of sMATTERings and further information can be found on our web site at [www.midwesttox.org](http://www.midwesttox.org). The conference hotel is conveniently located near Chicago OHare International airport and has shuttle buses to take guests to the Metra train which has a direct line to downtown Chicago.

The Co-chairs of the meeting, Adam Negrusz ([anegrusz@uic.edu](mailto:anegrusz@uic.edu)) and Christine Moore ([cmmuk@yahoo.com](mailto:cmmuk@yahoo.com)), are in the midst of collating the scientific program as well as the social agenda. While technically the fun starts with a Sunday evening reception at the conference hotel, the Sheraton Chicago Northwest in Arlington Heights, IL on May 23<sup>rd</sup>, anyone interested in playing golf at one of the many area golf courses on Saturday May 22<sup>nd</sup> should contact Christine directly. (Green fees are not included !)

Back to science...Separate scientific sessions for each organization get underway on Monday May 24<sup>th</sup> and the joint session will take place on Tuesday morning, May 25<sup>th</sup> 2004.

The preliminary program includes sessions on Clinical Toxicology, Environmental Toxicology, Drugs in Cancer Research and Pharmacogenetics. The joint session will feature the treatment of pain management using hair, the epidemiology of adolescent populations involving hair, urine and oral fluid, and various clinical applications of hair analysis.

A detailed program, including specific speakers and topics, will be available in the next issue. There will be opportunities for meeting vendors and colleagues alike and we look forward to a really exciting meeting in the Chicago suburbs.

So please avoid disappointment and REGISTER NOW !

### NOTICE! NOTICE! NOTICE!

Information updates with regard to the upcoming MATT meeting in Arlington Heights can be obtained by visiting the MATT Website @ [www-midwesttox.org](http://www-midwesttox.org)



## 2004 MATT/SoHT Annual Conference

*Sheraton Chicago NorthWest, Arlington Heights, IL May 23-25<sup>th</sup> 2004*

**Registration Form: The deadline for registration is April 15<sup>th</sup> 2004**

Name: \_\_\_\_\_

Last

First

Agency: \_\_\_\_\_

Address: \_\_\_\_\_

Telephone \_\_\_\_\_ Fax \_\_\_\_\_ E-mail \_\_\_\_\_

	MATT MEMBER	Non- MEMBER	TOTAL ENCLOSED
<b>Basic Meeting Registration - per person</b>	\$ 160	\$ 250	\$ _____
Includes Scientific sessions, Exhibits, Program book Reception, 2 lunches, Banquet			
<b>Single Day Registration only</b>	\$ 85	\$ 130	\$ _____
<b>Please circle day      Monday      Tuesday</b>			
Accompanying Persons (includes Reception, 2 lunches, Banquet):		\$ 85	\$ _____
■ Additional Tickets:      Sunday reception	\$ 25	# of tickets _____	_____
Monday banquet	\$ 50	# of tickets _____	_____

**Method of payment:**

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Check made payable to **MATT**

Drawn on USA bank or Money Order. Must be paid in US dollars

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**MAIL:**      Adam Negrusz PhD, Associate Professor,  
                  Department of Biopharmaceutical Sciences, M/C 865,  
                  College of Pharmacy, University of Illinois at Chicago,  
                  833 S Wood Street, Chicago, IL 60612

**HOTEL:**      Make reservations directly with the Sheraton Northwest, Arlington Heights, IL  
                  at **1-888-627-8093**. You must identify yourself as attending the MATT/SoHT Conference

OR register on-line [www.sheraton.com](http://www.sheraton.com) Go to "Meeting Sites" then "Attend a meeting"  
 Use the meeting code **2285** to obtain rates of **\$109 per night** for Double/Double or King  
 (single or double) in Arlington Heights, Illinois

# **Society of Hair Testing: ANNUAL CONFERENCE 2004**

## ***Sunday May 23<sup>rd</sup> 2004: EVENING RECEPTION***

### ***Monday May 24<sup>th</sup> 2004:***

**7.30 - 8.30 am REGISTRATION**

**8.30 - 10.00 am**

- Physiology of Hair Growth
- Role of Melanin in Drug Incorporation into Hair

**10 - 10.30 am COFFEE BREAK**

**10.30 - 12.15 pm:**

Special Session: CANNABINOIDS IN HAIR

**12.15 - 1.30 pm LUNCH**

**1.30 - 4.30pm:**

**Special Session: HAIR TESTING- Birth to Death**

- Neonatal Hair Analysis and Child Exposure
- Documenting Drug-facilitated Crimes using Hair
- Hair Analysis for "Date-Rape" Drugs
- Hair Analysis in Driving and Employment Issues
- Post-mortem Hair Analysis

## ***Tuesday May 25<sup>th</sup> 2004:***

***MATT/SoHT Joint Session***

**8.30 - 10.15 am**

**Special Session: EPIDEMIOLOGY OF HAIR ANALYSIS**

- Differences in metabolic profiles in hair from various populations
- Epidemiology of an Adolescent Population using Oral Fluid, Urine and Hair

**10.15 - 10.45 am COFFEE BREAK**

**10.45 - noon: CLINICAL AND FORENSIC TOXICOLOGY**

**LUNCH – SOHT Business Meeting**

**1.30 - 2.00 pm**

Special Session: IMPROVEMENTS IN HAIR ANALYSIS METHODS

- Automated immunoassay screening for new drugs in hair
- GC/MS/MS

**2.00 pm - 4.30 pm**

**Special Session:**

**APPLICATIONS FOR LC/MS, GC/MS/MS and LC/MS/MS**

**END OF CONFERENCE**



## Membership Application/Renewal Form

Full member renewal = \$25

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suggestions

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Submit check drawn on USA bank or money order payable to **MATT**

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