American Association of Poison Control Centers August 2004 Webcast

Management Approaches for New Drugs

JEAN CLEARY: Hello, my name is Jean Cleary. I'm talking to you from the University of Texas Medical Branch from the southeast Texas poison control center. We would like to welcome you to the first of two broadcasts we are doing. We are very glad to come to you today. I would like to thank some, several people for making all of this possible. First I would like to thank HRSA for providing the grant and especially Maxine Jones who has been just phenomenal in making all of this happen. I would also like to thank the AAPCC board of directors for their continuing support of the education. This would not have been possible without their support as well. I also need to thank Rosanne Soloway, in work and getting all of this done. We would like to thank the people at the University of Illinois at Chicago, Matthew Murray and Don Rasmussen and their staff up there for the technical aspects of this webcast. I would also like to thank Kathi Macheart, also the co-chair of the spy committee, and the spy committee for the participation and support in making this possible. Lastly I would like to thank our speaker today, Wayne Snodgrass, and managing director, and everyone at the southeast Texas poison center for their support and encouragement and suggestions. Right now I would like to introduce our speaker, Dr. Wayne Snodgrass, who is the medical director at the southeast Texas poison con control center. He has been a friend for about 16 years, and I have known him well. He is also one of the best medical directors I think any poison center could have, and I hope that every poison center has a medical director just like him. So without any further delay, I would like to introduce Dr. Wayne Snodgrass.

WAYNE SNODGRASS: Hello, it's a pleasure to be here and am glad to have the chance to participate with you. I think this is a tribute for those who put together the proposal for HRSA, and also wonderful HRSA supports this type of grant, and hopefully this can be of some use to many SPIs. I know not all SPIs have the opportunity to come to the annual national meeting and so interaction with the peers is not always possible for everybody. This is really somewhat informal. I will try to go through most of the presentation to begin with, and then at the end open it up for questions. In the meantime, of course, you can email in questions at any time. The format is really very straightforward. What I have done is I was given a list of some months ago, a list of drugs to address, partly for their toxicity, partly what they are. And I can confess that I knew very little about most of them. These were indeed new agents. So I think I'll just start with them one by one and go through them. Perhaps what little information is known can generate more questions. Much of the information may not be actual poisoning or overdose information; all of these are new agents. But they do potentially show what might be coming down the pike for you as an SPI who is manning the phones and the kinds of things that might come in to your center. And being that almost all of these are going to be prescription agents, you can expect that, or some of these, they will mostly be calls from physician's offices or hospitals or emergency departments potentially about those, although some patients also may call about them. No particular order here, I am going to start with two or three that I think are perhaps of some greater interest because of prior agents that we deal with that are somewhat related or in some cases not related.

The first agent, first drug is one that has a generic name of, the way I'm going to pronounce it, DULOXETINE. You might say what is it? At least I did. I first was given the drug. The way I approached this was, it is not found in any of the more recent toxicology texts, I simply did a med line search. It turns out this is an antidepressant. It is a newer and at this did he -- antidepressant. It's not an SSRI. It is, and this is new terms, SN, as in Nancy, RI. So what an SSRI is a selective norepinefrine. Also similar to another, a couple of other drugs, I'll mention them, one is called MIRTAZIPAE, and another one, and all of these are said to be blockers of the up take or the block reuptake of both serotonin, and the way they go through reuptake is through the membrane of the nerve cell, a transporter, a protein that is basically a type of a pump. In the test tube this drug is more potent than lafaxine, that probably translates into a lower milligram of a clinical dose. So because it's that type of an agent, one would expect similar types of phenomenal overdose to Efoxor.

There would still be some potential risk perhaps of cardiac -or some seizures, and there may or may not, depending on the severity of the poisoning, some risk for hypotension. Being studied for interesting uses beyond its known efficacy for anti-, as an antidepressant, one area in which it's being studied, abbreviated SUI, stress urinary in it has to do with the receptor action. It does have some efficacy for treating urinary incontinence, it's while running, jumping, sneezing or coughing, and a number of patients have this. It increases the RHBDO and it does this by affecting the nerve that stimulates into the bladder area, it stimulates the alpha 1 and so-called type 2 serotonin receptors. It causes a contraction of that and decreases the stress urinary incontinence. They are

attempting to try these agents in models of behavior, behavioral types of testing, or laboratory rats. And it appears that with greater selectivity, you can select whether it has activity for an antidepressant.

Compared to some of the older things, and SSRIs, this blocks both serotonin, they think you could treat a greater number of patients for anti-depression, and it takes six to eight weeks, sometimes more, or the older anti-depressants to work I think patients. In some they might work earlier. And again, at least a third or more of patients may not even respond to some of the older antidepressants. So the attempt here is to get an agent to treat a larger percentage of the patients with depression, and perhaps have an onset of action, a matter of many days, at least several to many days rather than weeks. The kinds of calls we get in the poison center do not reflect all the kinds of problems that can occur with drugs and therapy. This drug, DULOXATINE is metabolized by the 450 epb seems, in the liver, and it is a group of different enzymes, each has a different numbering system. It is very complex and related to the call coming in at 12:00 midnight from the ER when you are busy fielding two, three calls in the last several minutes.

Relationship is one that if you block the ability of the body to get rid of this drug, you may build up levels at doses you would not otherwise think were a problem. The overdose setting, that may not be the initial problem since we think of that as being a large dose. But some patients may come in with very high levels who have accumulated this over a much longer period of time because they may have another drug they are taking that blocks the ability of the body to get rid of this drug, the first drug. It's metabolized by CY2,

2 as in number 2, D as in dog, six; it's one of the many types of the things that are known. You say why is that important, who really -- why should that be a problem or concern? Well, because if you inhibit the 2D6 you might build up more DULXOTINE, for example, and that could occur with some drugs that could inhibit that metabolism. By contrast, it turns out that this drug, the other complex part of this. At least therapeutic settings, here is a drug that metabolized by this particular P450 enzyme, but it turns out that it also self-inhibits that same enzyme.

How can that happen, metabolized and self-inhibit? Well, without going into the molecule stuff of all this, basically, it really does happen, and initially it can actually have a slower rate compared to later or might be the reverse of that. What is shown is other drugs like DEZIPROMINE, you can decrease the area of the curve by nearly three-fold with this drug DULOXTINE. So you can have different reactions between different drugs, it may or may not be a reason that the hospital would call you at the poison center, but keep in the back of the mind these go on and explain other symptoms or signs being discussed about the patient. So, if you have questions about this drug, feel free to email them in. I think that covers a lot of the initial material that I have about it. Again, overdose one would just predict that like a number of the other drugs, hopefully minimally so, hopefully more in the range of being like an SSRI having the lesser risk of toxicity, but still there could be some risk of seizures or cardiac problems, although probably fairly low, and more likely patients would have a decreased level of consciousness, perhaps possibly some blood pressure decrease. And those would be the most concerning issues, probably, with this agent. But

time will tell, since we, to my knowledge I am not aware of a single reported case yet of overdose with this agent.

Now the next agent, next drug, I would like to bring up next is one called LOFEXIDINE. It is basically, well, a drug cousin or chemical cousin to CLONADINE. I think most of us know what that is. CLONADINE can be used to treat high pressure. It can cause low blood pressure in overdose. LOFEXIDINE has less tendency to cause hypotension, decreased risk of causing lower blood pressure. Like CLONADINE, it is an alpha 2 receptor, partial AGONAT. Alpha receptors, alpha 1 is when epinephrine is in high dose, alpha 2, the brain, you stimulate those, you decrease the sympathetic output from an area of the brain. The bottom line is that the sympathetic output is decreased from the brain. As a result, you have decreased blood pressure. Turns out these drugs have another effect, that is the CLONADINE, and now LOFEXODINE can be used to detoxify opiate. They do that through the same mechanism, apparently. There may be other mechanisms, they work to some extent, and LOFEXIDINE has been used for that. It will tend to decrease or block nausea, vomiting, abdominal cramps, sweating, tachycardia and other things with the withdrawal, but unless METHODONE treatment program, it does not alleviate the generalized aching feeling and decrease the craving for the narcotic, or the opiate. So it would have a little bit of a limitation there. But it has been shown to be better than METHODONE for disrupting the sleep disruption. However, not as good as a newer agent called a BUPRNAFIN. It's been on the market in the United States, it's a synthetic opiate or narcotic, and now been shown that is probably, particularly in the combination of other drugs, but that is coming out to be a better form of therapy for opiate withdrawal.

And like CLONADINE, it's used in ADHD, attention deficit hyperactivity disorder in children, and there is some efficacy there.

Now in overdose, much like CLONADINE, similar things, a significantly decreased level of consciousness, possibly hypotension. The other things that go along with CLONADINE. I would categorize LOFEXODINE as that type in overdose. Now the next one, the next drug I'm going to talk about is one that is I think we could all say is probably new to us in the poison center arena, and is new in terms of a therapeutic category. This drug has a generic name of TIRILAZAD. TIRILASAD. What is this? Well, it's being used as a possible neuroprotective agent. Analogy will be, perhaps many of you are aware, a person with a final cord injury arrives in the emergency department, one of the first things that the physician or the neurosurgeon might do is to start IV METHYLPREDNISOLONE. It's been proven to have a long-term outcome with a spinal cord injury. Well TIRILAZAD is a product of thinking through how did the steroid work. It turns out that TIRILAZAD is not an active steroid. It has a little bit of the structure, but it has no actual, what we call GLUCOCORTICOID activity. This is a peptide analogy. Mostly given by the subcutaneous group. It's -- perhaps some of you are familiar with the fact that in the area of poisoning and overdose, we might recommend the administration of this itself in certain types of poison situations. One might be in an extremely severe calcium channel blocker poisoning, GLUCONON has not only effects on glucose, but of the heart. Some value in that situation. This is a GLUCONON analogy, or chemical cousin, if you will. What it does, it increases glucose dependent insulin secretion. It doesn't just do this without any regard to glucose. There has to be some glucose around for this to happen. It decreases

an elevated GLUCONON. It will suppress that secretion, at least partially. And it -- either a good thing or not a good thing, depending on your point of view here. Good thing if you wanted to get some charcoal in perhaps before something leaves the stomach, but may not be a good thing if later on there will be emptying, you'll have a delayed function of some substance.

The other interesting thing about this EXANTIDE, the peptide comes from what we have heard of, this is derived from the venom of the GILA monster. The Gila Monster lizard. It comes from that lizard, and it's being used for an activity that has to do with diabetes. Very interesting compound. The doses are very low, for example, the doses are currently used in some clinical trials are .05 to 0.2 of microgram dose. The worry we might have in overdose, anything that has to do with diabetes, can it cause hypoglycemia. If this becomes something, that makes it to the market and someone has given at least a decimal point, maybe two, three decimal points, the error, sub Q of this drug, you would clearly closely follow glucose. That patient would be sent to a health care facility and the glucose monitored for some period of time. That is given on an average 12-hour basis. It gives you some idea of maybe the duration of action. Overdose occasion, that would probably be extended quite a bit. So that's what I know, which is very little here, about EXENTIDE, it might possibly make it to the market, it has differences with other agents used for the treatment of diabetes.

Now, there is another drug that probably most of you have heard about, that was on the list that someone had requested. I think it's probably a very interesting drug to go through,

you may have heard about it, there may be more about it that you are unaware of in more recent times. This is the drug THALIDOMIDE, it causes birth defects. Many people have heard of that. There were major number of birth defects in Europe in the 1960s. In Germany, 10,000 babies were affected. And this was at a therapeutic dose. I don't remember the exact milligrams, 25 or 50 milligram dose. About 25% of all women who got this drug in the second, third or fourth week of gestation, particularly in that period of time, even longer than that, this is the critical time for limb development, that 25% of those babies were affected. 75% were not. So to this day we don't know why the other 75% didn't have this problem. And this is true of most TERADIGON, a strong one is 20, 25% of individuals are affected, the others are not. A few exception to that is the, a drug no longer used much at all, anti-convulsive, TRIMETHADIONE. One out of two women when took it in early gestation, had a problem, cleft pallet, for example. Because it was so unusual it was recognized early. I suppose this would be a good exam for the, a good test question on the SPI exam, what is worth going over THALIDOMIDE. The limb, the arms and legs, is called FOCOMELIA. This is from John in Michigan, he's going to take notes. We can all be prepared for John. So FOCOMELIA was the actual name for the effect.

The key point is, just like we can pick out trends occurring, and now Bill Watson, updating very, very frequently electronically, looking for trend analysis of the poison calls coming in, this same thing happened in Germany. Pediatricians in Germany had only seen, one or two cases of something like this, and in a matter of, I think three, four, five months after this drug came on the market, he saw four, five cases. So he knew that something is very different, and with careful questioning it became clear that it was the drug THALIDOMIDE.

Why would we be concerned about this? What happened, by the way, as another perspective on this, the 1962 addendum to the FDA, regulatory authority was significantly expanded because of THALIDOMIDE. As a result, the FDA requires further testing, including reproductive and developmental testing. Prior to this it was not that extensive. As an aside, this involved children. Those of you may not be aware, 1938 law that gives the FDA most of the regulatory authority was also based on a disaster, one of the first antibiotics that came on the market in 1935, in 1937 there were no laws about safety, purely a matter of a pure chemical. No requirement for efficacy testing, either. And the drug company that made SULFAMICIDE, needed a liquid solvent, found various solvents that tasted about and dissolved it, it turned out to be anti-freeze. This was subsequently marketed, and within weeks of being on the market, within four, five, six months or so, 101 or 102 children that died in the United States due to renal failure.

Now you know, Ethylene GLYCOL -- and that further strengthened the authority. It is on the market now, and it's approved for a specific indication. Something called, it's a complication of leprosy. The turns out it's marketed in the United States, specific FDA approval for something called NODSOM, a complication of leprosy. It's an overgrowth or increased growth of some of the areas of the skin, and it has to do with the phenomenon of blood vessel growth, increased amount of blood vessel growth. And if you want to block that, just as you would for some cancer therapy, you cut off the blood supply and have a cancer therapy effect, you want to do that. And it turns out this has that type of activity. It's called an anti-ANGIO genesis. So ANGIO genesis is an increase in blood vessels, anti is to block the activity. This has been shown in some human trials; you can

get some anti-proliferation activity of THALIDOMIDE. And it's useful in a few tumors. 25% of patients with MYELOMA get a response when you add it in. And one of the most big ones is colon cancer. In a very small study, a few patients, 20% of patients got an additional bit of a response, small but definite response when THALIDOMIDE was combined with another agent. These are based on more specific molecular approaches to the mechanism in what's happening in colon cancer. So it seams to be rejuvenated to some extent. So it is going to be around. And you might ask well, so what? Well, it's a really potent human TERADIMINE. You know it will have a warning about birth defects. The question is, how you going to prevent it from ever, 280 million population of the United States, ever being taken by a woman who is pregnant? Well, there is something you need to know in the poison center, and that is that for THALIDOMIDE, the FDA has required the company, and they have a program called S.T.E.P. Stands for system for THALIDOMIDE and prescribing safety. And the S.T.E.P. program means all prescribers are registered. So if you are going to write the prescription, you have to be registered. It also means that all pharmacies that dispense it are registered. So this regulars industry -- registry will have the physicians that prescribe it and the pharmacies that dispense it.

And thirdly, the registry will have the name of every patient that receives it. So prescriber, pharmacy, and the patient will be part of a registry. One part of the attempt to decrease the availability of this. Very similar, not identical to what happens with ISOCRATINONIN. You'll see a questionnaire there, and the physician will have it, the patients are required to read and sign the questionnaire before they get a prescription for ACUTINE. Suzie might get the prescription, and share it with Sally. And try and prevent the women in the child

bearing years from taking the agents. Aside, I might say that prior to that requirement for -- it would be known, by the mid 1980s, or late 1980s -- it was already known that based on epidemiology studies, you could extrapolate there were 1,000 babies in the United States that had some kind of a malformation from that then. They do not reach the poison center very often. Although I think you have had the experience of having a call, wanting to know if drug X is something capable of causing a birth defect. And I think many of us don't feel in the poison center arena, totally adequately prepared to deal with this for a variety of reasons. Many of you are aware the mother at risk program in Toronto is one major resource that is potentially available, as well as many written resources.

There are individual information centers in some parts of the country. Well, THALIDOMIDE then has the various issues. The other issue regarding pharmacy dispensing, and the right patient, is there is significant concern, addressed by many of the pharmacy groups, even in hospitals, and inpatients, how are you going to carefully control the distribution so the correct patient gets this? It's of less concern than on the OB delivery service. By that point it's not an issue unless you are talking about delivering a baby that's well earlier than 20 weeks, which is not viable, but it is of concern on, you know, child bearing age nowadays, or at least risk of getting pregnant, the onset of puberty through the 50s, so a variety of different settings, somebody could get this. It has to be carefully controlled if it's available in the hospital and it will be because of cancer patients getting this, appears to be an adjutant. In an overdose, what does it do? Certainly one would think of sedation, therapeutic doses, perhaps some moderate levels of coma.

Therapeutic doses, longer term, it causes a peripheral NEUROPATHY. It can even cause nausea. I think this is of interest because of the kind of history it's had and the effects it can have, and because of the kind of close, tight control that is going to be on in the distribution and availability. All right. Now we have gone through a number of agents. I think what I will do is try to address perhaps two or three more to give you some feel for other agents that are coming down the pipe, so to speak. One that I think you might find of interest, we certainly deal with this in poison centers, is a drug called, say it and spell it for you, ALVIMOPAN. What is that? Well, I would never have had a clue from its name. It turns out it's an opiate, narcotic, an tagonist. It's much longer acting, no, it's not. This drug has minimal absorption after oral dosing. That turns out to be a reason for the existence of this drug. It is an opiate or narcotic antogonist. It seemed to have a reasonable efficacy for treating postoperative intestinal ileus. It seems to let you have bowel sounds earlier, and where you have narcotic induced bowel function, morphine can cause constipation, this may be helpful in that area as well. It turns out it is a drug that is, two factors in how it can work. One is that, of course it binds to the opiate receptors, and it's an antogonist.

One factor is it has very little absorption through the intestine, the other is what does get absorbed does not cause a barrier to a large extent. It's certainly restricted to peripheral opiate receptors, and lower doses will be relatively restricted to within the intestine itself. And it appears that there are some are saying that it nearly normalizes bowel problems, in people that are having an abdominal lapratomy. You still get the pain relieving effect of

the other narcotic, like morphine, for example, that you are giving. So that drug is ALVOMIPAN. What do we expect in overdose? Well, overdose, an oral drug not very well absorbed, overdose, certainly more will get absorbed but not a lot. It will be like giving NALTROXONE orally, so a massive overdose, you could begin to get some, there is data in higher dose, clinical studies, you might get some opiate withdrawal, if the patient is on a narcotic. If they are not on a narcotic, you probably would not have that problem. In theory, this is purely theory, if it were like NARCAN, you would have a very wide margin of safety.

Doses in animal studies work that has been done, extremely high doses, 100 times the usual dose used, does not cause respiratory depression. So possibly this drug would be of a similar relative safety. Although again, in large overdose, and a person who is physically dependent on an opiate, narcotic, there may be be some opiate withdrawal, narcotic withdrawal that has started. Again, I would never have guessed from the name ALVIMOPAN. So the naming committee, I really don't know whether to say a positive or negative comment about that. By the way, maybe you are not aware, there is an attempt, internationally to try to deal with drug names. This is a real, real problem. Thousands of drugs on the market now, so that there is an international naming committee, or nomenclature committee, and the pharmaceutical houses are attempting to, and regulatory agencies are adding into this to be semi rational about naming a drug. The PRIL drugs, we know those are an ace inhibitor, and they are categories.

Another drug, many other things we could talk about, and maybe that will come up in questions, another drug that you have probably been familiar with or at least maybe have seen the name. It's an anti-convulsive drug, not very widely used. At least not to my knowledge it's not. This drug has a name of BIGAVATRIN. It's kind of a lesser used anti-convulsive. You add in with a patient particularly with partial epilepsy, or some temporal lobe epilepsy. But epilepsy more difficult to control, BIGAVATRIN might be added in. The BI, a bit of a clue, the next letters, GAVA are another clue to what the drug structure is. Turns out GAVA, that's gamma amino BUTURIC acid, normally in the brain. A neuro-transmitter. The VI is vinyl, VINYL, like vinyl on the floor, vinyl, vinyl chloride. Vinyl chloride, a starting material for a lot of polymers, and in industrial settings has led to two, 300 cases in the last two, three, four decades of a rare liver cancer called ANGIOSARCOMA. This is the gamma portion of gamma position of the GABA molecule, it's gamma vinyl GABA. You know the vinyl group, you look at that from a structure point of view, that's sort of a reactive chemical, it might bind the tissues or cause tissue damage. It has three bonds in that carbon to carbon structure.

Vinyl groupings tend to be more reactive in biological systems than in people. One that you expect that you might have, for example, you might predict, and there is some of this, this could have a little liver damage as an example. Large single overdose I would really make sure that I recommended liver function tests. These, just on that basis alone. Now it turns out that on a they are -- they are therapy basis, this is causing a high risk problem asymptomatic originally, restricting the visual field in patients, and in a few outright optic atrophy. Blindness is a side effect. A real big problem here. And that many patients, it

appears now that the majority of patients on this for a while, probably more than a few to several weeks, could have detectable visual field testing could have detection there was some constriction of the visual field. And all of us hope this was reversible, it's not totally reversible in many patients. So that has really changed the benefit risk ratio for this. Another thing it can do, cause a hearing loss. And again, you tend not to recover hearing loss. Like GENTOMICIN, you don't regrow that. If you are a young patient, if you have renal damage you tend to recover that. But the hearing loss you don't recover. Those cells do not regrow. So this has some significant adverse effects in overdose with the vinyl grouping, one would be suspicious there could be some liver damage, see some liver dysfunction, and that would be one thing to monitor. But to be aware that if a patient has been on this, that perhaps it's good to have it checked. The business of constricted visual field is something that needs to be addressed if not already addressed. Okay.

JEAN CLEARY: You have more time. If you would like to go.

WAYNE SNODGRASS: Okay. Well, we'll do that. We do have more time. There's a couple of other agents here that I can talk about, and will finish with those and then we can open it up to some questions. One drug that again, I did not know what it was, and the name also did not give me a clue, one more to go to the naming committee here, this drug's name is TENIDAP. TENIDAP. And a great question to put that on an exam and say what is it, you know. Well, of course I didn't know. It turns out this is an anti-inflammatory drug. Somewhat like the non-Steroidal drugs, but it has an additional activity that makes it a little different. One part of the activity, the anti-inflammatory is like

ibuprofen, ENDOMETHACIN, the non-Steroidal inflammatory drugs. It's like those, and it affects the COX1 enzyme. Prostaglandin prohibiting activity, there's a COX1, and COX2, that other enzyme inhibition, you have VIOXX, for example, and you have less stomach irritation at risk for stomach ulceration as an example. Not totally true, but somewhat in that direction. This drug is like the more classic older agents, a COX1 inhibitor. The other activity is in general terms, CYTOKYNE, month -- saying it has a big activity. What are CYTOKYNE? They are things that are secreted by CYTOs, which are cells.

So cells can secrete or release various substances. Some of these include substances like, that are increasing inflammation. Inflammatory mediators. They increase inflammation. One of them is interLEUKIN, interLEUKIN 6. Abbreviated as IL, and whatever the number is, IL6, IL-1, and another CYTOKYNE, called TNF alpha, that stands for tumor necrosis factor alpha. If you take those three, IL-6, IL-1, and TNF alpha, those three inflammatory mediators, what this drug does, it decreases their release, and their secretion from MACROFAGES and other similar cells. By doing that, it's an additional action. It turns out that ibuprofen, neproxin, all of those standards don't do that. Steroids do not do all of that, actually. Some cases they do to some extent in different ways. Another activity is that TENADAP inhibits NO. It's a local kind of active substance in a variety of tissues. Aspirin and sodium SOLISALATE can inhibit it. It turns out that steroids and hydro Cortisone don't inhibit the production. And this information I'm citing you came from cartilage taken from patients that had osteoarthritis. So it's human data. So as a result of being both an anti-inflammatory drug, and the so-called CYTOKYNE activity, it turns out in trials, in rheumatoid arthritis patients, not simply an inset, which it

has some of that activity, but also one called a DMARD, all capital letters. DMARD. Stands for disease modifying anti rheumatic drug. DMARD.

So some drugs like, for example, CLORAPIN, it doesn't just stop the inflammation but seems to actually, as is implied here, the disease process seems to get a little better and somewhat more improved. So TENIDAP, therefore, is going to have some broader spectrum of activity. And in fact, clinical trial data showing that rheumatoid arthritis, it is more effective for rheumatoid arthritis than is one called CURAXICAM. I use that as a lead-in. Overdoses of ibuprofen or Motrin, or NAPROXIN, they lose a level of consciousness, decreased consciousness, rarely, but need to be intubated, other than that they seem to do well. Elderly patient you worry about a kidney dysfunction, you have to follow that. A single large overdose is relatively more benign than one might think an otherwise healthy middle-aged adult in the 30s or 40s, as I have already mentioned, an elderly patient with possible compromised renal function to begin with, that would be of more concern. Generally speaking, we don't think of these as being such a problem. But therapeutic doses some drugs can be a problem. One of the nuances of the insets as a group is if you look carefully at therapeutic dosing for long periods of time, again, ibuprofen and NAPROXIN are over-the-counter. There are various categories, and FELDENE, or some others, the point I want to make here is for chronic therapeutic use, the OXICANs tend to be more toxic.

Not talking about single large overdose, talking about long-term therapeutic doses. And the end point that I will bring up as one to be aware of, it's, it's very uncommon. We are

talking about perhaps less than one in 5,000 or one in 10,000 that kind of risk right here, but when it occurs it's life-threatening or fatal. That is the risk of Stevens Johnsons syndrome, SJS, or TEN, toxic epidermal necolysis. SJS or TEN. These patients appear with initially a skin rash, and it develops further into a major skin disorder, and even sloughing of skin. Major mucosal involvement. Life-threatening. Other drug groups, classes, Dilantin can cause it, again, it's very uncommon, perhaps one in 5,000 a risk rate. But when it occurs it can be fatal. The point I'm Mikeing -- making there are some things like the oxidants can do this, and sulfas, if he -- and even in this group of drugs, some have more of a risk than others. Again, the poison center arena, most likely you or I are not going to be called for Stevens Johnsons syndrome. It's not an overdose, therapeutic dosing. Something to be aware of in the back of your mind, particularly with regard to calls that come in and what drugs are the patient on, and by the way, are they having a skin rash, or something else going on. And this can be part of the evaluation.

Now TENADAP like other drugs, or anti-inflammatories can have adverse effects in therapeutic dosing, like other insets, they combine fairly tightly to albumin, and can displace or knock it off. Other drugs are bound tightly. And Dilantin this has been studied, and it can increase the free land bound by 25% potentially. The patient that goes down to the corner drugstore and buys ibuprofen and takes a hefty dose, can interfere with the activity. You are blocking the VASODILATORY in the kidneys, and decreasing the ace inhibitor. One is very significant, the patients on Lithium, we all know in the centers that Lithium is one of the really bad actors. Lithium has a very narrow margin of safety. Lithium has a tight blood range. .5 to 2 per litter, and if you get much above that and are

chronically on Lithium, they can get into significant trouble, renal failure, you get a call you have a Lithium overdose, that's a red flag we might have something potentially that is significant and severe, and be calling somebody for additional input. And Lithium, severe overdoses, toxicity, probably require hemodialysis, it's a real issue. This drug, like most insets, increases serum Lithium concentration. This effect can be significant. You can double, triple, quadruple or more. It's interacting at the tubular level in the kidneys. You are not getting rid of it. The level goes up and the patients can get into some real problems. So that's one interaction.

Not only just for TENADAP, the interaction with Lithium is a red flag to be aware of. Hopefully it would not be very common, you would hope that most physicians who are treating a patient that is on Lithium would know that in fact taking an inset is a bit of a risk and would have counseled the patient that kind of activity would go on. Another adverse activity is an uncommon finding of something called EOSYNAFLIC pneumonia. If he writes the question, you have heard the answer. TENADAP, it's a very uncommon, I don't know how uncommon, probably, who knows, less than one in 1,000, surely, adverse effect, therapeutic doses, usually in first two, three, months, EOSINOPHILIC, pneumonia. And one way such a patient might present is that they have started taking this drug, or any other inset, and within a couple, three weeks or so, have a cough and feeling bad and, or more difficulty breathing. By the end, who knows, two, three, four weeks they are in respiratory distress, and might have a few chest X-ray findings and physical findings on exam, but one of the many white cell components, the ESONIPHIL wouldn't would be up. Probably running at least ten, maybe 15 or 20% as a serum percentage in the blood.

And if you do a bronchial lavag, double that. Normally it's way down, 1% or less. And as a result, what happens, are the reason they get the pneumonia, a number of products secreted by ESONIPHILs. They will secrete basic protein, and it is a protein that can be really destructive to cell membranes, as an example. TENADAP can do that. I think all of us deal with the phone call where the physician or somebody, nurse, somebody has called in and patient's on drug X, having the various problems, and sometimes it's pneumonia. And is it or is it not related. Most of the time we think it's an infectious process. Perhaps sometimes it could be drug-related. All right. I think I could stop with this. I think with he have done a long time, and maybe concentration time is getting to the end of that, and we have been here an hour and a half. I thought maybe we would leave plenty of time to maybe discuss some questions.

WAYNE SNODGRASS: That would be great. If any of you have questions out there, please good ahead -- go ahead and send them. We are ready to take questions of any kind.

JEAN CLEARY: We have questions pending?

WAYNE SNODGRASS: We have no questions pending at the moment.

JEAN CLEARY: I did have a couple of questions. Is there any data from EXONODINE in pregnancy?

WAYNE SNODGRASS: There's no data, so remember that this EXONOTIDE is a peptide. It has about 39 IMUNO acids in it. It would be digested. I'm not aware of any data in pregnancy. And that's a very good point because two issues, one is would this peptide cross the placenta, no data. Probably the data is known and I don't know what it is. I would expect that it probably could cross the placenta. But you never know. Placenta is to some extent, it's like drug brain barrier. It's going to cross the placenta. A few exceptions, the GLUCO protein P, there's a drug, a transporter, many forms of it, actually, and that keeps out certain drugs or keeps in certain drugs, depending on which way it's transporting through some tissues, and that can make a difference in a placenta as well as in the barrier. For a peptide like this, hard for me to predict. But I think the concern would be the conservative approach, maybe a transporter to transport it into the fetus.

And if that were the case, particularly in higher dose, an overdose setting in a pregnant woman, then I would be concerned the fetus would be at risk for hypoglycemia. We would maintain the mother's glucose in a reasonable range. I don't know the exact data to address the question here. But I can tell you this, that because this is derived from the venom of the GILA monster lizard, it makes me think of the snake venom, there are a few cases of poisoning in pregnant women, and the fetus was toxic. Or the late pregnancy seemed -- soon to be infant was toxic. Some component of snake venom did cross the placenta. Some are large and others are not. This may well cross and it would be a potential concern.

JEAN CLEARY: Okay. Great. We do have a question. From Marguerite, and she asked if an overdose taken with Tylenol and DULOXETINE, and that's all that I have on here. Not exactly sure what the question

WAYNE SNODGRASS: Maybe the question is, if they are taking it together as an overdose.

JEAN CLEARY: As an overdose, let's try that.

WAYNE SNODGRASS: Sure. That would be similar to, say, again you might compare EFEXOR, if you have a liver toxin in large overdose, Tylenol, you would treat them more or less individually. I'm not aware that one enhances the toxicity of the other. There is some data, and maybe one of the issues in that question would be that if you have an inhibitor, can you block -- there -- welcome to greater risk from the FDA, because the FDA was pushed into this by other political forces, but the point being that this drug, the DULXETINE, I would not expect it to be such an inhibitor. I'm not aware of data that says DULOXETINE blocks CYTOchrome 50. If it did block it, then you would expect decreased acefytominofen. Long-term it become an inducer, if an acute overdose of acefytominofen arrives at the hospital, and they give IV ethanol, that will work, if the patient is known not to be a chronic alcoholic. If the patient had a drink a day, and probably not that, the patient is known not to drink control, a large overdose, ethanol will block the metabolism to the toxic. But the reverse is, if you are a chronic alcoholic, which in the medical arena, that's defined as five drinks or more per day. By the way, 10% of adult white males in the

United States meet that definition. Then if you are a chronic alcoholic, you have induced CYP2E1. So now you are at more risk for it.

JEAN CLEARY: How long would you give the alcohol for, how many hours or days would you do that?

WAYNE SNODGRASS: What I would do in the United States, I would use an ASTIOSITENE, orally, not IV. There are patients where for a variety of reasons it's, you know, it turns out to be just more immediate or sometimes the patient's best interest, but I would use -- if, all I had available waseth -- ethanol, I would give it for three days.

JEAN CLEARY: The three-day period would not start inducing the enzyme?

WAYNE SNODGRASS: No, it's not enough time. Usually you need a couple of weeks to begin to get the induction for ten days or so. Probably by the third day there might be a little induction, you are probably still mostly blocking.

JEAN CLEARY: Here is her follow-up question. If the overdose was Tylenol and DILUXETINE, would you treat tie -- Tylenol at a lower level?

WAYNE SNODGRASS: No, I would not. I would treat Tylenol at the same level. If you are thinking you would treat Tylenol -- the question would you treat Tylenol overdose at a lower serum level, you are thinking it might have induced it. And that's a good point.

What it has been shown to do, these are short-term experiments, doesn't really answer your question, it can be self-inhibiting of the 2E1, if this were 2E1 it would apply, but it's not, so it's not an issue. If it were, the enzyme would activate the acetaminophen. It's metabolized by it over time. So you would think longer term there might be some induction. And then at that time you might treat in a lower level. It's not applicable in this case, there's been no data to the best of my knowledge that it induces CYP2E1.

JEAN CLEARY: Go ahead and send your questions. Dr. Snodgrass is waiting with baited breath.

WAYNE SNODGRASS: Happy to try to happy out. Or if you have had any recent good cases to share with the others.

JEAN CLEARY: Getting back, you mentioned about the vinyl GABA potentially causing liver problems. And would this be a therapeutic value?

WAYNE SNODGRASS: Well, there are data showing that even for not, non-chemical induced liver dysfunction, even for other kinds of liver dysfunction, NAC enhances liver cell repair. So the answer is yes, I would certainly consider it. And there are reasons to think for the vinyl grouping, and liver injury, that it would be worth considering as an agent to give. ANESTOCISTINE.

JEAN CLEARY: what is the --

WAYNE SNODGRASS: There is a little data for that. The -- find what I had on that. I think the dosing intervals, the dosing interval I found published was twice a day, or roughly every 12 hours. So I'm assuming it has a duration of action something in the, at least six to eight, if not ten to 12 hour period of time. So that would be the best guess I have there. Probably is much more specific data that I have, but knowing that it's dosed twice a day would suggest that maybe probably no more than 12-hour duration or action, somewhere in that approximate range. An overdose, all bets are off, right? If you have a 10 or 20 or 30-fold increase amount in this, you might have a greater risk than a hypoglycemia, and it would be rhythmically related to the dose. If you go up by a log, you have probably at least doubled if not more the actual duration of action, in this case of hypoglycemia.

JEAN CLEARY: So the therapeutic or toxicology might be longer?

WAYNE SNODGRASS: Monitoring, monitoring, any drug that could increase the glucose, the risk of brain damage, permanent brain damage from hypoglycemia, monitoring, monitoring, for a drug like this, a large overdose sub Q, sort of like well, okay, that's therapeutic duration of action, but this might be a day. Two days. You know. So you have to really monitor that patient, and be convinced, 24, 36 hours, convinced the glucose is stable. In the meantime, when you have to give extra glucose. That's a very good question from the point of view of the risk factor being might not monitor long enough.

JEAN CLEARY: Another question from Marguerite Campbell. She asked, was BIGLITAN the drug this can prescribe blindness. If prescribed obvious, why?

WAYNE SNODGRASS: BIGAVITAN. On first examination, you think now it's known, in clinical trials it was not discovered because even though they did monitoring for adverse eye effects, this takes a little bit of time to develop. And those clinical trials were not required to be that long. They simply wanted to know if it had efficacy for treating seizures, and resistant type of seizures. It was a drug you used because the patient wasn't in other things. Given all that as part of the benefit risk consideration. Now in the last two, three years or so it's discovered the visual constriction exists, and it exists in more patients than was previously recognized. That does change your risk assessment, so to speak, your benefit risk ratio for prescribing. It does not mean that you don't prescribe it. Not every patient, I may have misled you there, I didn't mean to. Not every patient actually develops this. Not everybody. But what it does mean is that you may well have a patient where they are on one or two other agents, they have a very difficult to treat epilepsy, and because of that you'll try to agent and it happens to work.

And if it works in that patient, and they have real benefit, then you know that you are going to be monitoring the eye grounds, you'll be doing eye exams very frequently. And if that happens to be one of the patients that doesn't develop this, then they can continue on it. But if they do develop it, you know you have to stop and switch to another agent. There are patients where even if we think we know the molecular mechanism of drugs, some patients respond to one drug and not another. I think the best example I can give you is

many decades of clinical experience about the old H-1 blockers, a variety of drugs, some patients respond to one and do not respond to another. And the variability of patient response is unpredictable for a number of different groups of drugs. This is another example of anti-epileptic. You might have benefits, and you closely examine the eyes, and do the field testing, and that patient might benefit from a long time to come from that agent.

JEAN CLEARY: Okay. We have another question from Sharene, and like insulin, does it have poor solubility.

WAYNE SNODGRASS: Yes, it would have poor oral viability, because the peptide it's going to be broken down by peptide agents in the intestine. Giving it orally is not much of an option.

JEAN CLEARY: A follow-up to that. TRIATIDE something you could consider?

WAYNE SNODGRASS: Yes. That's a good question. If you have hypoglycemia risk that is something you could try.

JEAN CLEARY: We have a comment from Marguerite Campbell. Thank you, that was very informative.

WAYNE SNODGRASS: I hope it was helpful.

JEAN CLEARY: Do we have any other questions out there? Please be sure and send them. Do we have anything else? I'll just, while I'm waiting for the questions, we'll just take a little bit of time to make sure that you fill out the evaluation form at the end of this webcast. It does help the technical people for future webcasts. And it also kind of helps us in the way of, you know, is there something different we need to do, do we need to speak up louder, do we need to, you know, look prettier. Anything like that? This webcast will be archived and it should be archived by the end of the week. At the HRSA website, and that is going to be WWW.MCHCOM.com. And our understanding is that it should be up there for the next couple of years for you to enjoy at your leisure. There were also be continuing education credits. It mate be a couple months -- it might be a couple months before we get that together. We are having some logistic problems with that, but continuing education for nurses and pharmacists. Any other comments?

WAYNE SNODGRASS: No.

JEAN CLEARY: Okay. Good.

WAYNE SNODGRASS: Thank you very much.