

Bob Barrett: This is the podcast from '*Clinical Chemistry*'. I am Bob Barrett. Oral fluid testing has gained acceptance over the past decade as an alternative biological matrix for detecting cannabis smoking. Testing oral fluid offers several advantages over the currently available testing paradigms by offering non-invasive and observed specimen collection, making sample tampering more difficult. There is no need for special collection facilities or same sex collectors.

The tetrahydrocannabinol or THC in oral fluid derives primarily from deposition into the oral mucosa following ingestion of oral and smoked cannabis, and later, at much lower concentrations from diffusion from blood. Recently, a different analyte, Carboxy-THC was identified in oral fluid, which is important because Carboxy-THC results from THC metabolism, and is not present in cannabis smoke. The discovery of Carboxy-THC in oral fluid tests suggests actual drug use limiting second-hand exposure as a source for cannabinoid positive oral fluid results.

In a paper published in the August issue of '*Clinical Chemistry*', Marilyn Huestis, Chief of the Chemistry and Drug Metabolism branch of the National Institute on Drug Abuse examined oral fluid concentrations in chronic, daily cannabis smokers during sustained abstinence to maximize the diagnostic sensitivity of oral fluid test results, reduce the potential of passive smoke exposure, and account for residual cannabinoid excretion in chronic, daily cannabis smokers. Dr. Huestis is our guest in this podcast.

Dr. Huestis, what are the advantages and disadvantages of oral fluid over conventional biological matrices like blood and urine for drug testing?

Dr. Marilyn Huestis: Well, oral fluid is a non-invasive and fully absorbed collection. So it offers those large advantages. It also is less safety concerns with using oral fluids than, say, blood, and it offers a unique window of drug detection different than blood and urine. But some of the disadvantages are you certainly collect less oral fluid than you do of urine and the rate of excretion of oral fluid or saliva can vary based on whether or not secretion is simulated or not.

Bob Barrett: What were your objectives in performing this study?

Dr. Marilyn Huestis: This is a very exciting time for oral fluid testing. So oral fluid is the hot matrix right now and it's being considered for driving under the influence of drugs, pain management testing, drug treatment testing, and actually the Substance Abuse Mental Health Services Administration is right now considering whether or not they are going to include oral fluid for federally mandated workplace drug testing. Our objectives were to look in the study at excretion of

cannabinoids in oral fluid of chronic daily cannabis smokers and this had never been done before and it was very important to know what that window of detection was because different programs that would use oral fluid testing may be interested in recent drug use versus long-term detection. So it was very critical that this research be performed so that we could provide scientific information for the people who are drafting drug policy.

Bob Barrett: What is the importance of monitoring Carboxy-THC in oral fluid?

Dr. Marilyn Huestis: Well Carboxy-THC, or 11-nor-9-Carboxy-THC is an inactive metabolite of THC and the critical thought about monitoring Carboxy-THC is because it is not present in cannabis smoke. Therefore it can't come from passive exposure; it comes from actual cannabinoids in the blood that then are transferred into oral fluid. So it offers a way of eliminating the issue of passive exposure and before we did this study that was the main reason. But doing this study provided some important new information about what Carboxy-THC could do for us if we measured it in oral fluid.

Bob Barrett: Why did you utilize two separate analytical systems to quantify cannabinoids; one for THC cannabidiol and cannabinal and other for Carboxy-THC?

Dr. Marilyn Huestis: Really good question. The issue is these are different chemical structures and they are detected by different analytical systems. So the neutral non-polar cannabinoids, THC, cannabidiol and cannabinal are well-detected and present in concentrations that are easily detectable by electron impact mass spectrometry.

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Carboxy-THC on the other hand is a very non-polar substance and it is present in oral fluid in very low concentrations requiring that we do negative chemical ionization detection by mass spectrometry. And another major issue was being able to extract all of these compounds that are from very different physical chemical characteristics in one extraction which we were able to achieve.

Bob Barrett: Are such low concentrations of Carboxy-THC important, and how did you accomplish this analytically?

Dr. Marilyn Huestis: Well, we developed a solid phase extraction procedure that was able to elude all of these different cannabinoids and then as I just mentioned, we used two different analytical systems to detect them, and it turns out that such low concentrations of Carboxy-THC are very important not only

to rule out passive contamination from cannabis smoke in the environment, but it turns out very important for eliminating and reducing the detection window in chronic daily cannabis smokers.

Bob Barrett: Why would characterization of cannabinoids in oral fluid of chronic cannabis smokers be important for interpreting test results?

Dr. Marilyn Huestis: It depends on the purpose of your drug monitoring program. So if you're interested in workplace drug testing which is what's being considered and developed right now by SAMHSA, then you are interested in the longest drug detection window possible, but you definitely want to rule out passive exposure. On the other hand, if you are interested in driving under the influence of drugs, you want to know about recent cannabis use. You don't care that someone used the drug a week or two weeks ago; you want to know if they used the drug recently that would affect their ability to drive a car.

In pain management, where samples aren't taken frequently, they also are interested in a very long detection window. In drug treatment, which many Clinical Chemistry laboratories are involved in drug monitoring, you would like an intermediate period of detection because if it's too long, you don't know when the person relapse and you will receive multiple positive urine samples, for instance, after one drug relapse.

Oral fluid offers the opportunity to have a shorter detection window, so you could monitor more closely when people actually relapse. So it depends on the purpose of the drug monitoring program on whether you want a long or short detection window. And by monitoring more than just THC delta 9-tetrahydrocannabinol, the primary psychoactive component in cannabis, you can tailor the detection window for the purposes of the program.

Bob Barrett: Okay. So for how long did chronic cannabis smokers stay positive for THC under continuously monitored abstinence with their analytical THC limit of quantification of 1.5 micrograms per liter?

Dr. Marilyn Huestis: Chronic daily cannabis smokers were positive as long as 24 days. This was a real surprise. It had never been seen before. But recently, we have shown in these individuals who build up very large body burden of cannabinoids in their system. We have shown extended detection windows in whole blood, plasma, urine, and now in oral fluid. So although most chronic daily cannabis smokers, and that's really important, this is not your typical population. These are individuals who are using in this study up to 10 cannabis

joints per day for as long as 10 years. In this cohort of individuals, you could have positive tests as long as 24 days. So this might be a positive attribute for workplace drug testing, but a serious limitation for driving under the influence of drugs.

Bob Barrett: What is the SAMHSA proposed cannabinoid cutoff in oral fluid and what are the oral fluid cannabinoid cutoffs currently being used in the driving under the influence of drugs, alcohol and medicines program?

Dr. Marilyn Huestis: So in 2004, SAMHSA proposed a screening cutoff for THC, of four micrograms per liter, and a confirmation cutoff of two micrograms per liter. However, those proposed cutoffs were never put in place, and we have had an additional seven years of research which have really added to our scientific database for proposing cutoffs.

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So although those were proposed by SAMHSA, everything is being considered right up to the minute on the latest research and I think it's quite probable that those cutoffs might change.

In Europe, in the European Union, they have a very strong program. They are already using oral fluid testing on a routine basis for driving under the influence of drugs. And in their program, they are using a one microgram/liter cutoff concentration. That is a confirmation cutoff compared to the SAMHSA proposed two micrograms/liter. They don't require that you screen at a higher cutoff; they just require that you confirm at the one microgram/liter level.

Bob Barrett: So with these higher cutoffs, what are the detection windows for cannabinoids and oral fluid in the chronic cannabis smoking population?

Dr. Marilyn Huestis: So what we found was that using a one microgram/liter like DRUID, we had most people who were negative within 96 hours, but two individuals were positive for a much longer period of time. And at the higher proposed 2 micrograms/liter SAMHSA cutoff for just THC, we've the same program with detection for a very long in the terms of 24 or more days.

But if we combined THC with Carboxy-THC cutoff of 20 nanograms/liter, we could reduce the detection window to less than 48 hours. And also if we included cannabidiol or cannabinol, we could reduce the detection window to less than 24 hours. So there is very good reason for including multiple cannabinoids rather than just THC to define your detection window.

Bob Barrett: What are the goals for oral fluid testing in these two different programs?

Dr. Marilyn Huestis: Well, for SAMHSA, it's specifically directed toward workplace drug testing, and the interest there is for the longest detection window that the biological matrix can offer you. However, for workplace drug testing, you certainly don't want there to be any concern about passive contamination.

For driving under the influence of drugs, you want the detection window to be shorter matching the intoxication or impairment window. So they have quite different goals.

Bob Barrett: Are there other programs that might benefit from oral fluid testing for drugs of abuse?

Dr. Marilyn Huestis: Absolutely. There are many programs. Almost any possible idea of drug monitoring could use oral fluid testing. So for instance, in drug treatment programs, where they right now are primarily using urine testing, oral fluid offers many advantages for them.

First of all, most treatment programs have observed urine collections, and this is very difficult for both the donor as well as the staff. It also means for a personal point of view that they have to have men available to collect specimens for men and women for women.

An oral fluid test can be performed by either gender and it's fully observable, meaning that there is much less possibility for adulteration. In drug treatment programs, we know there is a high incidence of adulteration of urine samples.

So oral fluid testing offers great advantages for drug treatment. And as I was discussing earlier, based on the cutoff you select, you can make an oral fluid testing window of detection more like 48 hours or 72 hours and this would be very helpful, because if an individual uses drugs on a Sunday afternoon, they will be positive on Monday and this will bring up discussion between the counselor and the individual about the relapse and the causes and results of that relapse. But when they come in on Wednesday with a urine test, they are very likely to be positive again, and now the counselor does not know whether they relapsed a new or whether the positive in urine is due from the use previously.

Oral fluid testing generally would give you about a 48-hour window of detection, so that you would know if they were positive on Wednesday, they probably used again. So this is another example. Pain management is another possibility

and forensic accident investigations, other programs might really benefit from this new technology.

Bob Barrett: What physiological factors could contribute to residual cannabinoid excretion and what do you expect THC detection windows in occasional cannabis smokers to be?

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Dr. Marilyn Huestis: The more cannabis that an individual uses, the larger the store of cannabinoids in the body tissues. Cannabinoids are very lipophilic and you build up a large depot in your body when you continually use the drug.

If an individual has a large body mass, they may have more drug stored in their body, and certainly, we believe that one of the factors that contributes to residual cannabinoid excretion is exercise. There are not very good research studies to support this, but there is a tremendous body of literature. I am called by medical review officers almost once a week saying they have a chronic daily cannabis smoker who is been in abstinence and in treatment and been monitored on a regular basis with numerous negative samples. Then they begin to exercise and lose weight and suddenly they produce a positive result. And it's believed that this is the release of this cannabinoids that are stored in the body. So that's one factor that could contribute to this residual excretion.

So in occasional cannabis smokers, we're doing that research right now and I can tell you preliminary non-published data that we're finding surprisingly some individuals to be positive longer than 22 hours.

So we had thought that in an occasional user, the detection time would be something less than one day. So we're doing additional research that should be completed by the spring that will tell us fully what this occasional cannabis smoker window of detection is.

Bob Barrett: In the paper, large into personal variation in cannabinoid oral fluid concentrations as well as detection times reported, what could cause such variability?

Dr. Marilyn Huestis: That's a really good question and I don't know that we have all of the answers to that. Certainly, body mass is one factor, exercise is another factor, but the biggest ones are going to be the amount of cannabis they use on a daily basis so the frequency of use and then certainly the chronicity of use and the length of time that the individual has been using the drug are the primary factors.

Bob Barrett: Well, finally, Dr. Huestis, what other areas of Clinical Chemistry and laboratory medicine can potentially benefit from including oral fluid testing?

Dr. Marilyn Huestis: I think we've discussed many of them, but also there is a very good use for this in the routine annual checkups with individuals, using this as part as physician care, if they are concerned or suspecting that drug use might be a component of their patient's issues or problems, oral fluid testing would certainly be easily incorporated into the physician's office, and even in small laboratories. There are onsite detection devices being developed, so that it will be easy to perform even, for instance, at the work site. It may not even be necessary for individuals to go to a large collection facility or to a large laboratory. These devices can collect oral fluid and screen them and then if positive, confirmatory specimens would need to be send to a laboratory that could perform mass spectrometry. So there are really many, many possibilities for this technology, improving our ability to monitor drug use in the population.

Bob Barrett: Dr. Marilyn Huestis is the Chief of the Chemistry and Drug Metabolism branch of the National Institute on Drug Abuse. She has been our guest in this podcast from '*Clinical Chemistry*'.

I am Bob Barrett. Thanks for listening.

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