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Are THC Levels in Oral Fluids and Blood Plasma Comparable after Oral Ingestion of Edibles Containing Cannabis or THC?

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Guest: Dr. Bertha Madras is a Professor of Psychobiology at Harvard Medical School at McLean Hospital and is cross-appointed at Massachusetts General Hospital.

Bob Barrett: This is a podcast form *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

The recreational use of marijuana has become legal in many states. Questions remain about the legal limit of cannabis-induced impairment. THC, the psychoactive component of cannabis, alters thinking and perception, increasing risk for accidents and fatalities on the road and in the workplace. Understanding how THC concentrations change in the body after the exposure to different forms of cannabis is important for determining who is too high to drive.

There has been a shift from inhaled or vaporized use of cannabis to oral ingestion, but there is a serious void of associated data with implications beyond impaired driving. Ideally, there would be a defined limit for impaired driving and accurate roadside test available as is the case for alcohol. However, the biology of THC is complex and not much is known about how THC concentrations vary over time in oral fluid, and how onsite oral fluid screening devices performed following edible cannabis administration.

In the March 2017 issue of *Clinical Chemistry*, original research by Dr. Marilyn Huestis and her team addresses some of these knowledge gaps related to edible cannabis use. The issue features an expert commentary of this article provided by Dr. Bertha Madras, who joins us for this podcast. Dr. Madras is a Professor of Psychobiology, Harvard Medical School at McLean Hospital, and is cross-appointed at Massachusetts General Hospital. She has edited several books on the brain and addiction and authored the 2015 WHO report "Update of Cannabis and its Medical Use." She is also the Former Deputy Director for Demand Reduction in the White House Office of National Drug Control Policy.

Dr. Madras, what did the Dr. Huestis' team find, and why is this important?

Dr. Bertha Madras: I think the most important thing is to understand why she did the study in the first place. She did it because the excursions of blood or oral THC levels, after one ingests cannabis, either by smoking or by eating edibles, it's become a very important issue in terms of traffic accidents, traffic fatalities, as well as in the workplace. So being able to measure THC levels with some accuracy is critical. What she did was hone in on three areas that are really very poorly understood.

The first area was, "How do oral THC and blood -- how do they compare after you eat edibles?" That's important because it's now apparent that about 30% of all marijuana or cannabis that's being consumed is being consumed by eating rather smoking or vaping, and there's a huge void in the literature on this. So what she did was do three things. She excavated the literature and looked at what was found with regard to blood and oral THC after edibles.

The second thing she did was review the findings of devices that try to address the amount of THC in your body onsite, right after an accident. The third thing she did was actually conduct her own experiments on people, after eating cannabis preparations, a cannabis brownie in this case, and she tried to see what levels of oral THC or blood levels can you measure and how accurate are they. All of this was done designed to address a very compelling and contemporary problem with regard to the growing use of cannabis throughout the country.

What did she find? Well, she found that it's very difficult to do -- I mean that's the first take-home message. She found that there was a lot of invariability between different subjects in terms of oral or blood THC after they consumed edibles. The blood levels were erratic. They were unpredictable, and there was a not very strong relationship to how much THC they had consumed. The other thing she found is that oral and blood THC concentrations are poorly correlated following consumption of smoked or vaporized or edibles or medically-approved dronabinol. Essentially, the conclusions are that oral fluid concentrations don't reflect blood concentrations, and yet there are advantages of measuring them in oral fluid, because you can measure recent intake and it will not be confused with whether or not you've used prior -- in other words, it will not be confused of whether or not you have a long history of using cannabis or you've just started recently.

So that was number one finding. The second finding was, how do these devices measure up, these sorts of roadside testing devices? What she found is that the cutoff points are fairly high to get very good reproducibility. So, if you put a

cutoff point between one and two micrograms per liter, or nanograms per ML, you're not going to get a high level of sensitivity and specificity for these two screening devices. The best cutoff points are at five micrograms per liter, five nanograms per ML. So sensitivity and specificity was achieved at greater than 80% with these high cutoff values.

That's a problem, because there is enough indications that five microgram per ML levels may be too high. You may have to go down lower, between one and two, to really get good correlation with impairment. That's probably going to cause some concern with experts who feel that you have to be below that cutoff point to really address whether or not you're getting a correlation with impairment.

The third study, as I said, is the one she did with her own subjects in a laboratory setting. That was a very important one because she -- under very controlled trials, subjects were given brownies laced with THC. What she found, fascinatingly, is that in contrast to blood THC levels which reflect combined use of prior use with immediate use, the oral fluids only seem to reflect what was used immediately, so that you can read out differences between heavy long-term users and immediate users by using oral fluids and not blood levels. So I think that's a very important finding.

The second finding she found in her own experiment is that the monitoring 10 hours after consumption, THC concentrations were similar for both frequent and occasional users, throughout the time course of monitoring. So even if you monitored one hour or you do it at five hours later, there is a parallel between immediate users, or not chronic users, and those who are, so that there's a level of inherent accuracy in using oral fluids after ingestion of cannabis that you would not necessarily find with blood levels, so that sensitive roadside devices, if you confirm with oral levels as well, you would get a fairly reasonable picture of whether or not the individual has been using recently.

The other obvious conclusion is that mismatch between oral and blood concentrations make blood confirmation unreliable and maybe even unnecessary. That is essentially what she found. As I said, in terms of the relevance of this, policy changes that increase cannabis use are likely to generate a broad spectrum of an unintended consequences. These consequences can range from impaired thinking, perception. It can compromise driving, performance in the workplace, and other elements of daily life.

At this point, we need accurate methods to find out if the quantities of THC are in oral fluids or in blood, and especially for a growing use of edibles, how fast it clears the body, and

most importantly, whether or not the levels correlate with traffic accidents, fatalities, workplace injuries, lower productivity, and all of this. The measurements are also, they could be at the heart of forensic legal battles over medical and psychiatric consequences. Also, it's really important in the future, because right now we have no regulations in terms of, very few regulations. And in the future, it will be important to apply this information to help guide the forming of regulations with regard to THC content in marijuana.

Bob Barrett: Doctor, how accurate are the current methods to analyze for THC and cannabis? Why focus just on THC and not the other hundred or so cannabinoids found in the cannabis plant?

Dr. Bertha Madras: That's an excellent question. The accuracy in the analytical lab is very high. The real question is, how accurate is it in terms of roadside testing, and what are the limits of measuring it in oral fluids, which is much more accessible than blood draws and all that, with regard to the forensic and legal issues. The accuracy in the analytical lab is high. The accuracy on roadside testing is less than ideal, currently, with these two devices that have been developed.

It's clear that if you want accurate levels, you basically use oral fluids which are easily attainable in roadside without having to have a specialist who's going to do the blood draw. So, I think that's a tremendous advantage. But the real question is, why THC? Why not some of the other 100 or -- the last I counted was 104 -- cannabinoids in the cannabis plant?

THC is primarily the root of the psychoactive and impairing effects of a cannabis plant. All of the other cannabinoids are of a lesser significance in value because their concentrations are very low. And if you extract the THC from cannabis and compare it to marijuana, whole plant, you'll get very similar effects, and you can block the effect of THC by just using an antagonist for its known target which is the CB1 receptor.

THC, however, does get converted into 11-Hydroxy-THC, which is an active metabolite. So, measuring 11-Hydroxy-THC is also quite important. In your worst case scenario, if you don't have analytical chemical lab beside you and you want to the roadside testing, measuring THC is a good first approximation. But if you want to have very exquisitely detailed analytics, you would have to measure -- in terms of psychoactive properties, you would have to measure 11-Hydroxy-THC which is a metabolite.

The second cannabinoid, in terms of concentration in the plant, is cannabidiol. Cannabidiol is a very intriguing molecule. It resembles THC chemically. It has one less ring, but it is not psychoactive. It has candidate therapeutic properties without psychoactivity and unlike THC, it does not produce psychoactive effect. It has no known addictive potential. It is not psychotomimetic. In other words, it does not induce sensations of psychosis in individuals who are prone to it, or even if they're not.

It has anti-seizure activity whereas THC could be pro- or anti-seizure. So, it has effects that are opposite to THC, but because it has no abuse liability and no psychotomimetic effects, measuring it is not that important if your objective is to identify a metric that could be related to impairment and to adverse consequences.

Bob Barrett: Why is it important to measure oral fluid levels of THC in roadside testing devices?

Dr. Bertha Madras: It's really important. They obviate the need for a medically supervised blood draw, and they obviate the need for a lengthy time to store, deliver, and process the sample offsite, and all of these things could compromise the findings. So, if you could validate oral fluid roadside testing, you would have something that is much more convenient and potentially much more accurate.

Bob Barrett: Are traffic accidents and fatalities increasing in states with legalized cannabis, and do all states have uniformed standards for testing THC?

Dr. Bertha Madras: Traffic fatalities and accidents that are associated with cannabis are increasing. In Washington state, the data is clear, and also in Colorado. So that it's really important to be able to gather statistics on the amount of THC that could correlate with these traffic accidents and/or fatalities. The problem is that states do not have uniform standards for testing of THC and they do not have uniform cutoff points. Some of them have one to two nanograms per ML. Others have five. Others have ten. So, without a uniformity as there has been in the federal government for alcohol standards, which have a fairly general consensus among all the states, we don't have it with THC. That is quite unfortunate, because it creates chaos with regard to data collecting and robustness of the data. The less data that you can combine from different states, the less robust the statistics are.

Bob Barrett: Roadside testing for alcohol is fairly easy. You get out, you blow in the thing, and they tell you whether you're over the limit or not. Is roadside testing that easy for cannabis?

Dr. Bertha Madras: It's quite the opposite. Roadside testing for alcohol consists of two components. One is the breathalyzer test, which is fairly accurate and reproducible. The reason the advantaged alcohol has, if I can apply a misnomer to it, because it is freely distributed in liquids and fluids and organs all over the body, what you see in your breath is what there is in the brain. There is no mismatch between breath and brain.

The problem with cannabis is that there's clearly a mismatch between oral fluids and blood fluids, and there is a fairly growing sense that there is a mismatch between what's in the blood and what levels are in the brain that could be impairing. So the mismatches with THC in terms of oral fluids, blood levels, brain levels, is much greater than alcohol and THC is converted to 11-Hydroxy-THC which is active as well, whereas alcohol's metabolites are not active. The other problem in that comparison is that when you use cannabis, either by smoking, or by oral ingestion by edibles, you get different levels of the active metabolite. You'd get a different rate of conversion of THC to 11-Hydroxy-THC. So, it's a far more complicated picture. I think Dr. Huestis is one of the giants in the field, pioneering in trying to develop scientific evidence to standardize testing and, at least, to acknowledge the strengths and weaknesses of our current testing methods.

Bob Barrett: Just to quickly follow up on that and close this out, does eating cannabis-laced brownies or other edibles, have the same effects to the body as smoking or vaping?

Dr. Bertha Madras: It's a problem because smoking or vaping gives rise to immediate responses. The sensations are felt within 15 minutes or so. The duration, the most robust duration can be about three or four hours and then it wears off. With edibles, the onset time is much longer. It takes much longer to get to the brain. It has to go through the liver. There's a whole different pharmacokinetic picture than there is with vaping or smoking. The oral bioavailability is lower than it is for smoking. It's considerably lower, depending on the individual as well as the type of edible. So that the onset time is much longer, it takes much longer, and the duration could be much longer as well. Because somehow what is in the digestive tract or in other depot sources in the body, they just leach and leach out over a much longer period of time.

The interesting thing about this is that there have been much more reports of -- increasing reports of emergency department mentions due to oral cannabis, because people buy a brownie and they're instructed to eat one eighth of it

and of course, they take a bite and it's sweet and it's tantalizing, and they don't feel anything.

So they think that whoever gave them the advice to just eat a fraction of it is wrong, and they'll take another bite and another bite and other bite and pretty soon the entire brownie is consumed. Within three hours, they are in a state which is very different than the smoked state or the vaper state, because they haven't titrated their doses and they haven't been aware of the long onset time and the long duration of effect.

Bob Barrett: So if they made these things taste like castor oil, they'd be a lot better off?

Dr. Bertha Madras: Precisely. When you look at the edibles, you find that almost invariably, they are laced with a sweet taste. Either liquids, lollipops, gummy bears, or brownies or cakes, it is a deliberate source of marketing, because it is so much more tantalizing to eat something that's sweet which is almost universally appreciated by people, and the cost/benefit equation is just emerging now in terms of the high cost.

Bob Barrett: Dr. Bertha Madras is a Professor of Psychobiology, Harvard Medical School at McLean Hospital, and is cross-appointed at Massachusetts General Hospital. She's been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barret. Thanks for listening.