

Transcript of FDA Press Conference on Issues Related to Codeine

FTS HHS FDA

Moderator: Susan Cruzan

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Coordinator: Good morning and thank you for standing by, at this time all participants are in a listen only mode.

After the presentation we will conduct a question and answer session, to ask a question at that time please press star 1.

Today's conference is being recorded, if you have any objections you may disconnect at this time.

I'd like to introduce your host for today Ms. Susan Cruzan, ma'am you may begin.

Susan Cruzan: Thank you all for joining us today, this is part of FDA's ongoing effort to communicate about drug safety issues.

And today we will be discussing issues related to codeine, joining us today are Dr. Janet Woodcock, Commissioner and Chief Medical Officer for the Food and Administration and Dr. Sandra Kweder the

Deputy Office of New Drugs and Center of Drug Evaluation and Research with FDA.

Dr. Woodcock and Dr. Kweder will provide brief remarks and then we will open this up to Q&A for the media only and we'll need you to provide your name and affiliation.

I will now turn this over to Dr. Sandra Kweder, thank you.

Sandra Kweder: Good morning everyone, today we are - FDA is issuing a public health advisory about another area where we have - there is a clear evidence that genetics and genomics can influence people's individual's metabolism of drugs.

We have some important new information about a very rare but serious side effect in nursing infants whose mothers take - are taking codeine.

And differences in drug metabolism among mothers taking codeine can - the evidence clearly shows can contribute to side effects in nursing infants.

To be more specific infants of nursing mothers who are taking codeine may have an increased risk of narcotic particularly morphine overdose.

If the mother is an ultra - what's called an ultra-rapid metabolizer of codeine? When codeine enters the body and it gets metabolized it actually changes as a normal process, it changes to morphine and it's actually the morphine that relieves pain.

There are a lot of factors that affect codeine metabolism and problem one of the most important is a person's genetic makeup.

Some people have a variation and a liver enzyme that can change the codeine to morphine more rapidly and more completely than it does - that happens in other people.

These - so hence the term that these people are called ultra-rapid metabolizer's.

And ultra-rapid metabolizer's are more likely to higher than normal levels of morphine in their blood when they use codeine at usual doses.

So nursing mothers taking codeine, may also - who are also, rapid metabolizer's may also have higher morphine levels because it's higher in their blood in their breast milk.

And these higher levels of morphine and breast milk obviously can affect the baby and can lead to very severe even life threatening side effects in nursing babies if they are not addressed.

Unfortunately in most cases because of the lack - because this has not really been paid a lot of attention to before, most people don't know if they are an ultra-rapid codeine metabolizer.

Now just too kind of take a step back, codeine has been used safely for many years in nursing mothers.

It's an ingredient and many prescription pain relievers and even in some over the counter cough syrups.

And it's once the body changes codeine to morphine, it's the morphine that relieves the pain or the cough, and also is responsible for a lot of the side effects that people experience like you know some - what may a little bit of drowsiness or some constipation.

However infants, who are exposed to very high levels of morphine through breast milk, can experience those side effects very severely and in fact get an overdose of the drug.

Our - this was really brought home to our attention in a medical journal last year that described a 13 day old breast feed baby who died from a morphine overdose.

That babies mother was actually taking less than the usual amount of codeine that's normally prescribed for a - you know standard pain and for episiotomy.

And laboratory testing clearly showed very high levels of morphine in the baby's blood and that the genetic testing showed that that baby's mother was clearly an ultra-rapid metabolizer of codeine.

So we're issuing this public health advisory to inform health care professionals and nursing mothers about some key pieces of safety information.

First, when prescribing codeine for a nursing mother as is commonly done, doctors should prescribe the lowest dose for the shortest amount of time to relieve the symptoms being treated.

And doctors should talk to their nursing patients about how to recognize signs of high morphine levels in themselves, but especially in their babies.

Second, if you're a nursing mother taking codeine call your doctor if you become extremely sleepy to the point where you're having difficulty taking care of your baby.

It could be a sign that you're metabolizing the drug more rapidly than most people.

Third, for newborns - breast babies particularly usually nurse every two to three hours and don't usually sleep for more than four hours at a time.

So babies show sign increased sleepiness, difficulty breastfeeding and especially breathing difficulties or limpness nursing moms should call the babies doctor immediately.

And if that doctor can't be reached, the baby should be taken to an emergency room or - right away.

And finally nursing mothers should obviously talk to their doctors if they have any questions about their pain medicine in particularly codeine.

Just a couple more points, how - you know one question that comes up is how common is this ultra-rapid metabolizer profile in people.

It varies a lot - it appears to vary a lot among different population groups, the range is you know from less than 1 in a 100 to in some - you know sub group countries or ethnic groups up to 28 per 100 people most of the studies are on the small side that describe this.

But and so - but the real point is that anyone can be an ultra-rapid metabolizer without knowing it.

And the only way to know if you are is with a genetic test, there is a FDA cleared test that's pretty widely available in specialty labs to determine whether a patient is - has this genetic profile.

But there is not a lot of information about its uses in the general population and looking specifically at you know its application to codeine.

And our message is while the test is widely available and we expect it to be more - better developed for this particular use, its not - it can be useful but not a substitute for a doctors judgments.

We have asked the makers of prescription codeine containing products, to include information about these differences in codeine metabolism and particularly considers with breastfeeding in all their drug labels.

The use of codeine products to manage pain afterbirth is very common, and fortunately in FDA's databases reports of serious side effects in nursing infants are extremely rare.

The only death report that we're aware of is the one that was published last year by a group in Toronto.

But nonetheless these are preventable side effects and so the doctors who prescribe codeine need to be aware of the potential for the risk to actually transfer because of the mother to safety concerns in the baby.

I'll now stop there and turn it over to Dr. Woodcock.

Janet Woodcock: Thanks Sandy, so I'm going to talk a little about the general implications of this, this is another example of the scientific basis for why some people get side effects from a medicine where other people don't.

And current - one of the interesting facts about codeine there is also a group of people who don't metabolize it at all and while they don't get any side effects from codeine, they also don't get any pain relief.

And so then we see two sides of the story here with codeine, sometimes very serious side effects could occur in these ultra-rapid metabolizer's, and other people the drugs is actually ineffective.

Now yesterday we did an announcement about Warfarin the blood thinner, and again some of the genetic basis of differences in dosing in people that could lead to either side effects in some people, or lack of effectiveness quickly in other people.

And this is a theme that we are trying to develop that looks at the scientific basis for why people respond differently so that we can predict and then prevent safety problems in people that are based on these known mechanistic causes.

As this is - this effort is part of our critical path initiatives, and the critical path initiative seeks to rapidly apply new science. In this case to genomic science but there is a lot of other new sciences were trying to apply to drug development and evaluation.

So with - in the case of case of Warfarin and codeine these are very old drugs they've been around quite a long time. But we can apply new science to them and we think make them safer.

In drug development, we can apply the same new science to drugs that are just being studied and investigated and have more information on how to use them properly and how to dose them properly in the population.

So that is our overall goal in the critical path initiatives, and I think this codeine today is a very good example of how we could prevent (sight) through knowledge - various side effects.

So I'll close there.

Susan Cruzan: We can now open it up to questions from the media, if you could state your name and affiliation, thank you.

Coordinator: Thank you we would now like to start the question and answer period, if you would like to ask a question, please press star 1. To withdraw your request you may press star 2.

Once again to ask a question please press star 1, one moment please.

(Lisa Richwine) from Reuters you may ask your question.

(Lisa Richwine): Hi thanks for taking my question, I wonder if they can tell us how many companies make these products, and mention who some of them are - are they all generic products?

And then you mentioned that there would be - you asked for a label change in the prescription products I wondered if anything would be going on over the counter products?

Sandra Kweder: I'll take that, there are dozens of companies that make codeine - codeine containing products.

I actually can't give you a number but there are many because most of them are generic products.

(Lisa Richwine): Okay.

Sandra Kweder: And yes you know I did say in the prescription products, but we expect that the over the counter products anything that contains codeine will contain - would contain similar information.

(Lisa Richwine): Okay thanks.

Susan Cruzan: Next question please.

Coordinator: Next question is from (David Brown) of Washington Post.

(David Brown): Yes thank you, can you give a little bit more idea of what the population prevalence of this genetic trait is in different racial and ethnic groups.

And also is this in a vaccine with other opioid's or it only with codeine?

Sandra Kweder: Those are two great questions, (David) I'll take that, first on the population prevalence if you just - so you have it in writing, we do have in our posted Q&A's on codeine, we have a table that describes that.

In Caucasians the estimate is about - it's a very - it's a broad estimate anywhere from 1 to 10 per 100 people - 1 to 10%.

African Americans it's probably on a lower end of that around 3%, Hispanics and Asians groups that have been looked at around very low around 1%.

Interestingly in North African Ethiopians in Saudi Arabia it's much higher, it's in the ballpark of - the list - the numbers I have here are 16 to 28% so that addresses the populations.

As far as the other products you - there is ultra metabolism absolutely can affect other narcotics the same set of enzymes.

You know things like Oxycodone or Hydromorphone, the difference here is that they are not converted directly to morphine, and it's the

morphine that really seems to be most is expected to be most problematic in breast milk in infants.

So it's - there is less complete information, on the other - about the metabolism profile.

On the other hand, you know those medications and the side effects of those that occur in the woman who is breastfeeding - is nursing can also - when the blood levels are too high that can also be transferred but it can also be transferred through breast milk to babies.

So the same clinical advice applies anytime a woman is taking any kind of a narcotic who is breastfeeding a baby, the baby needs to be watched carefully for any signs of ill effects and appropriate medical oversight needs to be assured.

(David Brown): So given that fact is the advice or the recommendation that actually any breastfeeding woman could go to the newborn who is prescribed an Opioid should actually get this tested before she starts taking the drug?

Sandra Kweder: I don't - that is not, that is not - that's not advice that we feel we have enough evidence to give very broad right now.

Because this is - codeine containing products are actually the most commonly utilized products in new moms.

They tend to be, the drugs doesn't hang around for a very long time, it's metabolized you know it's usually clear from the system very quickly, and it's been safely used for decades.

But this is just - clear - our point is pay attention.

(David Brown): Okay, thanks.

Susan Cruzan: You want to add something Dr. Woodcock?

Janet Woodcock: No I'm okay, I'm okay.

Susan Cruzan: Can we have the next question please.

Coordinator: (Jennifer Corbin) from Dow Jones you may ask your question.

(Jennifer Corbin): Oh thanks, most of my questions have been answered but one question I had I just want to make sure. You talked about codeine being changed to morphine?

Sandra Kweder: Yes.

(Jennifer Corbin): But what about if you're given morphine originally is it the same type of drug or not necessarily?

Sandra Kweder: Yes actually it is the same class of drug.

(Jennifer Corbin): Okay.

Sandra Kweder: And the reason people use codeine and morphine can't be taken - morphine it's not as readily available when taken orally in kind of a standard form, it's more common to use it you know intravenously.

But the normal path of metabolism is that codeine gets converted to morphine, and if there is morphine in the blood it can get into the breast milk.

(Jennifer Corbin): Okay.

Sandra Kweder: The conversion here of interest though is the codeine to morphine.

(Jennifer Corbin): Right.

Sandra Kweder: So if you're taking morphine metabolism or morphine is not the issue, it's the metabolism of the codeine to get to morphine in this case - does that help?

(Jennifer Corbin): Yes, yes it does.

Janet Woodcock: Yes because - this is (Janet), because the codeine is dosed, and this is kind of what we were talking about with Warfarin yesterday, codeine is dosed on a population basis.

And what you would do with these ultra-rapid metabolizer's is you'd give them less if you knew.

(Jennifer Corbin): Right.

Janet Woodcock: Okay, so with morphine - morphine doesn't need to be converted to morphine it always is morphine.

(Jennifer Corbin): Morphine.

Janet Woodcock: So that dose based on morphine but because it isn't absorbed very well when you give it by mouth - morphine, people give codeine instead and then it turn over.

In most people it sort of slowly turned over to morphine, and therefore you get kind of a nice level of morphine.

These ultra-rapid metabolizer's very rapidly turn it over to morphine and you get a real jolt.

Susan Cruzan: Can we have the next question please.

Coordinator: Next question is from (Anna Matthews).

(Anna Matthews): Just briefly is this is the first time a public health advisory has flagged the genetic factor or have you guys done that before?

Sandra Kweder: Public health advisory we - well we flagged yesterday in our announcements about Warfarin.

(Anna Matthews): That's a good point.

For that has there been any?

Woman: You know I don't recall - honestly (Anna) I don't recall any (Janet) do you?

Janet Woodcock: No I'm racking my brains here you never say never, but it certainly - these are - we really going into new territory here, and the reason

frankly is because of the new signs we actually have test that can identify these things, so we're talking about something real.

This is all real science, we understand this relationship because we have the genetic test and we can rapidly identify people who have these traits.

Before and that's the point, before we could say well we've observed this bad side effect, but we wouldn't have a explanation.

Susan Cruzan: Okay can we have the next question.

Coordinator: Next question is from (Joann Siberner) of NPR.

(Joann Siberner): Hi thanks for taking the questions, two questions here, one is did I understand you correctly that codeine containing compounds of the most frequently used products for new mothers?

Sandra Kweder: You know - we don't have any (Joann) I did say that and I don't have any statistics on that but they are widely used and many obstetricians prefer them because they are - because they are usually kind of short acting, they are usually in combination with something like you know acetaminophen or even ibuprofen.

So there - you know one of the oldest and sort of tried and true types of pain medicine utilized.

(Joann Siberner): And the indications are episiotomies and...

Sandra Kweder: Sort of any - almost kind of pain you know you can think of, you know any type of postpartum pain maybe it's after an episiotomy perhaps it's after a C-Section when you know the patients just you know still got some post operative pain.

(Joann Siberner): Great and then the second question is on the test, how much does it cost and how long does it take?

Woman: The genetic test.

Sandra Kweder: Right the genetic test, I do not have information on the cost of the test, usually - it's not something that you'd necessarily you know go to your standard lab to get, but it's available in some larger laboratories.

And I honestly don't know how long it takes (Janet) do you have a better sense of that.

Janet Woodcock: No I don't but I would call the lab and ask them what test would I be asking about.

Woman: 2D6 - (unintelligible) 2D6.

Woman: Okay thanks.

Sandra Kweder: CYP 2D6 Metabolism it's a liver enzyme and I don't know - you know we should probably be able to get the - there is a commercial name for this test, I don't recall it.

Woman: Right.

(Joann Siberner): Okay, thanks.

Janet Woodcock: So I think - 8, 10 it's actually pretty widely available and in fact with these types of - this type of information such as we're providing today becoming more common for various things, this type of testing is going to become more available and rapidly - fairly rapidly available.

Sandra Kweder: Yes, yes.

Susan Cruzan: Thank you can we have the next please.

Coordinator: Next question is from (Andrea Owen) of ABC News.

(Andrea Owen): Hi thank you for taking my question, just a question on the 13 day infant, when did that happen and was that totally contributed to the mother having this rare genetic makeup?

And also have there been other such cases recently?

Sandra Kweder: That's actually a good question, the case is actually published by a group in Toronto really one of the best clinical pharmacology and pregnancy groups that's around Gideon Koren K-O-R-E-N is the first author.

And I was published last year in the lancet, it came to our attention more recently and when we took a look at that case, these authors - investigators had really done a very, very, careful job of documenting that there was no question that this was a clear cut case of ultra-rapid metabolism in a mother it's a really very dramatic case.

We've had our experts in pharmacokinetics and pharmacogenomics look at it as well as some groups from the outside.

And we are all in agreement that this is really the first report - case that's so well reported.

We also went back and looked through FDA's adverse events database looking for any reported cases that we might have of a similar adverse affect.

And we were unable to - we were unable to find anything this clear cut. So the answer is no, nothing more recent.

But after our look at the science that went into this particular case report, we felt that it's really worth highlighting to the public because it gives us a window into the future of genomics and personalized medicine.

And also in the case, you know this is a preventable adverse event, and people can get a sense of whether or not they may have a problem simply by watching their baby, and also take care that they don't have a problem by watching their baby.

(Andrea Owen): Why has there been like other injuries related or reported related to this?

Sandra Kweder: Not that I am aware of, our focus today is clearly on the breast fed infants, but there is no question but that some people have much more dramatic side effects to codeine than other people.

And you know we - it you know we all assume - we all know that everyone of us doesn't react to the same medicines exactly the same way.

This gives us some understanding this genetic profile is just one piece of the puzzles in the groups you know when we're thinking about coding about why some people may have more severe problematic side effects than other people.

(Andrea Owen): Okay.

Susan Cruzan: Can we have the next question please.

Coordinator: Next question is from (Randolph Schmidt) of the Associated Press.

(Randolph Schmidt): Hi one quick question is you mentioned that codeine is in over the counter cough syrups, is it in other over the counter drugs where people might encounter it?

Sandra Kweder: No.

(Randolph Schmidt): Okay, only cough syrups.

Sandra Kweder: Yes only cough syrups and most of those over the counter cough syrups are not available - they are not available like out on the open shelf in a drug store they usually have to be provided by the pharmacist.

(Randolph Schmidt): You have to sign something to get them as that what it is?

Sandra Kweder: You don't I don't even - I'm not sure if you always have to sign something, but you - I've never - I have never been in a pharmacy where you can find a codeine containing cough syrup you know just walking down the aisle.

(Randolph Schmidt): Okay good thank you.

Coordinator: Once again to ask a question, please press star 1, one moment please.

Susan Cruzan: Can we have one more question?

Coordinator: One moment please.

Okay (David Brown) of Washington Post you may ask your question.

(David Brown): Hi I actually have two, I'm surprised that there is codeine in over the counter non prescription medicines I thought it was a scheduled drug that's one.

And the other one is give exact the population prevalence is you know 10% in (unintelligible) which is (unintelligible) or the majority group I guess in this country, why do you think you haven't more cases and are there people going back and looking at very early SIDS cases you know perinatal SIDS cases to see if you know this was the mechanism for the sudden death of infants.

Sandra Kweder: I think well I'll take a stab at that and (Janet) you can on the SIDS and going back.

You know the problem has estimated to be in the range of 1 to 10% and probably when you think about ultra-rapid metabolism you know even you take that range of 1 to 10% there are probably some people who express this genetic type more strongly than other people.

So the case that was reported was a very you know, a very dramatic case. And it may well be that other people who have the same profile are less affected or more affected by it.

I mean that's one of the things about these genetic profiles is, even if the genes are there how your body then expresses the gene in operationalizes it very tremendously.

As on the SIDS piece, you know I don't know if there has ever been any research to specifically look at genetic sub typing for drug metabolism in mom's or babies who've died of SIDS.

But you know as there is no question of that any time there is any infant death, there is a lot of investigation, looking at whether the mother was taking any kind of medication.

I'm not aware of any relationship of narcotic medications or pain medications and babies who - in breastfeed babies who've died of SIDS.

Janet Woodcock: Yes to further elaborate I think as we go through the what we think the signs might be that people should watch for, more likely this is this type of event is associated with a baby who has difficulty nursing and staying awake and so forth which is common in newborns for a variety of reasons anyway.

But this would be I would think the way this might manifest itself most commonly where the baby would (unintelligible) and be limp and would be sleepy and so forth.

And often then the mothers will give up nursing the baby because of those findings and switch over to formula which would solve the problem but it's probably not the best outcome from a public health standpoint.

So we don't know these estimates have the prevalence of ultra-rapid metabolizer's are just estimates because broad population studies haven't been done.

And you know so we don't really know the prevalence of each of these groups.

(David Brown): Okay and can you just again confirm that there are over the counter non prescription substances that contain codeine, because I thought codeine was a controlled intra substance.

Sandra Kweder: (Janet) do you want to do that.

Janet Woodcock: Well there are - I understand there are cough medications that contain if they have other ingredients as well, so that people can't you know take a lot of them because there is a wide variety of ingredients in them, they aren't just strictly codeine I don't think.

Sandra Kweder: Right and I think the key point as well technically they are - you know the codeine containing cough syrups have been under - you know (unintelligible) as a different mechanism than most prescription drugs.

They are not - I would not say that they are widely available I think that you know probably 40 years ago - 50 years ago they were widely available but today they are not widely available without a prescription.

(David Brown): Okay thanks.

Sandra Kweder: I also want to just add to this Susan if I might, one of our you know - women who are breastfeeding this does - this kind of - this information this announcement today absolutely does not mean that women who need pain medicine should not breast feed.

Janet Woodcock: Right.

Sandra Kweder: You know that is - we want to really emphasize that, you know the benefits of breast feeding are well documented I think national breastfeeding week was just a few weeks ago that reemphasized that.

But our point is that women who are breastfeeding who are taking pain medicines should simply be aware that everyone may - people may metabolize these pain medicines particularly codeine containing ones a little bit differently.

And if you as a mom are experiencing significant side effects you ought to be - you should absolutely be - watching your baby for the same kinds of things.

And be sure to talk to your doctor before you take a pain medication about what to watch for and if you have any concerns contact the pediatrician right away.

Susan Cruzan: (Sandy) thank you for wrapping up with that, that will conclude our call today.

I'm sure everyone of the call is aware that FDA and our Center for Drug Evaluation and Research has posted a public health advisor and Q's and A's associated with this.

And you're welcome to get in touch with me and the press office, Susan Cruzan at FDA.hhs.gov.

Thank you everyone and have a great day.

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