To: CN=Kenneth C Kwong/OU=AM/O=LLY@Lilly
CC: CN=James B Gregory/OU=AM/O=LLY@Lilly; CN=Cassandra Mehlman/OU=AM/O=LLY@Lilly; CN=Bram Goorden/OU=EMA/O=LLY@Lilly; CN=Debbie S Blake/OU=AM/O=LLY@Lilly; CN=Dirk Cuypers/OU=EMA/O=LLY@Lilly; CN=Fanny Verspeelt/OU=EMA/O=LLY@Lilly; CN=Henry Schmitt/OU=EMA/O=LLY@Lilly; CN=Jean-Marc Van Brandt/OU=EMA/O=LLY@Lilly; CN=Michele Sangeleer/OU=EMA/O=LLY@Lilly; CN=Padraig Wright/OU=EMA/O=LLY@Lilly; CN=Patrizia Cavazzoni/OU=AM/O=LLY@Lilly; CN=Walter Deberdt/OU=EMA/O=LLY@Lilly; CN=Bruce Kinon/OU=AM/O=LLY@Lilly; CN=John S Kennedy/OU=AM/O=LLY@Lilly; CN=Donald P Hay/OU=AM/O=LLY@Lilly; CN=Margaret O Sowell NONLILLY/OU=AM/O=LLY@Lilly
Date: 07/05/2001 11:25:16 AM
From: CN=Robert W Baker/OU=AM/O=LLY
Subject: Re: diabetes and antipsychotics comments on poster WCBP

Dear Kenneth:

Thanks for forwarding. Wilson (now at Nebraska) and the Cincinatti group have been presenting these findings at many meetings starting in 1999. I'd appreciate a copy of the poster from WCBP if it is available - they have promised to update when they finish "hand reviewing" risperidone cases. Attached is a summary of the 12/00 version of this poster that we had prepared prior to the 2001 APA.

Regarding soft drink use, my own clinical experience is that it is rather remarkable among patients with schizophrenia, and agree with Kenneth that there could be snowballing osmotic and glucose load if patients become polydyspsic secondary to spilling sugar.

Regarding proposal for baseline glucose tolerance testing, I'd suggest a more moderate step. We are increasingly encouraging clinicians to be attentive to the diabetes issue, and educating them that it is a mistake to limit such attentiveness to pts on olanzapine. To me it seems that many "DKA" cases are type 2 diabetes and perhaps would have been prevented by better detection and management. However, I doubt that GTT is indicated or appropriate for the great majority of pts and pending closer consideration and discussion with Patrizia/Missy advocate against recommendation for baseline GTT.

R

"New-Onset Diabetes and Ketoacidosis with Atypical Antipsychotics" - Dan Wilson MD, PhD, et al., Creighton University, sponsored by Janssen –This is a presentation of a chart review we have seen at numerous meetings since 1999. The abstract is unchanged from ACNP.

OVERVIEW: A STATE HOSPITAL CHART REVIEW WITH QUESTIONABLE FAIRNESS AND DUBIOUS CONCLUSION OF ELEVATED DIABETES RISK ON OLANZAPINE

SUMMARY: This poster reports on a retrospective case series of 14 patients out of 126 treated over 3 years with atypical antipsychotics at a Cincinnati area state hospital who developed "diabetes".
Only 21 of the 126 had any fasting baseline glucose data of which 14 had further workups conducted. 11 of the 14 cases developed after treatment with clozapine, olanzapine or quetiapine, 5 out of these 11 had 'ketoacidosis'
Interim data analysis of the ODMH statewide database indicates that the overall rate of diabetes among 2,542 patients treated with Olanzapine during 1998-99 was 10.9% (278 cases with 127 or 5% being "new onset"). They state that data for risperidone, clozapine and quetiapine have yet to be validated.
Author concludes that his findings indicate that Clozapine, Olanzapine and Quetiapine are "diabetogenic". He also states that best practice guidelines should be changed to include routine blood glucose monitoring for at least some atypical antipsychotics.

Comments:

This report is laden with dubious conclusions and questions of bias:

- in detailed review of "ketoacidosis" author mentions that one patient was on risperidone, entirely omitted from all the other discussions of which drugs are 'diabetogenic'
- analysis of state database only includes olanzapine; risperidone was not complete because of the need for 'painstaking hand chart review to clarify ambiguities and eliminate false positives'
- case reports of diabetic ketoacidosis are suggestive of misuse of that term for pts with less severe forms of diabetes
- Patients are not randomly assigned to treatment nor systematically monitored
- As is true for many of these studies of rates of "new" diabetes, it is difficult to confidently rule out new detection of existing cases – eg due to closer medical attention during hospitalization
- Prevalence of diabetes in olanzapine treated patients – 10% - is not out of line with rates in general population

Kenneth C Kwong

07/05/2001 09:55 AM

To: Walter Deberdt/EMA/LLY@Lilly
cc: Bram Goorden/EMA/LLY@Lilly, Dirk Cuypers/EMA/LLY@Lilly, Fanny Verspeelt/EMA/LLY@Lilly, Henry Schmitt/EMA/LLY@Lilly, Jean-Marc Van Brandt/EMA/LLY@Lilly, Michele Sangeleer/EMA/LLY@Lilly, Padraig

Wright/EMA/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, Robert W Baker/AM/LLY@Lilly, Debbie S Blake/AM/LLY@Lilly

Subject: Re: diabetes and antipsychotics comments on poster WCBP

Dear Walter,

I would like to thank you for presenting the poster. Then name Hammond and Ohio Department of Mental Health sounds familiar to me, I think she might have seen an abstract of similar findings in the past. At any way, Pharmacovigilance will get in touch with her to make sure that the olanzapine case be entered into Clintrace database. We would also ask her to send us a copy of her poster presentation.

Her findings are compatible with hyperglycemia as a class effect, as suggested by the AdvancePCS study. It is my impression that not all patients who experienced diabetes while taking olanzapine had substantial weight gain. Positive dechallenge was noted in some spontaneous cases where glucose levels were over 600 mg/dL. When glucose levels are very high, the problem goes beyond insulin resistance (insulin deficiency is required). Hyperglycemia causes osmotic diuresis, dehydration and thirst. Thus, drinking couple gallon of sugared water might be a sequela of dehydration, rather as the cause of hyperglycemia.

Best regards,

Kenneth Kwong

Walter Deberdt

07/04/2001 03:36 AM

To: Patrizia Cavazzoni/AM/LLY@Lilly, Kenneth C Kwong/AM/LLY@Lilly

cc: Jean-Marc Van Brandt/EMA/LLY@Lilly, Dirk Cuypers/EMA/LLY@Lilly, Bram Goorden/EMA/LLY@Lilly, Michele Sangeleer/EMA/LLY@Lilly, Henry Schmitt/EMA/LLY@Lilly, Fanny Verspeelt/EMA/LLY@Lilly, Padraig Wright/EMA/LLY@Lilly

Subject: diabetes and antipsychotics comments on poster WCBP

Patrizia, Kenneth,

I had some interesting discussions while presenting the poster yesterday. There were two people from Astra-Zeneca to whom I made it clear that at a therapeutic dose of quetiapine the risk was as high as in the other groups. More important I had a good discussion with a lady from the Ohio Department of Mental Health, Mrs. Hammond, who herself presented a poster on diabetes/ketoacidosis cases with olanzapine, clozapine and quetiapine (first author D. Wilson, Cincinatti). I don't know how far in detail Lilly US is following up on these cases, but I think it could be worthwhile to get a better understanding of what really happened there through an invitation of this doctor to discuss these cases with us. I wonder if the usual screening for hyperglycemia/diabetes by taking one fasting glycemia (at least this is the usual screening in Belgium) at the start of an hospitalisation is sensitive enough, especiallly in the light of what we know now on the situation of psychiatric patients being at high risk and the findings of for example Thakore. If then such a patient, who in fact can have a normal fasting glycemia but a really bad glucose tolerance, is drinking a couple of galons of sugared soft drinks a day under influence of the appetite changes with for ex Zyprexa, I can imagine there is a clear risk of a "sudden" ketoacidosis which looks like to be caused by Zyprexa without any relationship to weight gain, and which may require at least temporarily insulins.
Henry (our Belgian CRP, specialist in Internal Medicine and dealing with insulins since he was born), what do you think of my hypothesis and especially of the idea to push our psychiatrists to do **systematically at the beginning of therapy/hospitalisation a more sensitive glucose tolerance testing** in order to avoid the severe hyperglycemia problems which are catastrophic not only for the patient, but also for the image af Zyprexa, while Zyprexa plays no or only an indirect role (through a change in eating/drinking habits)?

Regards,

Walter