A REVIEW OF ALL SPONTANEOUS CASES OF HYPERGLYCEMIA REPORTED IN THE LILLY SAFETY DATABASE (CLINTRACE) IN THE FIRST 21 MONTHS OF MARKETING OF COMMERCIALLY AVAILABLE OLANZAPINE

(27-SEP-96 - 30-JUN-98)

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1. INTRODUCTION

This review was conducted to examine the nature and patient characteristics of all spontaneous cases of hyperglycemia or related events voluntarily reported and temporally associated with the administration of commercially available olanzapine (referred to as spontaneous adverse event reports). The occurrence of these events does not imply that olanzapine is an etiologic contributor to the events. This review covers the first 21 months of commercially marketed olanzapine worldwide. This task was undertaken to fulfill the commitment made to the CPMP in the PSUR covering the period from September 27, 1997 to March 31, 1998. Particular attention was paid to distinguishing between patients with or without history or risk factors for hyperglycemia.

It should be noted that hyperglycemia is a relatively common condition. Besides diabetes mellitus, there is a lengthy list of pancreatic and endocrine conditions that can result in hyperglycemia. For example, pancreatic insufficiency due to alcohol abuse, chronic pancreatitis, hemochromatosis, cystic fibrosis and various malignancies of the pancreas can lead to hyperglycemia. In addition, endocrine disorders such as acromegaly, Cushing's Syndrome, pheochromocytoma, hyperaldosteronism, hyperparathyroidism, hyperthyroidism as well as renal insufficiency, and hepatic insufficiency can also result in this event. Moreover, exogenous abuse of corticosteroids or extreme stress due to severe illness (myocardial infarction, sepsis, neuroleptic malignant syndrome, etc.) that mobilizes endogenous release of glucogenic hormones such as glucocorticoid, growth hormone, and glucagon can also result in hyperglycemia. Lastly, since borderline diabetes is frequently unrecognized, dietary indiscretion and fluctuating activity levels can lead to sporadic presentation of hyperglycemia in some people.

2. METHODOLOGY

This review of the spontaneous safety database was performed for the period of 27-Sept-96 through 30-Jun-98 for all olanzapine spontaneous adverse event reports involving one or more of the following COSTART terms HYPERGLYCEMIA, DIABETES MELLITUS, DIABETIC COMA, DIABETIC ACIDOSIS, and KETOSIS. There were 168 patient reports generated from our spontaneous safety database using these search criteria.

These 168 cases were then categorized into the following 3 categories for further review.

The categories used are as follows:

Group 1: Patient with a diagnosis of insulin or non-insulin dependent diabetes mellitus (Type I or Type II) or a baseline history of persistent hyperglycemia that could be suggestive of diabetes prior to the event(s) in the report.

Group 2: Patient without a known history of a hyperglycemia or diabetes but with risk or confounding factors for the development of hyperglycemia.

Group 3: Insufficient details were available to fully evaluate the report despite multiple attempts to secure follow-up.

Demographic information and dose/duration of treatment for each of these 3 patient groups are also included.

3. RESULTS

The patient reports were placed in the categories as displayed in the table below. Approximately38% of the patients were known diabetics and 40% had a known risk or confounding factor(s) for hyperglycemia/diabetes.

PATIENT GROUP	NUMBER OF CASES	% OF TOTAL
Group 1 (Known Diabetes)	63	37.5%
Group 2 (Risk/Confounding Factors)	67	39.9%
Group 3 (Insufficient Details to evaluate)	38	22.6%
TOTAL	**168**	**100%**

A further review of the patient characteristics of each group follows.

A. Group 1: The patients placed in this group had a pre-existing diagnosis of either Type-I or Type-II diabetes mellitus or displayed a history of hyperglycemic episodes suggestive of such diagnoses. There was a total of 63 patients in this group. 32 were males and 29 were females. With 2 patients the gender was not available. The age ranged from 17 to 79 (mean 48.3, median 51). The mean dose of olanzapine treatment was 12.5 mg/day with the mean duration of treatment being 57 days. Among the 63 cases reviewed, peak blood sugar was stated in 40 Type II and 4 Type I diabetic patients. Thus, a total of 44 of the reports (70%) provided the peak blood sugar. The mean peak blood sugar was 441 mg% for the Type II patients and 548 mg% for the Type I patients. Unfortunately, the majority of the patient reports (29/44) with a peak blood sugar did not have baseline blood sugars accompanying the peak blood sugar. Among the 15 patients with a baseline blood sugar (14 Type II and 1 Type I), the mean baseline blood sugar was 135 mg% and the mean peak blood sugar was 429 mg%. Thus, the general level of increase was relatively mild and consistent with the normal fluctuation of glycemic control among these patients. Of note, these values were likely random glucose values as there was no mention of a fasting status for these patients in the reports.

Blood sugar control is known to be difficult among patients with diabetes because it depends on the diet, activity level, compliance to medications, natural progression of the diabetic condition and other confounding conditions such as infection, concomitant medication usage, etc. These factors need to be put into perspective in reviewing these cases, especially for many schizophrenic patients in which compliance with medications and life-style restrictions may be a problem.

B. Group 2: This group contained 67 patients of which 46 had risk factors for diabetes and another 21 displayed confounding factors potentially predisposing to or causing hyperglycemia. 39 were males and 27 were females of the patients with a known gender. One patient did not have the gender specified. The age of the patients ranged from 14 to 72 (mean 38.5, median 40). The mean olanzapine dose of the patients with a specified dose was 13.9 mg/day with the mean duration of treatment being 123 days. In addition, some patients had more than 1 risk or confounding factor potentially accounting for the hyperglycemia. Among the 67 cases, 40 had single factor, 23 had two factors and 4 had three or more factors. However, for ease of visualization, if multiple factors were involved, the most clinically significant factor is listed in the following table:

GROUP 2	FACTORS IN HYPERGLYCEMIA	# of Cases	Percentage
Risk Factor	Family history of Diabetes	13	19.4%
(N=46)	Obesity	28	41.8%
	Significant recent weight gain*	5	7.5%
Confounding Factor	Lithium therapy	6	9.0%
(N=21)	Alcoholism	4	6.0%
	Pancreatic disorder	3	4.5%
	Binges with high concentrated sugar beverages	3	4.5%
	Severe Illness (sepsis, hepatic failure, NMS)	3	4.5%
	Pregnancy with obesity	1	1.5%
	Total Parental Nutrition administration	1	1.5%
Total		**67**	100.0%

*Recognized as a risk factor associated with olanzapine treatment

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C. Group 3: This group consisted of 38 cases for which sufficient details were not provided for further evaluation despite multiple attempts to secure follow-up. 23 were males and 10 were females with the gender of 5 patients not provided. The ages of 18 of the patients were missing and the age range for the remaining 20 patients was from 12 to 75 years(mean 35.1, median 35). Dose and duration of olanzapine treatment were generally lacking for the majority of the patients. Among the 38 cases, only 19 had a blood sugar value provided to verify the hyperglycemia status with the remaining cases that the information were so sketchy that hyperglycemia was not even confirmable. Unfortunately, even among those cases with confirmed hyperglycemia, important clinical information such as the patients' weights, dietary habits, past medical history of pancreatic diseases and glycosylated hemoglobin levels were unavailable to further evaluate these cases. Thus, these cases are mostly unevaluable and no definitive conclusion can be drawn.

4. CONCLUSION

The prevalence of diagnosed diabetes is estimated to be 5.1% in the general adult (≥ 20 years of age) population, the prevalence of undiagnosed diabetes is approximately 2.7%, and the prevalence of impaired glucose tolerance (i.e., borderline diabetes) is 6.9% within the US population[1]. However, the prevalence of diabetes in the US schizophrenic population is considerably higher, 24.5 % [2]. Similarly, the prevalence of diabetes in an Italian schizophrenic population has been found to be 15.8%, with the prevalence in the Italian general population being 2.1%[3]. In addition, as discussed in the Introduction Section, there are multiple other disease conditions such as pancreatic and endocrine disorders that can result in hyperglycemia. Among the 168 cases reviewed in the current report, approximately 38% were known diabetics and another 40% had known risk or confounding factors that accounted for the event observed. In the remaining 22% of the cases, there were insufficient clinical details to conduct a meaningful assessment of the cases.

Among the 168 cases categorized above, 63 were exacerbations of known diabetes and adopting the most conservative approach (counting the 38 cases lacking sufficient clinical detail to evaluate as hypothetical new onset cases), 105 were cases of new onset diabetes. Given a worldwide olanzapine estimated patient exposure of 1,472,000 as of June 30, 1998, the incidence of exacerbation of diabetes is 0.004% and the incidence of newly diagnosed diabetes is 0.007%. The actual incidence figures may be 5 to 30-fold higher than these reported figures [4-8]. Using the most conservative 30-fold multiplier, the incidence of exacerbation may be 0.120% and the incidence of newly diagnosed diabetes may be 0.210%. Given the multiple factors which can destabilize glycemic control and the prevalence of diabetes especially among schizophrenics, definitive conclusions regarding the relationship between olanzapine and hyperglycemia cannot be drawn and these data cannot be viewed as supporting a causal relationship between olanzapine therapy and hyperglycemia. However, the possibility of some idiosyncratic contribution by olanzapine to the etiology of hyperglycemia cannot be entirely excluded in all the cases reviewed.

We appreciate the importance of this clinical event. We are aware of anecdotal literature and indirect data suggesting at least a temporal association between treatment with other antipsychotics sharing some pharmacologic properties with olanzapine and hyperglycemia[9-12]. Although there are reports to the contrary[13-15], additional data[16] suggest the possible association between antipsychotic therapy in general and hyperglycemia. We therefore are proposing to add the term hyperglycemia, as a rare event, to the adverse reaction section of the Olanzapine Summary of Product Characteristics.

5. REFERENCES

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