

Analysis of Treatment Emergent Diabetes Data

April 2002

Prepared for MHLW

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1. Introduction

This report was prepared at the request of a fax received on 06-Mar-2002 from MHLW to provide analysis of Eli Lilly global trial data on weight gain and hyperglycemia associated with the use of olanzapine.

Diabetes and diabetes related events are frequently associated with schizophrenia and related disorders. A number of factors may explain this phenomenon. These include an unknown genetic link, obesity, sedentary lifestyles and impulsive eating behavior.

2. Methods

- Subjects were taken from 23 studies of patients with schizophrenia or schizoaffective disorder (**Appendix A**).
- The number of patients in different therapy groups was not evenly distributed. Generally, olanzapine patients, by study design, are studied for a longer period of time.
- Subjects considered in the analysis either had a diagnosis of diabetes or had both baseline random glucose tests above 200 mg/dl.
- The Fisher's exact test was used to calculate if a significant difference existed between therapy groups for the treatment emergent glucose dysfunction events.

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3. Results

- Due to the small sample size, the analysis was not sufficiently powered to be able to detect statistically significant small differences between therapy groups.
- As indicated by the below values, there was a wide inter-subject variability in the random glucose measures.
- For baseline to endpoint mean change analysis none of the overall or pairwise p-values are significant at the 5% level.
- There were no statistically significant treatment differences for glucose change between therapy groups.
- Within each therapy group mean random blood glucose decreased during treatment.

3.1. Mean change in Random Glucose Analysis

Table 3.1.1. Mean change in random glucose from baseline to endpoint at one year

Drug	N	Mean	SD	vs. Hal	vs. Risp
Hal	31	-22.1	141.4		0.835
Olz	70	-4.9	99.9	0.485	0.490
Risp	11	-30.4	104.8		

Patients either had a known diagnosis of diabetes mellitus at baseline or had a baseline random glucose > 200. NS= not-significant.

Table 3.1.2. Mean change in random glucose from baseline to endpoint for six weeks

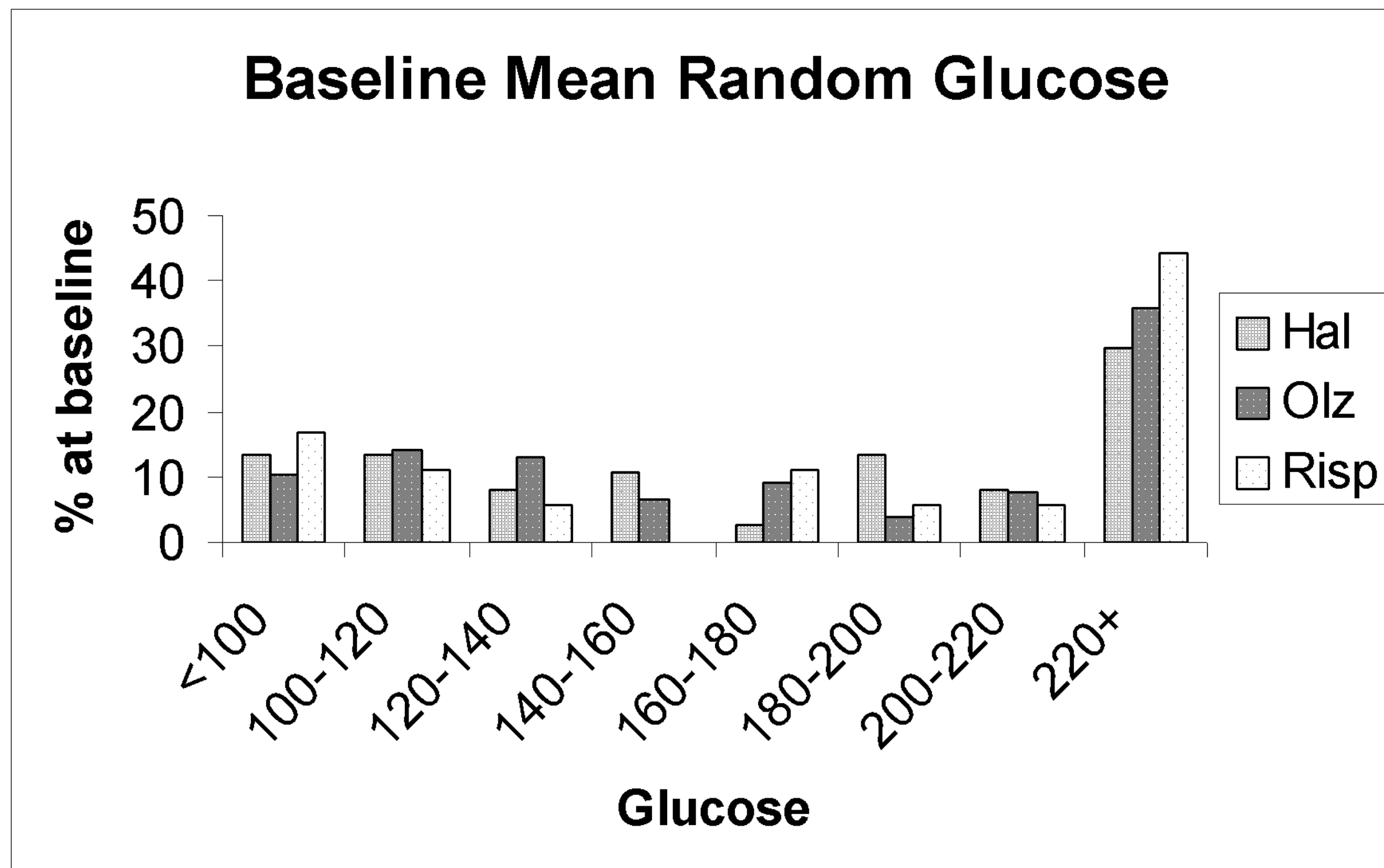
Drug	N	Mean	SD	vs. Placebo
Olz	63	-0.3	120.3	0.895
Placebo	6	-7.0	83.4	

Patients either had a known diagnosis of diabetes mellitus at baseline or had a baseline random glucose > 200. NS= not-significant.

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Figure 3.1.1. Distribution of mean random glucose at baseline for patients treated with haloperidol (Hal), olanzapine (Olz), or risperidone (Risp).



- For haloperidol patients, 37.7% (n=14/37) had a baseline mean random glucose above 200mg/dl.
- For olanzapine patients, 43.6% (n=34/78) had a baseline mean random glucose above 200mg/dl.
- For risperidone patients, 50.0% (n=9/18) had a baseline mean random glucose above 200mg/dl.

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4. Conclusion

- In all treatment groups (olanzapine, risperidone or haloperidol), the majority of patients entering the trials had abnormal random glucose measurements at baseline (> 140 mg/dL). In addition, a significant proportion of patients entering the trials had a baseline random glucose > 200 mg/dL (haloperidol: 37.7%; olanzapine: 43.6%; risperidone: 50.0%).
- While high rates of glucose abnormalities were present at baseline in all therapy groups, overall, mean random blood glucose decreased during treatment within each therapy group.

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