Beta-blocker-associated Hypoglycemia in Pediatric Patients: Findings from FDA Adverse Event Reporting System, National Poison Data System, Medical Literature, and Sentinel Distributed Database

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Background

- Hypoglycemia is a known risk with all beta-blockers (BBs). However, little is known about BB-associated hypoglycemia in pediatric patients in the post-market setting.
- BBs can induce hypoglycemia by inhibition of hepatic gluconeogenesis, and reduction of glycogenolysis and lipolysis through inhibition of autonomic counter-regulation.
- Pediatric patients may be especially vulnerable to BB-associated hypoglycemia because of their higher glucose utilization rates during long fasting state (i.e., sleep) and lower glycogen stores.
- Younger pediatric patients may be vulnerable to severe effects of hypoglycemia given diminished ability to communicate symptoms and delay in recognition and treatment due to non-specific signs of hypoglycemia.

Objectives

- To describe pediatric hypoglycemia cases associated with BBs in FDA Adverse Event Reporting System (FAERS), National Poison Data System (NPDS), medical literature, and to characterize this adverse event in the population-based Sentinel Distributed Database (SDD).

Methods

FAERS and Medical Literature:

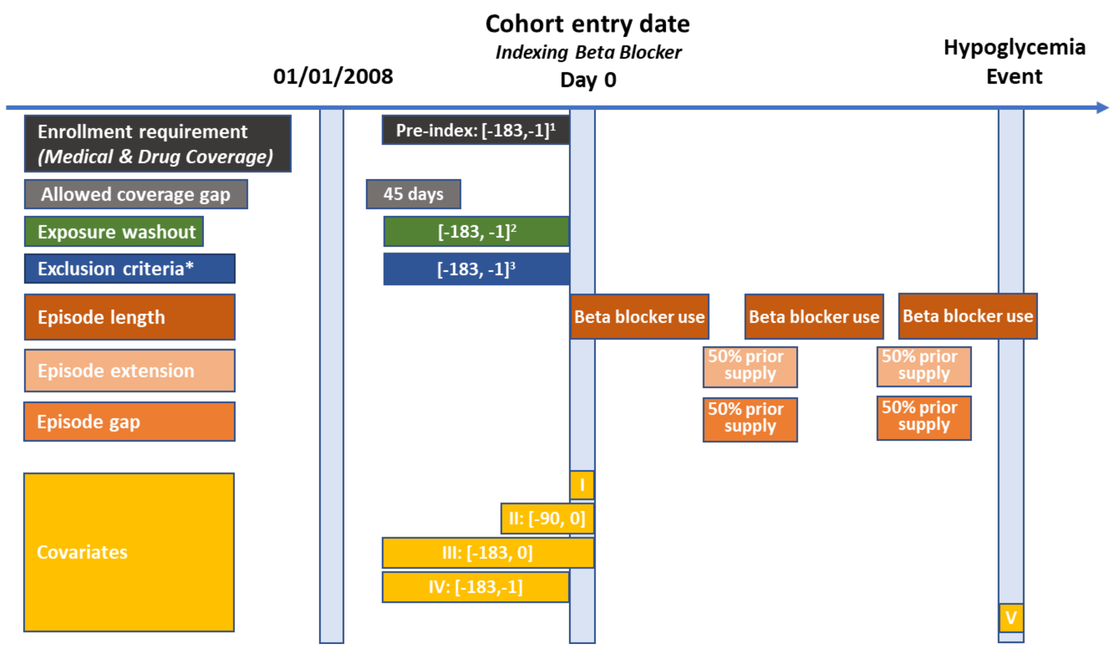
- We used Empirica Signal software to analyze disproportionality of reporting of BB-associated-hypoglycemia in the FAERS data as a class for all reports, for adult reports (≥18 years) only, and for pediatric reports (≤17 years) only.
- Case reports of BB-associated hypoglycemia in pediatric patients (≤17 years) were identified by querying FAERS through Jan 2022, and searching literature in Pubmed and Embase from inception to Jun 2022.
- We included reports that showed a temporal relationship between BBs and hypoglycemia with clinical signs and symptoms and/or blood glucose values consistent with hypoglycemia.
- We assessed causality using the modified World Health Organization—Uppsala Monitoring Center (WHO-UMC) causality assessment tool.

NPDS:

- Reports of BB-associated hypoglycemia in pediatric patients (≤19 years) were searched in NPDS through Dec 2021.

SDD:

- We used administrative claims data from five Data Partners in SDD consisting of both U.S. commercial and public health insurers from Jan 2008 to Feb 2023.
- We identified pediatric patients (≤ 0-17 years) with evidence of new BB dispensing during the study period (defined as no dispensing in the prior 6 months, or no dispensing since birth for infants under 6 months of age).
- We followed users of most utilized BBs in pediatrics (atenolol, carvedilol, labetalol, metoprolol, nadolol, or propranolol) from BB initiation until outcome events of interest (**Figure 1**).



Exclusion Criteria: Beta blocker use
Covariates
Window I: Age, year, sex
Window II: Potential indications for beta-blocker use
Window III: Diabetes, insulin use, chronic kidney disease, chronic liver disease
Window IV: Hypoglycemia
Window V: Hypoglycemia care setting
*Enrollment requirements will be less than 183 days for patients under 6 months of age.

Figure 1. Study Design Diagram for the Query in SDD

Results

- In FAERS, hypoglycemia was disproportionately reported with the BB class overall (EBGM 2.2) and more so within the pediatric subset (EBGM 10) **(Table 1)**

Table 1. Disproportionality Analysis of Beta-blocker (Class) Associated Hypoglycemia Reports in FAERS Stratified by Age

Product active moieties (PAM)	Age Subset (years)	N	EBGM	EB05	EB95
All beta-blockers	All reports*	2050	2.17	2.09	2.24
	≤17	**399**	**10.019**	**9.218**	**10.874**
	≥18	1199	1.684	1.605	1.765

N = number of reports
*All reports include reports with age and null age in the structured field and may not add up to total reports in subsets
EBGM = Empirical Bayes Geometric Mean
EB05 lower bound of the 90% EBGM confidence interval, EB95 upper bound of the 90% EBGM confidence interval

- In FAERS and medical literature, we identified 116 cases of pediatric hypoglycemia associated with propranolol (n=78), nadolol (n=20), carvedilol (n=8), sotalol (n=7), timolol (n=2), and atenolol (n=1). Most cases were reported in children 0-1 year (n=61) and 2-5 years (n=41). Cardiovascular conditions (n=70) and hemangioma (n=35) were the most frequently reported indications. The median time-onset was 152 days. **(Table 2)**

Table 2. Characteristics of Cases Reporting Hypoglycemia Associated Beta Blockers in FAERS Through Jan 2022 or Medical Literature Published by Jun 2022 (n=116)

Selected Characteristics	Propranolol (n=78)	Nadolol (n=20)	Carvedilol (n=8)	Sotalol (n=7)	Timolol (n=2)	Atenolol (n=1)
Age (years)						
0-1	50	3	2	3	2	1
2-5	22	11	4	4	-	-
6-12	4	6	2	-	-	-
Not reported	2	-	-	-	-	-
Sex						
Male	44	12	8	5	-	-
Female	28	8	-	2	2	1
Not reported	6	-	-	-	-	-
Hypoglycemia signs/symptoms†						
Autonomic	18	2	2	2	-	-
Neuroglycopenic	76	20	8	7	2	1
Behavioral	1	-	-	1	-	-
Non-specific€	1	-	-	-	-	-
Time-to-onset£ (days)	(n=60)	(n=13)	(n=7)		(n=2)	
Median (range)	152 days (2 hrs.–3 yrs.)	304 days (4 mon.–5 yrs.)	486 days (2 mon.-2.6 yrs.)	730 days (5 days-3 yrs.)	1 day	-
Blood glucose level (mg/dL)	(n=66)	(n=18)	(n=7)	(n=5)	(n=2)	
Median (range)	25 (1-67)	22.5 (11-40)	18 (11-24)	27 (21-40)	27	-
History of Poor oral intake/illness/fasting for surgery	(n=62)	(n=13)		(n=3)	(n=1)	
Yes	56	11	8	3	1	1
Clinical outcome						
Death	-	-	2	-	-	-
Neurological damage	3	-	1	-	-	-
Recovered¥	75	20	5	7	2	1
Clinical intervention†	(n=41)	(n=6)	(n=7)			
Discontinued BB	36	6	6	7	2	1
Restarted same BB	5	-	-	-	-	-
Switched to another BB/medication	2	2	-	2	-	-
Causality assessment						
Possible	54	9	8	4	-	1
Probable	24	11	-	3	2	-

hrs.= hours; mon.= months; yrs.= years; "-" = relevant information is not reported
£Time-to-onset refers to the time from BB initiation to the occurrence of adverse event of hypoglycemia
†More than one hypoglycemia sign/symptom, clinical intervention, may have been reported per case
€ non-specific symptoms = headache, nausea, tiredness, hunger
¥ Recovered includes cases that required intervention (i.e., treatment with glucose)

- In NPDS, single-substance BB exposure and hypoglycemia was most frequently reported in pediatric patients (n=183) with propranolol (n=82), metoprolol (n=34), and nadolol (n=11). Most cases involved children ≤5 years (n=138). Hypoglycemia occurred commonly after acute BB exposure (n=119) followed by acute-on-chronic exposures (n=38), and chronic exposures (n=23).
- In SDD, hypoglycemia developed in 1,178 treatment episodes (1.3%; incidence rate [IR]: 1.35 per 100 person-years [PYs], **Table 3**). The median time-to-onset was 34 days (IQR: 8 to 117 days), with most events occurring within 90 days of BB initiation (70.6%). Younger children were more prone to develop hypoglycemia (IR per 100 PYs: 2.64 [0-1 year]; 2.64 [2-5 years]; 0.72 [6-11] years; 1.09 [12-17 years]).

Table 3. Hypoglycemia post Beta Blocker Initiation in the SDD from Jan 2008 to Feb 2023

Exposure Group	New Users	New Episodes	New Episodes with an Event	Crude Incidence Rate per 100 Patient-Years at Risk (95% CI)
Most utilized BBs	244,266	262,099	1,178	1.35 (1.27,1.43)
Labetalol	6,374	6,578	52	3.03 (2.31, 3.98)
Carvedilol	4,678	5,164	56	1.92 (1.48, 2.50)
Metoprolol	21,144	22,235	120	1.40 (1.17,1.68)
Propranolol	174,771	185,483	773	1.40 (1.30,1.50)
Atenolol	32,739	35,477	120	0.90 (0.75, 1.07)
Nadolol	6,614	7,266	29	0.80 (0.56, 1.16)

Conclusion

- The FDA updated all BB labelings with additional language to mitigate the risk of BB associated hypoglycemia, particularly in pediatric patients unable to communicate early warning signs or symptoms. Further risk language was included regarding hypoglycemia risk associated with BB use especially during periods of fasting (i.e., surgery, not eating regularly, or are vomiting).

Disclaimers

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