



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 21, 2007

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Subject: Review of Serious Adverse Event cases in Pediatric Patients
(follow up to 1 year Post Exclusivity BPCA review)

Drug Name(s): Metoprolol succinate (Toprol XL)

Application Type/Number: 19-962

OSE RCM #: 2007-2100

1 INTRODUCTION

The Office of Pediatric Therapeutics requested a follow up review of pediatric adverse events reported in patients taking metoprolol succinate¹ from the AERS database. Events of interest included fatigue, CNS effects, aggravated respiratory events, and fetal exposures based on adverse event observed in a trial of metoprolol succinate in pediatric patients².

2 AERS SEARCH AND RESULTS

A search of AERS was performed on October 19, 2007 to identify *all serious cases*³ (since marketing approval-January 10, 1992) reported in those <17 years of age in association with metoprolol succinate use. Twenty cases were identified. Of these, four cases were presented in the previous OSE review⁴. Three other cases were miscoded with regard to age (27, 59 and 69 year olds). There was one duplicate. The remaining 12 cases are reviewed below.

Congenital Abnormalities

ISR 4822738 (Germany): A 3 day old female neonate (full term) experienced apnea and drop in oxygen saturation; she was diagnosed with patent foramen ovale. The mother received metoprolol succinate (dose duration unreported) during pregnancy; the pregnancy had been complicated by oligohydramnios, pre-eclampsia, and placental insufficiency. The baby recovered and was discharged.

ISR 3022340 (Sweden): A pregnant female took metoprolol succinate 25 mg and felodipine 5 mg daily throughout her pregnancy for the treatment of hypertension. A baby girl was born after labor was induced preterm (weeks gestation unreported) due to hypertension. When the child was 10 months old she was diagnosed with a skeletal abnormality of her lower extremities (right caput nucleus smaller on left than right); she walked with a slight limp. No information on follow up is available.

ISR 3515045 (Germany): A pregnant female received fenoterol HBr for preterm labor and metoprolol succinate 100 mg daily to reduce heart rate at 33 weeks of pregnancy. She also received betamethasone, magnesium oxide, and folic acid (dose, duration unreported). After about 1 month the metoprolol succinate and fenoterol were discontinued. At an unreported time after the discontinuation, a baby (gender unreported) was born. Soon after delivery the newborn vomited blood and experienced anemia. Endoscopy revealed multiple ulcers in the esophagus and stomach. No information on follow up is available.

¹ The Dosage and Administration section of labeling for metoprolol succinate contains the following: "If selected for treatment, the recommended starting dose of TOPROL-XL is 1.0 mg/kg once daily however, the maximum initial dose should not exceed 50 mg once daily. The minimum available dose is one half of the 25 mg TOPROL-XL tablet. Dosage should be adjusted according to blood pressure response. Doses above 2.0 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients."

² Batsky DL et al. Efficacy and safety of extended release metoprolol succinate in hypertensive children 6 to 16 years of age: A clinical trial experience. *Journal of Pediatrics* 2007: 150; 134-9.

³ Those with an outcome of death, hospitalization, life threatening, disability, congenital abnormality, or required intervention.

⁴ 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review, Metoprolol Succinate, August 29, 2007, Mary Ross Southworth, RCM # 2007-253.

Pharmacy Dispensing Error

ISR 4793871 (US): A 12 year old female received Toprol XL 25 mg instead of Topamax (topiramate) 25 mg due to a pharmacy dispensing error. She experienced difficulty breathing, chest pain, dizziness, and blue hands and feet. It was unclear from the report how long she took Toprol XL.

ISR 4735781 (US): An 11 year old female received a bottle of Toprol XL (dose unknown) from the pharmacy instead of Tegretol XL. Her mother noticed the error and the child never took the incorrect medication.

ISR 4337403 (US): A 15 year old male received Toprol XL 100 mg instead of Celexa 20 mg due to a pharmacy dispensing error. It was unclear from the report whether the child ingested any of the Toprol XL.

ISR 4585471 (US): A 7 year old female received Toprol XL (dose unreported) instead of Zoloft 25 mg due to a pharmacy dispensing error. The mistake was noticed by the caregiver, and the child did not ingest any Toprol XL.

Accidental/Intentional Overdose

ISR 3847348 (US): A 2 year old male accidentally ingested approximately ½ of a 100 mg tablet of metoprolol succinate and was hospitalized. No further information is available.

ISR 4596269 (Bulgaria): A 16 year old female took her grandmother's antihypertensive medications in a suicide attempt. She took 60 tablets of metoprolol succinate 50 mg and 6 tablets of indapamide. She experienced somnolence, hypotension, and bradycardia. She was treated in the ED with stomach lavage and diuresis. She improved and was discharged the next day.

ISR 4657440 (US): A 14 month old male ingested unknown doses of morphine, metoprolol [sic], hydrocodone with APAP, an antihyperlipidemic, a benzodiazepine, and trazodone. He experienced lethargy, somnolence and first degree heart block and was treated in the ER and PICU. He was treated with naloxone and IV fluids. He recovered and was discharged 2 days later.

Other Adverse Events

ISR 3411433 (US): A 16 year old female received metoprolol succinate 25 mg QD (increased to 50 mg QD) for treatment of neurogenic syncope (duration unreported). While on 50 mg, she experienced epigastric pain and was admitted to the hospital; her amylase level was elevated. Follow up information revealed that the patient subsequently underwent an appendectomy and had an ovarian cyst removed.

ISR 3503435 (Norway): A 15 year old male received metoprolol succinate (dose, duration, indication unreported) and experienced a mild retinal vein occlusion. No medical history was reported. Concomitant medication was methylphenidate HCl (dose, duration, indication unreported).

3 DISCUSSION

The serious adverse events in pediatric patients associated with metoprolol succinate largely involve cases of accidental/intentional overdose and dispensing errors by pharmacies. Each dispensing error involved a dispensing error with a different drug; therefore, no trend of one particular product causing "name confusion" was identified.

Three cases of congenital abnormalities in children born to mothers who had taken metoprolol succinate were identified. It is impossible to ascertain from these cases whether metoprolol succinate played a contributory role.

In the remaining two cases, it is difficult to draw any conclusion about the use of metoprolol succinate and the adverse event. In the case of epigastric pain and amylase elevation, limited information was reported regarding the time course of the events. In any case, the patient ultimately underwent appendectomy and ovarian cyst removal; these underlying diseases most likely were the main contributors to the events reported. In the case of retinal vein occlusion, key data points were not reported (medical history, drug indication, time course of events), making it difficult to make any association between metoprolol succinate use and the event.

None of the serious cases involving pediatric patients in AERS reported fatigue, CNS effects, or aggravated respiratory conditions.

4 CONCLUSIONS AND RECOMMENDATIONS

In conclusion, this review did not identify any serious unexpected events associated with metoprolol succinate use in pediatric patients. None of the cases reviewed reported fatigue, CNS effects or aggravated respiratory conditions. We will continue to monitor reports of adverse events associated with metoprolol succinate and will notify you of any potential safety signals in the pediatric population.

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/s/

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