Surveillance for adverse events associated with oseltamivir in a healthcare claims database

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Background

- 2009 H1N1 influenza pandemic resulted in unprecedented use of anti-influenzal drugs
- Two compounds recommended for pandemic H1N1 influenza
  - Oseltamivir
  - Zanamivir
- Need for enhanced surveillance of adverse events with these compounds in pandemic environment
- FDA leveraged an existing contract to access data on antivirals from a large healthcare database

Overview of previous observational studies of oseltamivir

- Roche-sponsored observational studies of oseltamivir-treated versus untreated influenza
  - Fewer respiratory complications (Orzeck, Shi & Blumentals, 2007; Nordstrom et al., 2005; Peters et al., 2008; Gums et al. 2008)
  - Fewer cardiac events (Enger et al., 2004)
  - Generally fewer neuropsychiatric events (Blumentals & Song, 2007; Smith & Sacks, 2009, Enger et al., 2004)
    - Smith & Sacks reported a positive association specifically for episodic mood disorders in pediatric patients
- Dept. of Defense study: reduced neuropsychiatric events with oseltamivir-treated versus untreated influenza in children (Casscells et al., 2009)

Purpose

Conduct surveillance for adverse events of interest with neuraminidase inhibitors using the OptumInsight (formerly Ingenix) healthcare database

Data source

- OptumInsight (formerly Ingenix) Research Database
  - Medical claims data, pharmacy claims data, and laboratory results
    - Medical claims = inpatient, outpatient visits (includes emergency departments, physician offices, clinics)
  - Diagnoses from International Classification of Diseases, Ninth Revision (ICD-9_CM)
  - Pharmacy claims data includes only outpatient prescriptions
- In 2006, included approximately 14 million individuals
  - Few over 65 years old
  - Southeast and Midwest geographic regions over-represented

Methods: Aperio

- "Aperio" application interfaces research database
- Creates propensity-matched samples for 1:1 comparisons
- Includes patients with at least 6 months of data prior to prescription/event of interest
- Provides descriptive information on patients receiving prescriptions
- Analyzes selected inpatient or outpatient diagnoses appearing in the medical claims
- Data anonymous for privacy considerations

Methods for this analysis

Cohort definition

- Influenza = ICD-9 487 or 488
- Influenza treatment = 5 day prescription plus influenza on day dispensed
- Untreated influenza = no antiviral within +/- 7 days of diagnosis
- Matched cohorts:
  - Oseltamivir for treatment: untreated influenza
  - Zanamivir for treatment: untreated influenza
  - Oseltamivir: zanamivir comparisons--still undergoing analysis

Methods for this analysis, continued

- Selected categories of adverse outcomes to be evaluated
  - Neuropsychiatric
  - Colitis Skin
  - Thrombocytopenia
  - Bleeding
  - Respiratory complications

- Newly observed outcomes = no such diagnosis during 6 month baseline period
- Risk window: up to 30 days following prescription

Methods for this analysis, continued

- Analysis
  - Propensity-score matching to generate drug: influenza pairs
  - Subgroup by age after matching
    - Pediatric age group emphasized in this presentation
  - Relative risks for outcomes with 95% confidence limits
    - Not corrected for multiple comparisons
    - Considered exploratory

- Time Frame
  - Antivirals dispensed 10/01/2007 through 09/30/2009
  - Last possible follow-up: 10/30/2009

Results: patient characteristics

Characteristic	Oseltamivir treatment vs. Influenza, < 18 yo (n = 6,264 /n = 11,783)	Oseltamivir treatment vs. Influenza, 18+ yo (n = 19,817 /n = 14,298)
Modal age band (%)	10-17 y (93%)/0-9 y (55%)	30-39 y (27%)/30-39 y (26%)
% female	48%/48%	54%/55%
Modal region (%)	South 71%/South 79%	South 55%/South 58%
Race:		
African-American	4%/5%	4%/7%
Asian	3%/3%	4%/4%
Hispanic	10%/10%	9%/10%
White	57%/52%	58%/55%
Other	1%/1%	1%/1%
Unknown	25%/29%	25%/24%

Results: Adults

Thirty-day risks for newly observed outcomes associated with oseltamivir or influenza, Aperio database, patients 18+ y.o.

Outcome	Oseltamivir treatment (n=19,817)	Influenza, no antiviral (n=14,298)	Relative risk, oseltamivir/influenza, 95% CL		
	N	N	RR	LB	UB
Colitis	99	84	0.85	0.63	1.15
Neuropsych	207	163	0.92	0.74	1.13
Skin	3	0	undef	0.32	undef
Thrombocytopenia	13	13	0.72	0.32	1.65
Hypothermia	0	0			
Bleeding	74	61	0.88	0.62	1.25
Pneumonia	276	228	0.87	0.73	1.04
Otitis media	116	104	0.80	0.61	1.06
Other respiratory	2005	1549	0.93	0.87	1.00

Results: Pediatric subgroups

Newly Observed Outcomes within 30 days	Ages 0-9					Ages 10-17				
	Oseltamivir (N=416) N	Influenza (N=6,467) N	Relative Risk and 95% Confidence Interval RR	LB	UB	Oseltamivir (N=5,848) N	Influenza (N=5,316) N	Relative Risk and 95% Confidence Interval RR	LB	UB
Pneumonia	6	91	1.02	0.41	2.43	26	31	0.76	0.44	1.32
Otitis Media	10	255	0.61	0.31	1.18	47	86	0.50	0.34	0.72
Other Respiratory	34	646	0.82	0.57	1.17	379	401	0.86	0.74	0.99
Colitis	2	30	1.04	0.17	4.44	15	8	1.70	0.68	4.38
Neuropsychiatric	1	8	1.94	0.09	15.13	23	23	0.91	0.49	1.68
Skin	0	0	--	--	--	0	0	--	--	--
Thrombocytopenia	0	2	0.00	0.00	63.02	0	4	0.00	0.00	1.39
Hypothermia	0	0	--	--	--	0	0	--	--	--
Bleeding	2	7	4.44	0.64	23.13	8	8	0.91	0.31	2.65

Exploration of specific neuropsychiatric events in pediatric age group

ICD9	Diagnosis
780.3	Convulsions
292	Drug-induced mental disorders
293	Transient mental disorders due to conditions classified elsewhere
295	Schizophrenic disorders
296	Episodic mood disorders
297	Delusional disorders
298	Other nonorganic psychosis
300	Anxiety, dissociative and somatoform disorders
311	Depressive disorder, not elsewhere classified

Thirty-day risks for newly observed neuropsychiatric outcomes associated with oseltamivir or influenza, Aperio database, patients < 18 y.o.

	Oseltamivir treatment (n=6,264)	Influenza, no antiviral (n=11,783)	Relative risk, oseltamivir/influenza, 97% CL		
Outcome	N	N	RR	LB	UB
Neuropsychiatric, any	24	31	1.46	0.83	2.56
Convulsions	5	4	2.35	0.55	10.38
Transient mental disorders due to conditions classified elsewhere	0	1	0	0	32.56
Schizophrenic disorders	0	0	-	-	-
Episodic mood disorders	5	3	3.14	0.66	16.49
Other nonorganic psychoses	1	1	1.88	0.05	68.63
Anxiety, dissociative and somatoform disorders	6	16	0.71	0.25	1.91
Depressive disorder, not elsewhere classified	10	6	*3.14*	*1.05*	*9.67*

Neuropsychiatric events by pediatric age subgroups

- Age 0-9 yrs oseltamivir treatment (n=416) :
  - 1 event in Neuropsychiatric category (convulsion)
- Age 10-17 yrs oseltamivir treatment (n=5,848):
  - shown on following slide

Thirty-day risks for newly observed neuropsychiatric outcomes associated with oseltamivir or influenza, Aperio database, patients 10-17 y.o.

Outcome	Oseltamivir treatment (n=5,848)	Influenza, no antiviral (n=5,316)	Relative risk oseltamivir:influenza, 95% CL		
	N	N	RR	LB	UB
Neuropsychiatric, all	23	23	0.91	0.49	1.68
Convulsions	4	3	1.21	0.23	6.79
Transient mental disorders due to conditions classified elsewhere	0	1	0	0	15.73
Schizophrenic disorders	0	0	-	-	-
Episodic mood disorders	5	2	2.27	0.39	16.87
Other nonorganic psychoses	1	1	0.91	0.02	33.17
Anxiety, dissociative and somatoform disorders	6	11	0.50	0.16	1.44
Depressive disorder, not elsewhere classified	10	5	1.82	0.57	6.09

Comments on pediatric results for oseltamivir versus influenza/no antiviral treatment

- Limitations:
  - Exploratory
  - Outcomes not validated by chart review
  - Transient psychiatric events may not generate claims
  - Small sample size

Comments on pediatric results for oseltamivir versus influenza/no antiviral treatment

- No clear indication of previously unsuspected adverse reactions to oseltamivir
- Some reduction in respiratory adverse events (as previously reported)
- In contrast to some previous studies, no reduction in neuropsychiatric events with oseltamivir
- Higher frequencies of certain mood disorder diagnoses with oseltamivir
  - Could be due to a posteriori subgroup analysis, or chance finding due to multiple comparisons, or confounding by age
  - Not statistically significant when appropriately subgrouped by age
  - Inferential meaning uncertain

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