Ranitidine fatality counts in the FDA Adverse Event Reporting System

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ABSTRACT

Introduction: The FDA maintains an Adverse Event Reporting System (FAERS) that monitors medication safety by allowing users to submit adverse events. Ranitidine is now a banned medication that has been used to treat various stomach acid production illnesses. Ranitidine had numerous adverse event reports added to FAERS beginning in 2020 after it was banned.

Methods: All the FAERS adverse events reported from 2019 to 2022 were analyzed to find the active substances with the highest number of fatalities associated with medications per year. Duplicate references to the same active substance in adverse event reports were merged into one. The counts of fatalities per active substance, the counts of fatalities per active substance per qualification type, and the counts of fatalities per active substance per report type were gathered.

Results: Starting in 2020, ranitidine was one of the medications most reported to be associated with fatalities. Unusually large percentages of lawyers began submitting reports, and unusually large percentages of spontaneous reports were being submitted starting in 2020.

Discussion: The safety profile of ranitidine is still not an absolute known entity. The FAERS data now makes ranitidine appear as if it were a pain medication, one which is frequently taken at the end of life and, therefore, more frequently associated with fatalities.

Conclusions: The safety profile of ranitidine is now even more difficult to discern due to the flood of adverse event reports into FAERS. The long-term dangers, such as cancer, will be harder to separate from the noise of the many adverse event reports. Short-term dangers like anaphylaxis reactions will be even more challenging to monitor.

INTRODUCTION

The United States Food and Drug Administration (FDA) maintains the FDA Adverse Event Reporting System (FAERS) to facilitate on-market safety surveillance of medications. [1] A recent phenomenon in the FAERS is the number of adverse event reports for fatalities associated with ranitidine. Ranitidine is a medication for the treatment of heartburn, gastroesophageal reflux disease, gastric and duodenal ulcers, and other stomach acid production ailments. [2] It has been removed from the market since April 2020 but continues to be reported in the FAERS for fatal adverse events.

METHODS

The data gathered for this analysis is the FDA's FAERS quarterly data extraction for the years 2019 to 2022. [3] The FAERS quarterly XML data files were read by a Python program and processed all the reported adverse events for the given year. The processing involved the following:

1. Remove all the events that are not associated with a fatality.
2. Retrieve the qualification, which is an indicator of whether the event reporter is a physician, pharmacist, other health professional, lawyer, or a consumer / non-health professional.
3. Retrieve the report type, which is an indicator of whether the event report is spontaneous, from a report study, other, or unknown.
4. Retrieve the active substance names for the medication referenced in the report.

5. Since there are sometimes duplicates of active substance names in each report, they needed to be made unique so that only one record would be created for each active substance.
6. The counts of fatalities per active substance, the counts of fatalities per active substance per qualification type, and the counts of fatalities per active substance per report type are accumulated.
7. The data is then transposed and sorted by the largest number of fatalities per active substance.

RESULTS

In Figure 1, we see that the fatality counts for 2022 are topped by ranitidine hydrochloride. Also, if we were to include the active substance name of just "RANITIDINE," the lead would be even greater over the other medications associated with fatalities. Also, note the large percentage of spontaneous reports associated with ranitidine hydrochloride.

2022 ADVERSE EVENT REPORTS BY REPORT TYPE FOR FATALITIES					
	Fatality Count	**Spontaneous**	**Report from Study**	**Other**	**Unknown**
RANITIDINE HYDROCHLORIDE	8159	8091	41	27	0
ACETAMINOPHEN	6986	4693	1893	398	0
APIXABAN	6061	4750	1244	67	0
DEXAMETHASONE	5483	3437	1801	242	0
FUROSEMIDE	4423	3003	1251	168	0
PREDNISONE	4352	2842	1029	481	0
RITUXIMAB	4247	2314	683	1250	0
ASPIRIN	4003	2440	1382	181	0
FENTANYL	3911	3450	425	36	0
LENALIDOMIDE	3848	2843	926	78	0
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RANITIDINE	1375	1232	84	59	0

Figure 1 2022 count of adverse event reports for fatalities by report type sorted with largest count on top, including ranitidine

In Figure 2, we see the same list of the largest fatality counts associated with active substances but also listing the counts by qualification of the reporter. Please note the large number of

lawyers who are filing adverse event reports in FAERS, especially “RANITIDINE,” where lawyers make up the majority of reporters.

2022 ADVERSE EVENT REPORTS BY QUALIFICATION FOR FATALITIES						
	Fatality Count	**Physician**	**Pharmacist**	**Other Health Professional**	**Lawyer**	**Consumer or non-health professional**
RANITIDINE HYDROCHLORIDE	8159	6948	5	22	978	206
ACETAMINOPHEN	6986	3057	448	2311	127	932
APIXABAN	6061	929	323	1015	13	3700
DEXAMETHASONE	5483	2414	244	2160	14	559
FUROSEMIDE	4423	1460	408	1179	160	1148
PREDNISONE	4352	1213	148	2147	60	700
RITUXIMAB	4247	1412	49	2494	1	258
ASPIRIN	4003	1168	325	1149	140	1117
FENTANYL	3911	3013	142	440	54	243
LENALIDOMIDE	3848	952	827	1272	3	768
…						
RANITIDINE	1375	147	8	58	1061	100

Figure 2 2022 count of adverse event reports for fatalities by qualification of reporter sorted with largest counts on top, including ranitidine

The same characteristics of the 2022 data are seen in the 2021 data. See Figure 3 and Figure 4. Ranitidine hydrochloride and ranitidine have large numbers of spontaneous reports, with a similar percentage to oxycodone hydrochloride. And ranitidine hydrochloride and ranitidine adverse event reports again have a very large percentage of lawyers as their reporters.

2021 ADVERSE EVENT REPORTS BY REPORT TYPE FOR FATALITIES					
	Fatality Count	**Spontaneous**	**Report from Study**	**Other**	**Unknown**
RANITIDINE HYDROCHLORIDE	11982	11114	57	811	0
OXYCODONE HYDROCHLORIDE	7513	7170	272	70	1
RANITIDINE	7247	7043	139	61	3
ACETAMINOPHEN	7050	4686	1875	477	10
APIXABAN	5560	4185	1302	70	3
DEXAMETHASONE	5498	3269	1963	264	2
FUROSEMIDE	5431	3522	1643	262	4
ASPIRIN	4977	3273	1486	213	4
PREDNISONE	4514	2744	1216	554	0
LENALIDOMIDE	4169	3376	758	35	0

Figure 3 2021 count of adverse event reports for fatalities by report type sorted with largest counts on top

2021 ADVERSE EVENT REPORTS BY QUALIFICATION FOR FATALITIES						
	Fatality Count	Physician	Pharmacist	Other Health Professional	Lawyer	Consumer or non-health professional
RANITIDINE HYDROCHLORIDE	11982	652	17	57	5843	5310
OXYCODONE HYDROCHLORIDE	7513	497	88	216	1456	5214
RANITIDINE	7247	232	29	138	2426	4357
ACETAMINOPHEN	7050	2605	640	2477	78	1058
APIXABAN	5560	944	261	1080	10	3215
DEXAMETHASONE	5498	2384	439	1982	5	601
FUROSEMIDE	5431	1716	453	1554	118	1344
ASPIRIN	4977	1489	364	1409	97	1387
PREDNISONE	4514	1246	165	2125	23	786
LENALIDOMIDE	4169	1480	1336	1041	1	298

Figure 4 2021 count of adverse event reports for fatalities by qualification of reporter sorted with largest counts on top

For 2020 the adverse event data for ranitidine can still be characterized as having a large percentage of spontaneous reports with a large percentage of lawyers as reporters. Ranitidine hydrochloride has fallen down the list of active substances with the largest counts of reports of fatalities, but it is still in the top ten. See Figure 5 and Figure 6.

2020 ADVERSE EVENT REPORTS BY REPORT TYPE FOR FATALITIES					
	Fatality Count	Spontaneous	Report from Study	Other	Unknown
OXYCODONE HYDROCHLORIDE	10793	10286	354	153	0
ASPIRIN	8734	6634	1946	134	20
ACETAMINOPHEN	7843	5500	2039	287	17
RIVAROXABAN	7272	6678	560	34	0
FUROSEMIDE	6748	4622	1940	174	12
DEXAMETHASONE	5740	3659	1871	197	13
APIXABAN	5270	3993	1223	50	4
PREDNISONE	5203	3526	1341	325	11
AMLODIPINE BESYLATE	4988	3449	1418	116	5
RANITIDINE HYDROCHLORIDE	4747	4617	116	14	0
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RANITIDINE	1798	1573	172	49	4

Figure 5 2020 count of adverse event reports for fatalities by report type sorted with largest counts on top, including ranitidine

2020 ADVERSE EVENT REPORTS BY QUALIFICATION FOR FATALITIES						
	Fatality Count	Physician	Pharmacist	Other Health Professional	Lawyer	Consumer or non-health professional
OXYCODONE HYDROCHLORIDE	10793	1063	78	289	2614	6706
ASPIRIN	8734	1799	470	2229	206	3714
ACETAMINOPHEN	7843	3069	733	2470	58	1318
RIVAROXABAN	7272	592	105	1609	256	4676
FUROSEMIDE	6748	1980	614	1842	114	1901
DEXAMETHASONE	5740	2460	610	1946	9	623
APIXABAN	5270	954	295	1277	13	2687
PREDNISONE	5203	1427	184	2430	34	948
AMLODIPINE BESYLATE	4988	2004	307	1328	62	1022
RANITIDINE HYDROCHLORIDE	4747	96	10	100	4025	416
…						
RANITIDINE	1798	197	46	243	998	242

Figure 6 2020 count of adverse event reports for fatalities by qualification of reporter sorted with largest counts on top, including ranitidine

For 2019 the data changes, and now a more typical mix of reporters is visible for fatal adverse events for ranitidine. Also, for 2019 a more even balance of reports that are spontaneous and reports from studies are evident in the data. See Figure 7 and Figure 8.

2019 ADVERSE EVENT REPORTS BY REPORT TYPE FOR FATALITIES					
	Fatality Count	**Spontaneous**	**Report from Study**	**Other**	**Unknown**
FUROSEMIDE	6444	4407	1931	98	8
ACETAMINOPHEN	6413	4374	1849	179	11
ASPIRIN	6382	4202	1992	174	14
DEXAMETHASONE	5057	3192	1726	107	32
NIVOLUMAB	5010	3039	1960	10	1
AMLODIPINE BESYLATE	4608	3175	1372	53	8
APIXABAN	4499	3301	1165	26	7
PREDNISONE	4477	3113	1246	111	7
LENALIDOMIDE	4383	3581	769	15	18
ESOMEPRAZOLE MAGNESIUM	3925	3409	501	14	1
…					
RANITIDINE	912	643	234	33	2
RANITIDINE HYDROCHLORIDE	632	482	145	4	1

Figure 7 2019 count of adverse event reports for fatalities by report type sorted with largest counts on top, including ranitidine

2019 ADVERSE EVENT REPORTS BY QUALIFICATION FOR FATALITIES						
	Fatality Count	**Physician**	**Pharmacist**	**Other Health Professional**	**Lawyer**	**Consumer or non-health professional**
FUROSEMIDE	6444	2090	570	1644	183	1400
ACETAMINOPHEN	6413	2590	458	1918	95	1114
ASPIRIN	6382	1907	502	1666	170	1663
DEXAMETHASONE	5057	2172	387	1844	5	572
NIVOLUMAB	5010	1655	232	1922	3	1188
AMLODIPINE BESYLATE	4608	1832	350	1054	105	862
APIXABAN	4499	1085	283	1133	12	1945
PREDNISONE	4477	1238	151	2111	42	725
LENALIDOMIDE	4383	1874	1214	971	0	315
ESOMEPRAZOLE MAGNESIUM	3925	596	88	543	912	486
…						
RANITIDINE	912	230	63	319	36	150
RANITIDINE HYDROCHLORIDE	632	132	29	134	63	149

Figure 8 2019 count of adverse event reports for fatalities by qualification of reporter sorted with largest counts on top, including ranitidine

DISCUSSION

Until 2019 ranitidine had been considered a safe medication for many years. [4] Then in September 2019 the FDA issued a warning to consumers to consider using other medications instead of ranitidine while it investigated the finding by the independent lab Valisure with

regards to elevated levels of N-nitrosodimethylamine (NDMA) found in ranitidine. In April 2020, the FDA then requested the complete removal of ranitidine from the market. [5] Later that April, the European Medicines Agency recommended the suspension of ranitidine also. [6] Effectively, ranitidine has been banned from consumers since April 2020.

Ranitidine may someday be declared wholly unsafe for consumers and never return to the market. Elevated NDMA levels appear to be a reproducible reality. [7] Even other ranitidine risks such as anaphylaxis have been published. [8] [9] [10] But the long term cancer risk from elevated levels of NDMA as seen in ranitidine is not yet a certainty. [11]

The perceived dangers of ranitidine may be completely overblown. Or as argued by the Wall Street Journal Editorial Board that the risks of NDMA in ranitidine are “junk science.” [12] It still appears that the true safety profile of ranitidine is not known fully yet.

The current data in FAERS for fatal events for ranitidine is now very similar to drugs that are administered for pain management, such as oxycodone, aspirin, and acetaminophen. These are administered at the end of life and therefore expected to be high on the list as the most associated with fatal adverse events. Also, these are more prone to cause overdose fatalities. Oxycodone, aspirin, and acetaminophen would be expected to be at the top of the list of medications a patient would be taking before death.

CONCLUSIONS

For someone who wishes to get an idea of the safety profile of ranitidine, the FAERS data is now of much less usefulness than before it was flooded with adverse events reports for a medication that was not available to consumers at the time of the adverse event report creation. The large number of adverse event reports when there should essentially be none has diminished the value the FAERS could have played in monitoring ranitidine.

Ranitidine is not a medication that is commonly administered at the end of life. Its safety profile has some possible dangers of sudden anaphylaxis reactions. But we will not be able to pick out the signal from the noise as the FAERS is being populated for possible litigation purposes. The long-term dangers, such as cancer, will be harder to separate from the noise of the many adverse event reports. Short-term dangers like anaphylaxis reactions will be even more challenging to monitor, obscured by the many questionable spontaneous adverse event reports.

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