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The Importance of Postmarketing Surveillance in the Identification of Early Safety Signals of Medication Errors in Patients Receiving a New Combination Antibiotic

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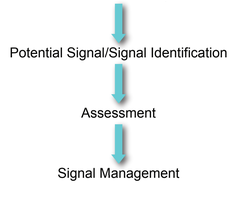
Background

- Postmarketing surveillance is fundamental in the identification of potential safety signals and mitigation of potential safety issues, including medication errors, once a product is approved for use
- Medication errors occur commonly in the medication use process and can include errors in[1]:
  - Drug procurement
  - Prescribing
  - Dispensing
  - Administration
  - Patient monitoring
- Given the voluntary nature of postmarketing reporting, signal detection concerns all stakeholders in the medication use process, including[2]:
  - Healthcare providers
  - Patients
  - Pharmaceutical companies
  - Regulatory authorities
- Consequently, prompt reporting with subsequent assessment and validation of potential safety signals including medication errors is key
- Medication errors have not been reported during the clinical trial program for ceftolozane and tazobactam
  - Recommended dosing of ZERBAXA® is 1.5 g IV (ceftolozane 1 g and tazobactam 0.5 g) every 8 hours for complicated intra-abdominal infections (cIAI) used in combination with metronidazole, and complicated urinary tract infections (cUTI) including pyelonephritis, with dose adjustments for moderate or severe renal insufficiency
  - Currently, there is an ongoing clinical trial for nosocomial pneumonia where the dose is 3 g (ceftolozane 2 g and tazobactam 1 g) every 8 hours for 8 to 14 days
  - No subject received more than the prescribed dose of ceftolozane and tazobactam 1.5 g every 8 hours in the completed Phase 3 studies
  - The highest single dose of ceftolozane and tazobactam received in clinical studies was **4.5 g (3.0 g of ceftolozane and 1.5 g of tazobactam)** given to healthy volunteers. At this dosage no adverse pharmacological effects or increased safety risks were observed
- Medication error reports have been monitored closely through spontaneous postmarketing cases received by Merck & Co., Inc., since US approval in December 2014. A signal was detected and rapidly addressed with actions taken in 2015

Methods

- Routine pharmacovigilance at Merck involves review of adverse event (AE) reports received
- After the launch of ceftolozane and tazobactam, Merck began receiving spontaneous reports associated with medication errors
- Four individual medication error reports were received during the first 3 months post-launch
- Each spontaneous report was analyzed to:
  - Identify potential safety signals
  - Determine if signals were valid
  - Determine next steps



Results

Characteristics of Spontaneous Ceftolozane and Tazobactam Reports Received after Launch in the United States

Report No.	Reporter	Patient Exposure to Medication Error (Dose Received)	Adverse Event Reported	Information Provided by the Reporter
1	Pharmacist	No	No	As the ZERBAXA® vial label does not provide a total dose, the pharmacy staff was uncertain on the number of vials to use to make a 3g dose. Pharmacists are used to seeing a total dosage for beta-lactam/beta-lactamase inhibitor drugs and there is a potential for medication error. There was no patient exposure in this instance.
2	Pharmacist	Yes (4.5 g)	No	The pharmacist was confused with the ceftolozane and tazobactam total dose as the vial label states 1g ceftolozane/0.5g tazobactam. The piperacillin/ tazobactam and ampicillin/sulbactam vial label has the total dose listed as 3.375g and 4.5g, respectively. The pharmacist thought she needed to use 3 vials to make the '3 gram' dose of ceftolozane and tazobactam. A total of 2 doses of 4.5g (3 vials of ceftolozane and tazobactam makes a combined dose of 4.5g) were administered to a patient instead of 3g. The pharmacist reported that the patient did not have any ''issues'' with the higher dose of ceftolozane and tazobactam.
3	Pharmacist	No	No	The pharmacist almost made a medication error because the 1g/0.5g of ceftolozane/tazobactam was confusing when figuring out dilution. Staff who work in the intravenous (IV) room are used to piperacillin and tazobactam vial label which provides the total dose of 4.5g. There was no patient exposure in this instance.
4	Pharmacist	Yes (4.5 g)	No	A patient started treatment with IV ceftolozane and tazobactam 3 g every 8 hour. The patient received 2 doses of ceftolozane and tazobactam 4.5 g instead of 3 g per dose without any AEs. Pharmacy staff interpreted the vial label (1g ceftolozane and 0.5g tazobactam) as requiring 3 vials to make a 3 g dose as they are used to see the total dose such as ampicillin/sulbactam and piperacillin/tazobactam. Patient received 2 doses of ceftolozane and tazobactam 4.5 g without any AEs.

- Two of the errors were intercepted at the pharmacy level
- In the other 2 reports, the patients received an overdose without an adverse event
- The root-cause analysis of the 4 medication error reports showed that the main issue was a misinterpretation of the vial strength by health care providers
- With other beta-lactam/beta-lactamase inhibitor combination products, US pharmacy staff are used to seeing the total dose per vial and not the dose of each component
- The presentation of the strength statement on the vial label was cited by the reporters as the cause of error and confusion resulting in the incorrect calculation of doses

- Actions in response to the medication error reports:
  - Immediately informed the FDA
  - Changed the vial label, carton, and product labeling, adding the total dose of ceftolozane and tazobactam to the vial label
  - Distributed a Dear Health Care Provider (DHPC) letter as per FDA request
  - The FDA issued a Drug Safety Communication regarding these errors via MedWatch in May 2015

Initial Carton and Vial Label

Revised Carton and Vial Label

Initial Dosage and Administration (USPI)

DOSAGE AND ADMINISTRATION

- ZERBAXA (ceftolozane/tazobactam) for Injection, 1.5 g (1 g/0.5 g) every 8 hours by intravenous infusion administered over 1 hour for patients 18 years or older with creatinine clearance (CrCl) greater than 50 mL/min. (2.1)
- Dosage in patients with impaired renal function (2.2):

Estimated CrCl (mL/min)	Recommended Dosage Regimen for ZERBAXA
30 to 50	Ceftolozane/tazobactam 750 mg (500 mg/250 mg) intravenously every 8 hours
15 to 29	Ceftolozane/tazobactam 375 mg (250 mg/125 mg) intravenously every 8 hours
End-stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of ceftolozane/tazobactam 750 mg (500 mg/250 mg) followed by a 150 mg (100 mg/50 mg) maintenance dose administered intravenously every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

Revised Dosage and Administration (USPI)

DOSAGE AND ADMINISTRATION

- ZERBAXA 1.5 gram (g) (ceftolozane 1 g and tazobactam 0.5 g) for injection, every 8 hours by intravenous infusion administered over 1 hour for patients 18 years or older with creatinine clearance (CrCl) greater than 50 mL/min. (2.1)
- Dosage in patients with impaired renal function (2.2):

Estimated CrCl (mL/min)*	Recommended Dosage Regimen for ZERBAXA (ceftolozane and tazobactam)†
30 to 50	ZERBAXA 750 mg (500 mg and 250 mg) intravenously every 8 hours
15 to 29	ZERBAXA 375 mg (250 mg and 125 mg) intravenously every 8 hours
End-stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of ZERBAXA 750 mg (500 mg and 250 mg) followed by a ZERBAXA 150 mg (100 mg and 50 mg) maintenance dose administered intravenously every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

* CrCl estimated using Cockcroft-Gault formula
† All doses of ZERBAXA are administered over 1 hour.

- Eight additional ceftolozane and tazobactam medication error reports were received after Merck initiated communications with FDA
- Two of the errors were intercepted at the pharmacy level
- In the other 5 reports, the patients received either 2.25 g or 4.5 g per dose without an adverse event
- In the remaining case, the reporter was uncertain if the incorrect dose had reached the patient

Additional reports received after Merck initiated communications with FDA

Report No.	Reporter	Patient Exposure to Medication Error (Dose Received)	Adverse Event Reported?
5	Pharmacist	No	No
6	Pharmacist	Yes (2.25 g)	No
7	Pharmacist	Yes (4.5 g)	No
8	Pharmacist	Uncertain (2.25 g)	No
9	Pharmacist	Yes (not reported)	No
10	Pharmacist	Yes (2.25 g)	No
11	FDA†	No	No
12	FDA‡	Yes (4.5 g)	No

†Received from FDA Freedom of Information Act Line Listing. Medication error event date not reported.
‡Received from FDA Freedom of Information Act Line Listing. Medication error event date reported as 16-Jul-2015.

Conclusions

- Postmarketing surveillance is essential for proactive identification of potential safety signals, including potential medication errors
- Pharmacovigilance facilitated rapid identification of a potential safety signal regarding medication errors, and, upon validation and confirmation, rapid development of risk minimization measures in order to minimize further errors and risk to patients

References

1. Institute of Medicine. *Preventing Medication Errors: Quality Chasm Series.* Committee on Identifying and Preventing Medication Errors, Aspden P, Wolcott J, Bootman JL, Cronenwett LR, eds. Washington, DC: The National Academies Press; 2007.
2. Guideline on Good Pharmacovigilance Practices, Module IX–Signal Management. European Medicines Association and Heads of Medicines Agencies; 2012.

http://tinyurl.com/zu378dc