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Adverse Drug Reactions Due to Oral Antibiotics Prescribed in the Community Setting - England

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Running title: Antibiotic –related adverse drug events in England

ABSTRACT

Background

Oral antibiotic prescribing in the community setting is commonplace with ongoing efforts to optimize this practice. There are several concerns that relate to the practice and include antibiotic cost, development of bacterial resistance to these agents, and associated adverse drug events (ADR). We therefore performed an analysis of ADR associated with oral antibiotic prescriptions in community care (non-hospital) settings in England with the goal of determining both ADR reporting rates and severity due to oral antibiotics.

Methods

Data for all oral antibiotic use in the primary care settings in England and the National Yellow Card Interactive Drug Analysis Profile were both abstracted for 2010 through 2017.

Results

Overall, there were 320,599,292 prescriptions issued for oral antibiotics during the eight-year survey. Although the overall ADR rate was relatively low, 58/1,000,000, the reported serious (63.6%) and fatal (1.21%) rates were striking.

Conclusions

Continued monitoring of ADR rates due to oral antibiotic prescribing in the community setting is warranted, considering the prevalence of serious/fatal reports identified during the eight-year study period in the Yellow Card profile. These data should be useful in developing strategies in securing optimal prescribing practices.

Key words: antibiotics, England, oral, community-setting, adverse drug events

INTRODUCTION

Prescribing oral antibiotics in the community (non-hospital) care setting may appear simple, but multiple factors are operative in defining the risk:benefit ratio of whether an antibiotic should be given to an individual patient. This approach is even more difficult in the primary care setting where diagnostic laboratory screening is not available or if performed, results often delayed. Among these factors, adverse drug reactions (ADR) associated with oral antibiotic prescribing have to be considered in this decision-making to optimally manage a patient [1].

In the present investigation, an analysis of prescription cost data for oral antibiotic prescribing in community settings across England was conducted. Our aim was to characterize and quantify the rate of reported adverse drug reactions (ADR) to these drugs.

METHODS

The Prescription Cost Analysis data held by NHS Digital (https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis) were abstracted to detect all oral antibiotics prescribed in the ambulatory care setting in England for 2010-2017. Prescriptions were submitted by physicians, nurse practitioners, and other health care providers, including dentists.

National Yellow Card Interactive Drug Analysis Profile data from the Medicines and Healthcare Products Regulatory Agency (MHRA) (http://yellowcard.mhra.gov.uk/iDAP/) were interrogated and data extracted for all oral antibiotics or where the route of administration was not stated (reactions to drugs administered parenterally, topically or by other routes were excluded) to define the "reported" ADR rate/million prescriptions calculated for the study period. The Yellow Card system provides an opportunity for patients and healthcare professionals to report ADRs to the MHRA. Reporting can be via either online submission or paper form mail-in, which is postage free. This system has been in place for over 50 years and has been crucial for identifying ADRs, particularly those detected in the post-approval period. The Yellow Card data were previously used

to examine the ADR rates of fluoroquinolones in the same population and ADR rates of oral antibiotics that were prescribed by dentists [2,3].

Because all data reported herein is anonymous, ethics approval was not required.

RESULTS

There were 320,599,292 prescriptions for oral antibiotics issued in the ambulatory care (non-hospital) setting in England during the eight years (2010-2017) of the study period. The overall reported ADR rate was 57.9/1,000,000 prescriptions with 63.6% of reactions classified as serious and 1.21% of them as fatal (Table 1).

The beta-lactam antibiotics, which included both penicillins and cephalosporins, widely varied in ADR rates (Table 1). For example, despite the relatively low use of ampicillin in the community setting, the overall reported rate of ADRs due to this agent was striking (683/1,000,000 prescriptions) with 437/1,000,000 classified as severe, 27/1,000,000 as fatal, and 219/1,000,000 as non-serious. In contrast, the overall reported ADR rates for amoxicillin, flucloxacillin, phenoxymethylpenicillin, and co-amoxiclave were much lower: 21.5/1,000,000 prescriptions, 44/1,000,000 prescriptions, 137/1,000,000 prescriptions, and 71/1,000,000 prescriptions, respectively. Amoxicillin had the lowest ADR rate of all individual antibiotics examined and cephalosporins, as a class, had the lowest reported ADR rate (27.4/1,000,000 prescriptions) of all classes of antibiotics examined (Table 1).

The reported ADR rates for some of the non-beta-lactam antibiotics were also high (Table 1). This included the fluoroquinolones (250/1,000,000 prescriptions), clindamycin (337/1,000,000 prescriptions), co-trimoxazole (388/1,000,000 prescriptions), and “other sulfonamides” (1,614/1,000,000 prescriptions). The fatal ADR rate for co-trimoxazole (21.2/1,000,000 prescriptions) was second only to that (27.3/1,000,000 prescriptions) of ampicillin (Table 1). Of note, the overall and fatal reported ADR rates for trimethoprim alone were much lower

(62/1,000,000 prescriptions and 0.6/1,000,000 prescriptions, respectively) – close to the average for all antibiotics studied.

DISCUSSION

Our country-wide investigation focused on reported ADR related to oral antibiotic prescribing in the community care (non-hospital) setting in England. The Yellow Card reporting system, which has included data from 1964 to present, enabled us to conduct this investigation.

The ampicillin reported ADR rates for serious and fatal events are striking in the current study. Certainly, penicillins have been recognized as more likely causes of ADRs, some of which are potentially life-threatening [4]. While it is difficult to explain the differences in these rates between ampicillin and amoxicillin and co-amoxiclave, the extremely low prescription rate for ampicillin with only a total of 25 ADRs reported for the three categories of non-serious, serious and fatal events over eight years could have exaggerated ADR rate results.

Clindamycin has a strong association with risk of *C. difficile* infection as compared to that for many other classes of antibiotics. In fact, in a recent meta-analysis, the odds ratio of developing *C. difficile* infection after clindamycin administration was 16.8 as compared to no antibiotic exposure, which was the highest of all classes of antibiotics examined [5]. It is therefore not surprising that clindamycin had such high rates of overall and fatal reported ADRs.

As expected, the reported ADR rate for co-trimoxazole was much higher (~6-fold) than that for trimethoprim and included a high rate of fatal ADRs; the rate for the "other" sulfonamides was extremely high, but the scant number of prescriptions issued for these drugs over the study period makes it difficult to make conclusions about severity of reactions.

The findings regarding macrolide/azalide use are not surprising (Table 1). The well-recognized gastrointestinal upset associated with erythromycin likely contributed to its ADR rate (47.2/1,000,000 prescriptions) [6]. The higher reported ADR rate (99/1,000,000 prescriptions) observed for clarithromycin, however, is difficult to explain, although it is tempting to speculate

that because clarithromycin is a more recently available macrolide as compared to erythromycin, a Yellow Card report is more likely to be submitted for clarithromycin.

Limitations

Dependence on passive reporting in the Yellow Card reporting system method for characterizing the rate and types of reported ADRs was a major limitation which prevented the ability to calculate a true incidence rate of ADRs and may encourage reporting, and therefore overestimation, of more severe reactions and reactions occurring with newer agents.. Nevertheless, the results of this investigation are consistent with our current characterization of ADR associated with the oral antibiotics prescribed in the community setting.

Conclusions

The Yellow Card profile data have been collected for over five decades in England and provides helpful information to clinicians regarding ADR rates for oral antibiotics commonly prescribed in the community setting. The current investigation provides an update on ADR rates and their severity for both beta-lactam and non-beta-lactam antibiotics which may be helpful in designing an optimal oral antibiotic treatment regimen for an individual patient.

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TRANSPARENCY DECLARATIONS

None to declare.

REFERENCES

1. Tandan M, Cormican M, Vellinga A. Adverse events of fluoroquinolones vs. other antimicrobials prescribed in primary care: a systematic review and meta-analysis of randomized controlled trials. Internation J Antimicrob Agents. 2018;52:529-540.
2. Baddour LM, Dayer MJ, Thornhill MH. Fluoroquinolone use and associated adverse drug reactions in England. J Infect 78 (2018), pp.252-254.
3. Thornhill MH, Dayer MJ, Durkin MJ, et al. Risk of adverse reactions to oral antibiotics prescribed by dentists. J Dent Res [epub ahead of publication].
4. Doi Y, Chambers HF. Penicillins and β-lactamase inhibitors. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennettt's Principles and Practice of Infectious Diseases. Updated edition, 20; 263-277.e3. Philadelphia PA: Elsevier Saunders;
5. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. Antimicrob Agents Chemother 57 (2013), pp.2326-2332.
6. Hansen MP, Scott AM, McCullough A, et al. Adverse events in people taking macrolide antibiotics versus placebo for any indication. Cochrane Database of Systematic Reviews. 2019; Issue 1. Art. No: CD011825. DOI: 10.1002/14651858.CD011825.pub2.

Table 1. Adverse drug reaction data for oral antibiotic prescribing – England 2010-2017.

		No of Adverse Reactions (2010-17)				Adverse Reactions/Million Rx (2010-17)			
	No of Rx 2010-17	Non-Serious	Serious	Fatal	Total	Non-Serious	Serious	Fatal	Total
Amoxicillin	101,663,837	956	1,214	14	2,184	9.4	11.9	0.1	21.5
Co-Amoxiclave	16,343,274	330	809	25	1,164	20.2	49.5	1.5	71.2
Ampicillin	36,590	8	16	1	25	218.6	437.3	27.3	683.2
Flucloxacillin	33,392,162	502	957	10	1,469	15.0	28.7	0.3	44.0
Phenoxymethylpenicillin	19,424,189	1,457	1,198	7	2,662	75.0	61.7	0.4	137.0
Cephalosporins	10,731,391	97	192	5	294	9.0	17.9	0.5	27.4
Tetracyclines	32,776,834	550	1,068	28	1,646	16.8	32.6	0.9	50.2
Azithromycin	3,969,992	48	182	3	233	12.1	45.8	0.8	58.7
Clarithromycin	17,398,169	543	1,140	22	1,705	31.2	65.5	1.3	98.0
Erythromycin	16,065,288	318	429	11	758	19.8	26.7	0.7	47.2
Clindamycin	681,841	69	159	2	230	101.2	233.2	2.9	337.3
Co-Trimoxazole	902,502	82	249	19	350	90.9	275.9	21.1	387.8
Trimethoprim	29,051,925	621	1164	17	1,802	21.4	40.1	0.6	62.0
Other Sulfonamides	7,437	2	10	0	12	268.9	1,344.6	0.0	1,613.6
Metronidazole	14,169,420	262	729	10	1,001	18.5	51.4	0.7	70.6
Fluoroquinolones	6,411,315	251	1,314	40	1,605	39.1	205.0	6.2	250.3
Methenamine	214,626	4	9	0	13	18.6	41.9	0	60.6
Nitrofurantoin	17,358,500	428	947	23	1,398	24.7	54.6	1.3	80.5
All Antibiotics	**320,599,292**	**6,528**	**11,786**	**237**	**18,551**	**20.4**	**36.8**	**0.7**	**57.9**

APPENDIX

Aminoglycosides were excluded from this investigation since their oral absorption is minimal to none and was only 0.002% of overall oral antibiotic prescribing. Similarly, fosfomycin was not included due to the limited use of the drug. Linezolid and tidezolid were not included for analysis since these agents are only prescribed by secondary care. A summary of the fluoroquinolone data will be included in the current investigation for the overall analysis of oral antibiotic use, although further details regarding oral fluoroquinolone use will not be included herein as they were the focus of a prior publication [2]. Oral antibiotics (isoniazid, rifampin, ethambutol, para-aminosalicylic acid, pyrazinamide, clofazimine, bedaquiline, rifabutin, rifapentine, dapsone, ethionamide, cycloserine, prothionamide, and delamanid) used primarily to treat mycobacterial infections were excluded from the analysis.