



CHANGING PATTERN OF REPORTING ADVERSE REACTIONS DUE TO COMMON ANTIBIOTICS USED IN FIELD OF DENTISTRY: A TREND ANALYSIS FROM 2008 TO 2018

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Conflicts of Interest: Nil

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Abstract:

Background: Overuse and misuse of antibiotics has been highlighted by various international bodies, a trend in indulging self medication / over prescription of drugs by the doctors has been observed among various groups across globe.

Aim: Thus this secondary data analysis was formulated with an aim to assess the change in reporting of adverse reactions of the commonly used drug in dentistry and distribution of the reporting across countries.

Design and setting: Secondary data analysis

Methods: A secondary data analysis of the FDA Adverse Event Reporting System (FAERS, formerly AERS) data base was carried out from period of 2008 to 2018.

Results: Among the commonly used drugs in dentistry amoxicillin usage was highest (54.9%) followed by metronidazole (38.5%). Amoxicillin drug usage was highest among those aged above 65 years (55.4%), and lowest among those aged below 18 years (2.1%). Reporting of serious ADE's was seen higher among female (59.3%) than male. Type of drug used and place of residence of the participants were significantly associated ($p < 0.005$) with serious ADE outcomes.

Conclusion: Amoxicillin drug tends to have serious ADE when compared to other antibiotics

Introduction

Antibiotics are the one of the prime drugs used in the practice of both medical and dental sciences. Most of the antibiotics used are to prevent or treat infections. The use of broad spectrum antibiotics have become more indispensable in our dental practice.(1) This is because, antibiotic prescription is empirical, i.e., the clinician does not know which microorganism is responsible for the infection as no sensitivity test of microbes is performed using culture methods. (2) As a result of the above, broad spectrum antibiotics are typically prescribed frequently by the clinicians and it has become habitual for the public to take non prescribed antimicrobials for oral infections.(3) Though there are evident benefits of antibiotic treatment there is always a drawback of these antibiotics represented by the undesired effects of their use. On one hand there are side effects with repercussions for the patient, such as gastric, hematological, neurological, dermatological, allergic and other disorders. Further, on the other hand the inappropriate and excessive use of antibiotics is a major factor in the emergence of antibiotic resistance.(4) Dentistry's contributions to the

problem of antibiotic resistance can be substantial because dentists prescribe ~10% of all common antibiotics. Consequently, surveillance of antimicrobial resistance, monitoring of antibiotic usage and attempts to improve prescribing attitudes have become crucial.(5)

Antimicrobial resistance (AMR) within a wide range of infectious agents is a growing public health threat of broad concern to countries and multiple sectors. A global action Plan on antimicrobial resistance was carried out among all the WHO (World Health Organization) regions was reported in year 2014, whose guidelines was made on April 30th, 2013. The key findings of the report stated extremely high rates of resistance (87.7%) have been observed in bacteria that cause common health-care associated and community-acquired infections in all WHO regions. There are significant gaps in surveillance, and a lack of standards for methodology, data sharing and coordination.(6)

Though this menace of overuse and misuse of antibiotics has been highlighted by various international bodies, a trend in indulging self medication / over prescription of drugs by the

doctors has been observed among various groups across globe. This practice not just aggravates the antibiotic resistance problem, but also poses a threat to the mortality rates of the public in the form of adverse drug reactions (7). Thus this secondary data analysis was formulated to assess the change in reporting of adverse reactions of the commonly used drug in dentistry and distribution of the reporting across countries. This would provide a better a proper platform to frame stringent laws for the public.

MATERIALS AND METHOD

DATABASE SOURCE

A secondary data analysis of the FDA Adverse Event Reporting System (FAERS, formerly AERS) data base was carried out. In 1969, FDA (Food and Drug Administration) US initiated a system to record adverse reaction of drugs which was further redesigned to ADE reporting database – the FDA adverse event report system in 1998. The database is used by the FDA and health care researchers to study safety-related issues for drugs. The dataset is publicly available on the FDA website and consists of multiple files that can be linked using unique event identifiers.

ELIGIBILITY CRITERIA

Data files for 2008 through 2018 were used for this study. Since the first global surveillance report on antibiotic misuse was submitted in 2014 by WHO, time frame before and after 2014 were chosen. Both U.S and non-U.S. reports were included to understand the impact of geographic variations in ADE reporting. A wide age range between 3 years to 85 years was considered to analyse the usage pattern among pediatric, young and geriatric population. Reports from clinical trials were excluded due to mandatory reporting requirements. Only those reports with complete information on the outcome were retained in the final analyses. Since FAERS data may contain more than 1 report per case when follow-up information is submitted, only the most recent report for a given case was included. We identified and ranked drugs that were most commonly used in field of dentistry as primary suspect in serious ADE reports i.e, amoxicillin and metronidazole. Drugs were identified by brand name or generic name and were recoded to the active ingredient name to determine the final count of the suspect drug. Only drugs listed as a primary suspect were included in the analysis. Drugs listed as secondary suspect were excluded due to the

uncertainty of the association between the drug and the ADE. Reports for medical devices, vaccines, dietary supplements, and illegal drugs were excluded.

Outcomes in the ADE reports were recoded and each report was assigned to one of 3 hierarchical categories: death > disability (disability or congenital anomaly) > or all other serious outcomes (hospitalizations, requiring intervention, life-threatening, or other serious outcomes). In present study the independent variables were age (3 to 12 years, 13 to 65 years, > 65 years), gender (male, female), date of reporting (2008-13, 2014-18), country of residence (low income, middle income, high income) and drug used (amoxicillin, metronidazole, combination).

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize data. Frequency and percentage were used to represent outcome measure. The association between independent and dependent variable was determined using Chi square test and multivariate logistic regression was performed with 95% Confidence Interval.

RESULTS

Among the commonly used drugs in dentistry amoxicillin usage was highest (54.9%) followed by metronidazole (38.5%). Amoxicillin drug usage was highest among those aged above 65 years (55.4%), and lowest among those aged below 18 years (2.1%). Reporting of serious ADE's was seen higher among female (59.3%) than male. The distribution of ADEs reports by age was highest for death (1.9%) among the 18 to 65 years, disability as ADE was seen highest (11.8%) among below 18 years of age and other serious outcomes as ADE seen highest (91.0%) among participants > 65 yrs. of age. Overall, there was an upward trend in serious ADE reporting. From 2008 through mid-2018, 4-fold increases in serious ADEs are reported to the FDA, although the reports of serious ADEs decreased drastically during 2014 and slightly during 2010 and 2016. A total of 934 serious outcomes were reported over the 10-year study period: 14 deaths, 66 disabilities, and 854 other serious outcomes, whereas the relative percentage of reports for deaths was highest during 2013 (28.6%). The percentage of reports of disability was highest during 2015 (24.7%) and remained below 15% throughout the remaining periods. The reports of other serious outcomes were less than 15% throughout the period. But overall, the other serious

outcomes category accounted for 91.4% serious ADEs reports.

Type of drug used and place of residence of the participants were significantly associated ($p < 0.005$) with serious ADE outcomes. A multivariate logistic regression showed that middle income countries reported serious ADE reactions 26.7 times more than countries from high and low income. Also, reports of serious ADE were seen 3.47 times higher among amoxicillin users when compared to other two drugs. Both the variables (drug used and country of residence) are found to be a good fit in the model developed.

Table 1: Shows demographic distribution, comparison of independent variables with Outcome measure.

variables	Frequency (%)	P value
Age		
0-18 years	78 (8.4%)	0.662
19-64 years	428 (45.8%)	
>/ 65 yrs	489 (52.4%)	
Gender		
Male	380 (40.7%)	0.382
Female	554 (59.3%)	
Drug used ^a		
Amoxicillin	513 (54.9%)	<0.001*
Metranidazole	360 (38.5%)	
Combination of both	61 (6.5%)	
Country of reporting ^a		
Low income	130 (13.9%)	0.002*
Middle income	662 (70.9 %)	
High income	142 (15.2%)	
Outcomes		
Death	14(1.5%)	-
Disability	66(7.1%)	
Other serious outcomes	854 (91.4%)	

a- Type of drug used and country of reporting were found to be statistically significant with the serious ADEs (Chi square test)

Table 2 Multinomial regression shows significant association between amoxicillin and middle income countries with Serious ADE

Variables	Exp [B]	p value
Drug used		
Amoxicillin	3.47	<0.001*
Country of reporting		
Middle income countries	26.7	<0.001*

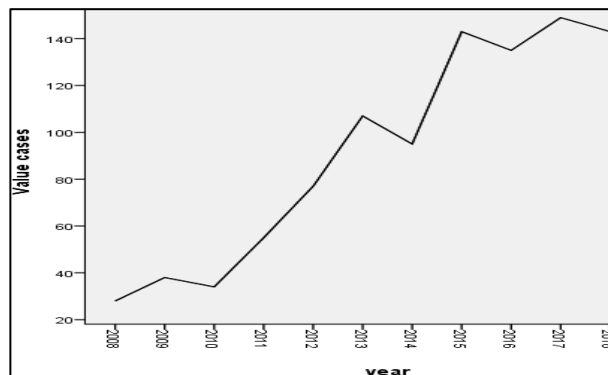


Figure 1 illustrates the trend of serious ADE reporting to FAERS over time.

DISCUSSION AND SUMMARY

Our study reported recent patterns of serious ADEs reported to the FDA—death, disability, and other serious outcomes—and demonstrates that the number of serious ADE reports were on a constant rise from 2008 to 2018 with a decrease of reporting during 2014, 2016 and 2018. This decrease in reporting could be due to the guidelines put forth by WHO on risks due to antibiotic overuse during 2014 and 2015. Interestingly, the reporting of serious ADE’s was highest during 2013 and 2015 which accounted for the need to formulate guidelines by the International health agency WHO(World Health Organization).(6)

STRENGTH and LIMITATIONS

This one of a few studies reporting the pattern of antibiotics usage across populations in globe for a decade. Since it is a secondary data analysis, it’s a cost efficient and time saving way to analyse the pattern. Also, this study compares the changing in pattern across various countries based on income thus making it easier for stakeholders to create policies accordingly.

Our study has several limitations. First, uncertainty regarding the drug’s role in a reported ADE exists due to the voluntary nature of reports. The role of other drugs that were used concomitantly with the primary suspect drug when the ADE occurred cannot be completely ruled out. Therefore, causal inferences between drug and ADE cannot be drawn from the data. Second, ADE reporting may be influenced by several external factors, such as duration the drug is in the market, litigation, and advertising or other media attention and these factors cannot be addressed in our analyses. Finally, reporting trends of ADEs have been shown to vary over time. Whether these variations in trends accurately reflect the actual variations in the occurrence of ADEs or are a result of

changes in reporting patterns cannot be ascertained. The results of our analysis must be interpreted in the context of these limitations.

COMPARING WITH EXISTING LITERATURE

Data on the age distribution of serious ADEs from our study show that 55.4% of the reported ADEs occurred in persons aged ≥ 65 years. A recent report by the CDC indicates that about 44% of the population of drug users falls into the ≥ 65 year age group. Thus, disproportionately high proportions (about 55.4%) of serious ADEs reports were among those ≥ 65 years. There remains ambiguity on whether these data actually indicate a higher rate of ADEs among patients in this age group, or if ADEs among older patients are more likely to be reported. In the present study least usage of antibiotics were seen among the pediatric population as most of the children do not need it. (8).

Our study reported that amoxicillin to be of highest usage whose reports of serious ADE were 3.47 times higher than other drugs searched. This is an alarming finding because amoxicillin is a broad spectrum antibiotic commonly used for multiple infectious conditions hence its use may contribute more to the global antibiotic resistance program.(9) The study also stated that middle income countries have higher reports of ADE than low and high income countries. This could be because of poor regulation of antimicrobials results from absent policies or, more commonly, from absent enforcement of policies among developing countries.(6) In contrast with developed countries where stringent by laws are imposed on clinician and pharmists to prevent usage of antimicrobials over the counter, under developed countries have limited access to antimicrobials, particularly to new drug classes, and drugs that are available often lack activity against these multidrug-resistant bacteria that are becoming more common, hence reducing the reports of adverse actions by these people (10).

IMPLICATIONS

Further researches on the change in pattern of antibiotic usage using qualitative and longitudinal studies are required for better understanding of the public, thus helping the policy makers to create policy that accustom to the nature of life.

CONCLUSION

Prescription drugs are a necessary component of the treatment of diseases and disorders, but the

occurrence of serious ADEs can cause the benefits of these drugs to be outweighed by the harm. Our study of FAERS indicates that reports of serious ADEs increased from 2008 through 2018. Amoxicillin drug tends to have serious ADE when compared to other antibiotics. FAERS is a key component of post-marketing surveillance and is a valuable resource that supports ongoing efforts to understand the public health burden of ADEs.

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