

Incidence of Diarrhea Associated with Different brands of Co-Amoxyclav in Pediatric Population

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Abstract

Background: Antibiotic associated diarrhea (AAD) is encountered in a considerable proportion of children who are treated with antibiotics. Widely used antibiotic combination of amoxicillin trihydrate and clavulanic acid has been reported to cause AAD in 5-25% of children. The novel manufacturing process PURIMOX is a biocatalytic synthesis of the active ingredient amoxicillin which prevents environmental pollutant contamination unlike the conventional chemical synthesis and may impact the incidence of AAD with this antibiotic.

Methods

A prescription database was used to extract total number of prescriptions of Co-amoxyclav over a period of one year. Prescriptions of the same population visiting for a subsequent follow up were also extracted. The objectives of this prescription data analysis were to evaluate the total number of Co-amoxyclav prescriptions with a co-prescription of a probiotic in the first visit and co-prescription of a probiotic and/or anti-diarrheal in the subsequent visit. Prescriptions of Clamp and Augmentin were analysed in detail.

Results

A total of 578328 prescriptions of Co-amoxyclav were analyzed over a period of one year; out of these Clamp accounted for 123526 prescriptions (21.35%) while Augmentin accounted for 74227 prescriptions (12.83%). Of these 31078 (5.37%) were given a co-prescription of a probiotic. Clamp had lesser (4.24%) number of co-prescriptions with probiotic compared to Augmentin (11.83%); (p value <0.001). During a subsequent follow up visit 15978 prescriptions were analysed [Clamp: 2519 (15.76%), Augmentin: 2499 (15.64%)]. At the follow up visit 9.7% of the total Co-amoxyclav prescriptions received a probiotic or an anti-diarrheal and Clamp had lower co-prescriptions with probiotics (8.7%) compared to Augmentin (18.5%); p value <0.001).

Conclusion

The study results demonstrated that a considerable number of Co-amoxyclav prescriptions were also co-prescribed a probiotic anticipating onset of antibiotic associated diarrhea. The number of prescriptions receiving a probiotic at the initial visit was lower for Clamp compared to Augmentin and similarly at follow up fewer prescriptions of Clamp required an addition of a probiotic indicating lower incidence of diarrhea associated with it.

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I. Introduction

Amoxicillin is an aminobenzyl penicillin and a beta lactam antibiotic. The drug is one of the several semisynthetic derivatives of 6-aminopenicillanic acid. β -lactam antibiotics have been in clinical use for more than 70 years and are currently the most widely used group of antibiotics. The β -lactam ring of 2-azetidinone ring is the common moiety of all β -lactam antibiotics, which is responsible for their bactericidal capabilities¹. The drug is a moderate-spectrum, bacteriolytic, β -lactam antibiotic in the aminopenicillin family that is used to treat bacterial infections caused by susceptible Gram-positive and Gram-negative microorganisms.² β -lactam inhibit the final stage of bacterial cell wall synthesis specifically inhibiting the D-alanyl D-alanine

transpeptidases or penicillin binding proteins which elongate and cross link the peptidoglycan in bacterial cell walls causing growth inhibition, cell lysis, and ultimately cell death.

The conventional method of synthesis of β -lactam antibiotics are complex chemical synthesis. Challenges associated with this conventional process is use of toxic solvents and chemicals as well as generation of considerable amounts of non-biodegradable wastes. This results in significant environmental pollution.

Co-Amoxycylav is largely safe and well-tolerated in the general population, with the vast majority of adverse effects being only mild gastrointestinal symptoms. The single most common complaint is diarrhoea occurring in 5 – 25%³ of all patients, but others include nausea, vomiting, loose stools, and abdominal discomfort. The incidence of diarrhoea is higher in amoxicillin-clavulanate compared with amoxicillin alone.

Antibiotic associated Diarrhoea can be defined as diarrhoea that occurs in conjunction with antibiotic administration that cannot be explained by another process.⁴ The symptoms and severity can vary from mild abdominal discomfort to severe colitis. The aetiology of AAD varies widely, but almost all antibiotics with a broad spectrum of antimicrobial activity have been associated with antibiotic associated diarrhoea. The disruption of the normal gut microbiota leading to overgrowth of pathogenic organisms and functional disturbances of the intestinal carbohydrate and bile acid metabolism results in osmotic diarrhoea. Allergic toxic and pharmacologic effects of antibiotics are also implicated in the aetiology.

Pathophysiology of antibiotic associated diarrhoea

The colonic bacterial flora normally metabolises nutritional carbohydrates and endogenous carbohydrates. Antibiotics which affect the anaerobic flora cause reduced bacterial fermentation and a subsequent increase in undigested carbohydrates in the colon and faeces⁵ resulting in osmotic diarrhoea caused primarily by carbohydrate malabsorption

Deficiency in short chain fatty acids (SCFA) is more likely to occur in hospitalised patients who are not receiving usual enteral nutrition. With a reduction in SCFAs, the colonic mucosa cannot efficiently perform its usual functions of reabsorption of water, electrolytes and SCFAs. SCFA deficiency, in combination with reduced bacterial fermentation from ongoing antimicrobial administration can cause diarrhoea⁶. Enteral and parenteral administration of antibiotics impairs the colon's inherent mucosal defence to adherent microorganisms. Although an organism such as *C. difficile* is often present in low concentrations, bacterial antagonism and the mucosa's resistance to bacterial adherence protects the host from developing diarrhoea. With the alteration in mucosal resistance, *C. difficile* or other pathogens can adhere to the colonic mucosa and readily proliferate, leading to the formation of pseudomembranes. This can lead to a secretory diarrhoea similar to an acute infectious organism.

The objective of the current study is to evaluate and compare incidences of reported diarrhoea in two specific brands of Coamoxycylav.

II. Materials and Methods

A cross sectional study was carried out between January 2019 to January 2020 with a total of 5,78,328 prescriptions of children less than 12 years of age collected randomly from OPDs of pediatric departments of private hospitals or private clinics using an electronic prescription database from 12 cities with around 1000 doctors. Prescriptions were collected irrespective of patient characteristics and diagnosis over a period of 1 year. Statistical significance was estimated using traditional methods as individual patient level data was not available.

The objectives of this prescription data analysis were:

- To evaluate the total number of Co-amoxycylav prescriptions with a co-prescription of a probiotic at the first visit.
- To evaluate the total number of Co-amoxycylav prescriptions with the addition of a probiotic or an anti-diarrhoeal or both at a subsequent follow up visit

Two brands of Co-amoxycylav were used for the analysis: Clamp manufactured by Dr. Reddy's Laboratories and Augmentin manufactured by GlaxoSmithKline plc.

III. Results

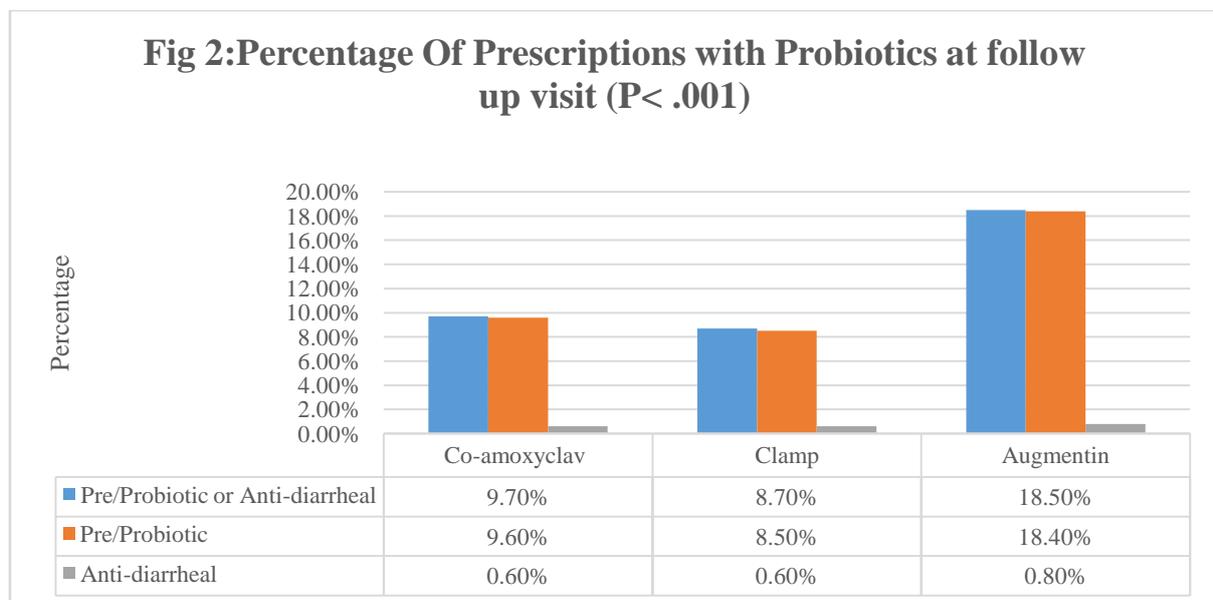
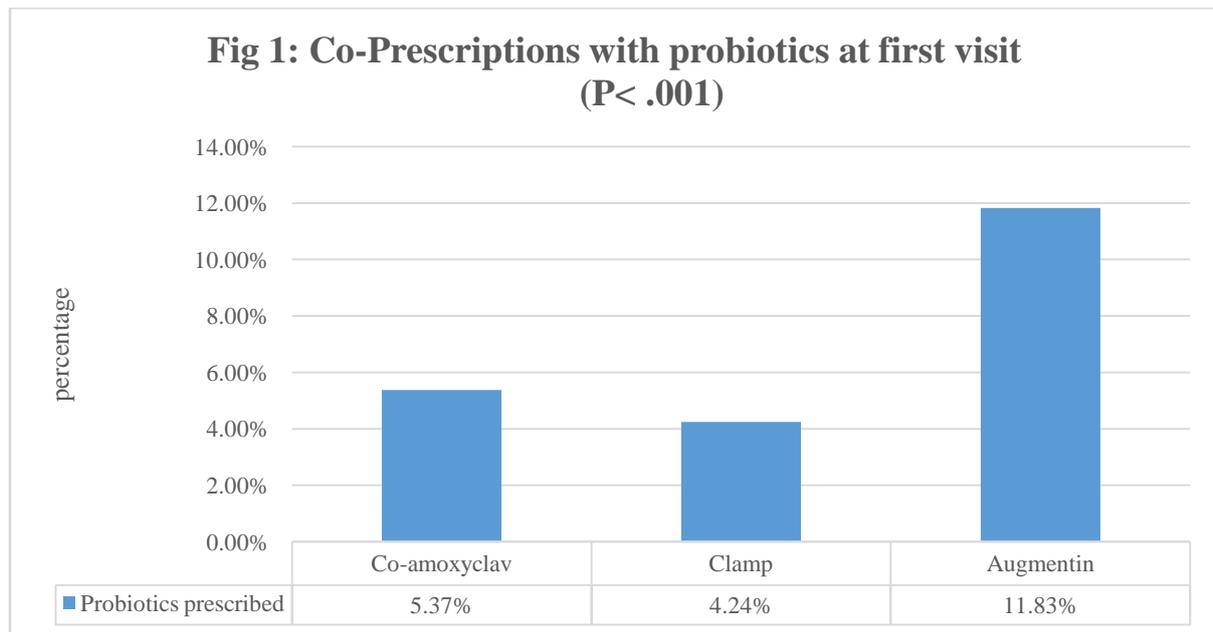
A total of 578328 prescriptions with a co-prescription of a probiotic at the initial visit were analyzed. The total number of prescriptions for Clamp was 123526 (21.35%) and for Augmentin was 74227 (12.83%). Of the total number of Co-amoxycylav prescriptions, 31078 (5.37%) were given a co-prescription of a probiotic at the initial visit. 87% of the prescriptions for co-amoxycylav were prescribed for a duration of 4-7 days.

The number of Clamp prescriptions with a co-prescription of a probiotic at the first visit was 5236 (4.24%) (Fig.1). Similarly, the number of Augmentin prescriptions with a co-prescription of a probiotic at the first visit was 8779 (11.83%). There was a statistically significant difference (p value < 0.001) between the brands in terms of a co-prescription of a probiotic at first visit.

Incidence of Diarrhoea Associated with Different brands of Co-Amoxycylav In Pediatric Population

A total of 15,978 prescriptions of Co-amoxycylav were extracted with follow up visit data and analysed to estimate the incidence of diarrhoea associated with use of each brand (Fig.2) Clamp prescriptions were 2519 (15.76%) and Augmentin was 2499 (15.64%). During the follow up visit 9.7% of the total prescriptions received a probiotic or an anti-diarrheal of which Clamp accounted for 8.7% of the prescriptions (8.5% were probiotic and 0.6% were anti-diarrheal) and Augmentin received 18.5% prescriptions of either a probiotic or an anti-diarrhoeal (18.4% were probiotic and 0.8% were anti-diarrheal). This was a statistically significant difference (p value < 0.001) between the two brands.

In the age group of 0-6 months, of the 21531 prescriptions of Co-amoxycylav, Clamp accounted for 3616 (16.79%), whereas Augmentin was prescribed in 2487 (11.55%). Similarly, of the 38086 Co-amoxycylav prescriptions in the age group of 6 months to 1 year, 7275 (19.10%) were prescribed Clamp and 5197 (13.64%) were Augmentin. Clamp was prescribed in higher proportion of total number of prescriptions of Co-amoxycylav in the older age group of 1-1.5 years and 1.5-2 years and above 2 years. (17.30% vs 14.81%, 17.48% vs 14.54%, 19.65 vs 14.93%) respectively.



IV. Discussions

In this prescription audit we included prescriptions of co-amoxyclov from the period Jan 2019 to Jan 2020. Out of these prescriptions two specific brands were analyzed (Clamp and Augmentin). Clamp was compared with Augmentin as it was the most prescribed Co-amoxyclov brand. The objective was to evaluate a co prescription of a probiotic at the first visit itself and addition of a probiotic or an anti-diarrhoeal at a subsequent follow up visit. The study found that 9.7% of Co-amoxyclov prescriptions are later added with either a probiotic or an anti-diarrhoeal at a follow up visit. Clamp received a co-prescription of a probiotic in 8.7% of the cases whereas for Augmentin it was 18.5%.

The active pharmaceutical ingredient of Amoxicillin Trihydrate is available in anhydrous, trihydrate, and sodium salt forms. International Pharmacopoeia (Ph. Int.) lists it as an odorless white or almost white, crystalline powder. Amoxicillin sodium is said to be a white, almost white, very hygroscopic, powder. Depending on the type of dosage form to be produced, amoxicillin API comes in two forms: i) Sterile sodium amoxicillin for injectable medicinal products (IM/IV); ii) Amoxicillin trihydrate for oral medicinal products.⁷

In terms of the industrial production described in the literature, the processes for obtaining amoxicillin trihydrate from the key intermediate 6-APA are chemical or enzymatic schemes⁸. The 6-APA is obtained from Penicillin G (PEN G/benzylpenicillin) after breaking the amide bond [-CONH-] using enzymatic or chemical methods. Numerous patents also exist and describe different routes of synthesis, or variations on the existing synthesis of amoxicillin. The conventional methods (using Dane salt for chemically obtaining) amoxicillin typically involve more than 10 steps, require low-reaction temperatures (-30°C), and use toxic solvents like methylene chloride and sialylation reagents. It is reported that the production of one kilogram of amoxicillin generates up to about 70 kg of non-recyclable waste. The majority of semi-synthetic β -lactam antibiotics are still synthesized by way of the Dane anhydride process, which can achieve yields as high as 90%. Despite recycling solvents and auxiliary reagents where possible, the Dane anhydride process still generates a large amount of non-biodegradable waste.⁹

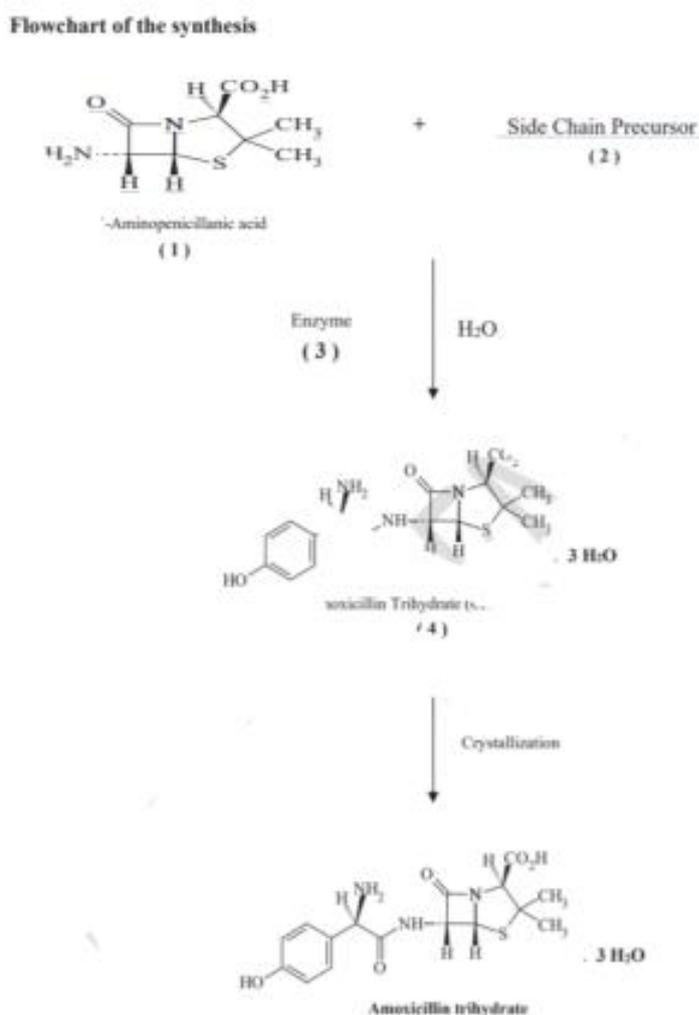


Fig 3: Flow Chart of Synthesis

In contrast, enzymatic methods require far fewer steps, use milder reaction conditions, and generate less waste. Biocatalytic synthesis occurs with the coupling of the β -lactam nuclei with the acyl side chain, accomplished enzymatically utilizing penicillin G acylase (PGA). A less studied enzyme, α -amino ester hydrolase (AEH), can also be used for this reaction when the acyl side chain has an amino group in the α -position. Furthermore, the coupling can be carried out under thermodynamic control, which utilizes a non-activated acyl side chain, or kinetic control, which requires an activated side chain (typically an ester or amide). The first published example of the biocatalytic coupling of β -lactam antibiotics on an industrial scale was not until 1997 when DSM (Delft, Netherlands) opened a production plant for cephalexin, marketed as Purilex®, in Barcelona, Spain. DSM has since expanded their production of enzymatically synthesized β -lactam antibiotics under the umbrella name of DSM PureActives™ to also include amoxicillin, marketed as Purimox®. The obvious disadvantage of the enzymatic coupling process in comparison to chemical coupling process is the lower yield of the product. However, the enzymatic coupling has undeniable advantages over the chemical coupling in terms of cost of raw materials, environmental impact, product quality, and ease of processing; due to the fact that it is carried out at ambient temperature, pressure and pH; and does not require toxic or hazardous reagents or solvents¹⁰.

Diarrhea is one of the most significant short-term adverse effect of antibiotic therapy. The prevalence of antibiotic diarrhoea is reported to be between 5-25%. Indian studies have shown that the highest incidence (18%) of AAD was in the 2 months to 2 years age group^{11, 12}. In most cases the diarrhea is mild and resolves without any treatment. In this group, there is no noteworthy adverse effect on the health status of the child. In some children probiotics are prescribed for faster relief from diarrhoea.

In the current study, it has been observed through clinic based prescribing pattern of clinicians that 5.4% prescriptions had a probiotic with the initiation of Co-amoxyclav treatment (Clamp: 4.24% and Augmentin: 11.85%). At a follow up visit 9.7% prescriptions of Co-amoxyclav were added with a probiotic of which Clamp accounted for 8.7% and Augmentin for 18.5% indicating onset of diarrhoea. Further studies should be considered to evaluate the association between clamp and lower incidence of antibiotic associated diarrhoea presumably because of novel manufacturing technique.

As is commonly observed in all prescription data sources and their analysis, this study also had a few notable limitations. The statistical significance was not established using standard statistical tool as data was collated from electronic medical records with anonymized data and individual level data sets were not available. A comprehensive analysis of all the brands of co-amoxyclav, indication for use of Co-amoxyclav and efficacy of the antibiotic could not be done due to incomplete or missing information.

V. Conclusion

The study results demonstrated that a considerable number of Co-amoxyclav prescriptions were also co-prescribed a probiotic anticipating onset of antibiotic associated diarrhea. The number of prescriptions receiving a probiotic at the initial visit was lower for Clamp and similarly at follow up, fewer prescriptions of Clamp required an addition of a probiotic indicating lower incidence of diarrhea compared to Augmentin.

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