GASTROINTESTINAL AND HEPATOTOXIC SIDE EFFECTS OF CO-AMOXICLAV IN ADULTS

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ABSTRACT

Background: Co-amoxiclav which is a combination of Amoxicillin & Calvulanic acid is one of the most commonly prescribed antibiotics so there was need to study the side effects of this drug. **Objectives:** This study was done to enlist the adverse reactions especially the gastroinstestinal and hepatotoxic adverse reactions in patients who were prescribed co-amoxiclav. **Patients & Methods:** This cross-sectional study was conducted on 200 patients, both indoors and out-doors in the Department of Medicine of Khyber Teaching Hospital (KTH), Lady Reading Hospital (LRH) and Hayatabad Medical Complex Peshawar, in months of August-October of 2013. The individuals included in the study were those treated as inpatient or outpatient with the diagnoses of uncomplicated UTIs, RTIs including Sinusitis and Pneumonia and the Skin infection. Those who were below the age of 18 years, requiring more than one antibiotic, having previously known chronic disease especially the liver disease or on any long-term medications, alcoholics and pregnant ladies were excluded from the study. A detailed questionnaire mentioning the age, sex and ethnicity of the patients, indications for the use of co-amoxiclav, duration of the treatment, base line LFTs including Bilirubin, SGPT and Alkaline Phosphatase and use of any concomitant drugs was devised. The patients were asked for follow up at weekly intervals for eight weeks after the course of treatment and assessed clinically and biochemically and LFTs recorded. This study which was approved by the Ethics Committee of our hospital was self-funded by the authors and informed consent was taken from every patient. The data was processed using SPSS version 16. **Results:** Amoxicillin- Calvulanate combination was seen to be well tolerated by most of the patients in our study subjects and adverse reaction were noted only in 36 (18 %) of the patients. The commonest side effect was diarrhea seen in 24 (12%) of the patients which was more severe in patients getting higher doses and for more than a week. Side effects were commonly seen in old patients 16 (8%) and in chronic smokers. Hepatotoxic side effects were seen in 6 (3 %) of the participants mainly cholestatic type of derangement on LFTs was seen and the toxicity was Mild i.e. Grade 1 in five of them as per National Institute of Cancer's , "Common Toxicity Criteria for Adverse Events, version 4.0 (CTCAEv4)" while one developed Grade 2 Hepatocellular type of Liver injury secondary to Co-Amoxiclav. Only 2 % of the patients were discontinued with the drug when they developed signs and symptoms of allergy on the 1st day of treatment while Oral candidiasis was seen in only 1% of the study subjects. **Conclusion:** Gastrointestinal and hepatic side effects are uncommon with Co-Amoxiclav and the commonest adverse reaction is diarrhea. Clinically obvious jaundice along with biochemically deranged LFTs is pretty remote possibility and can be reverted on stopping the drug and commencing the supportive treatment.

Keyword: Co-Amoxiclav, Adverse Reaction, Amoxicillin & Calvulanic acid

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INTRODUCTION

Infective conditions are very common in underdeveloped countries and that is why antibiotics are usually prescribed. Co-Amoxiclav is one of the commonest prescribed antibiotics from Primary Level to the Tertiary Level of Healthcare and in the Private Clinics. The addition of clavulanic acid, a potent inhibitor of beta-lactamases, to amoxicillin produces the combination co-amoxiclav (amoxicillin-clavulanate), which was first marketed in 1981.[1]

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This drug is usually well tolerated, however adverse reactions from the drug have still been seen. Hepatotoxicity with this drug was first reported in 1988.[2] Liver damage from the drug is usually Cholestatic and recovery is usual on stopping the drug and deaths extremely rare,[3,4] however sometimes hepatocellular and occasionally mixed type of liver damage is observed.[5]

Co-Amoxiclav damages liver through different mechanisms of which bilirubinostasis in the perivenular areas along with the presence of the ceroid laden reactive macrophages and inflammation of the portal system with focal damage to the interlobular bile ducts is notable.[1] Some previous studies have also mentioned the presence of granulomatous inflammation in the liver of the patients after taking the Co-Amoxiclav.[6,7]

Apart from other risk factors, age of the patient seems to be the most important risk factor for developing

liver injury associated with amoxicillin-clavulanic acid, however the prognosis is usually favorable and recovery is possible almost always on discontinuation of the drug.[8]

Common use of co-amoxiclav in our setup and possibility of side effects lead us to conduct this study to determine gastrointestinal and hepatotoxic side effects of amoxicillin plus calvulanic acid.

PATIENTS AND METHODS

This cross-sectional study was conducted on 200 patientsfrom 1st August to 31st October, 2013 in the Department of Medicine of Khyber Teaching Hospital, Leady Reading Hospital and Hayatabad Medical Complex, Peshawar. All the patients included were above 18 years of age, non-pregnant, not having any serious co-morbidities and not using any long term medications for any medical reasons.

Those who were alcoholics, having Liver disease or those who had ever shown significant allergy to penicillin were excluded from the study. On the 1st visit patients were assessed clinically and base line LFTs were performed and a detailed questionnaire mentioning the bio-data of the patient, indication for Co-Amoxiclav, the dose, route and duration of therapy and the type of preparation of the drug given was devised and filled for every patient individually. The patients were asked for follow up at weekly intervals for eight weeks after the completion of the course of treatment.

The drug was given only to those patients who were either having uncomplicated UTIs or RTIs or Skin infection while those who needed more than one type of antibiotics were not included in the study as well. Patients were advised not to take any other medication during the course of treatment and to make sure they take all the medicines prescribed. Informed consent was taken from every participant of the study and the study was approved by the Medical Ethics Committee of the hospital. Clinical and biochemical data were analyzed by using SPSS version 16.

The severity of the hepatotoxicity was graded according to National Institute of Cancer's "Common Toxicity Criteria for Adverse Events, version 4.0 (CTCAEv4)" as shown in the Table I.

In this system, the severity is graded on a scale of 0-4, with the values expressed as multiples of the upper limit of the normal range (ULN). The default ULN for ALT was taken as 40 U/L, alkaline phosphatase 115 U/L and bilirubin 1.2 mg/dL as suggested by the United States "National Institute of Diabetes & Digestive and Kidney Diseases" (NIDDK).[9] According to CTCAE, grades 0, 1, 2, 3, & 4 equal Normal, Mild, Moderate, Severe & Life-threatening Liver injury respectively.

Table I: Common Toxicity Criteria for Adverse Events, version 4 (CTCAEv4)

Feature	Grade 0	Grade 1	Grade2	Grade 3	Grade 4
ALT	Normal	1-2.5	2.5-5	5 to 20	>20
AST	Normal	1.2.5	2.5-5	5 to 20	>20
ALP	Normal	1-2.5	2.5-5	5 to 20	>20
GGT	Normal	1-2.5	2.5-5	5 to 20	>20
BIL	Normal	1-1.5	1.5-3	3 to 10	>10

The Pattern of liver injury due to Co-amoxicav was also classified as Cholestatic, Hepatocellular or Mixed on the basis of the pattern of LFTs derangements mentioned in the "American Association for Study of Liver Diseases (AASLD)" [10] and the "Davidson's Principles Of Clinical Medicine".[11]

RESULTS

A total of 200 patients who were included in study, 36 (18%) have different side effects, Diarrhea 24 (12%), hepatotoxicity 6 (3%), allergic reaction 4(2%). (Table II). All the patients 6 (3%) who developed hepatotoxicity, were followed up and it was noted that there LFTs started getting normal by 5th week and were within near normal limits by the 7th week of follow up after treatment. Out of these 6 patients, 4 were chronic smokers amongst them and the mean age of these six patients was 55 years.

Table II: Frequency of different side effects noted with Co-Amoxiclav

S.No	Side Effect	No (%)
1	Diarrhea	24 (12%)
2	Hepatotoxicity	6 (3%)
3	Allergy	4 (2%)
4	Oral Candidiasis	2 (1%)
Total		**36 (18%)**

It is also worth mentioning that 4(2%) of the patients developed skin rashes and itching on the 1st day of treatment and were discontinued with further treatment. Oral thrush was seen in 1% of the patient

in the second week of treatment and was treated successfully with topical antifungal agents.

Table III: Frequency of different types of hepatotoxic reactions and its severity according to CTCAE scoring and the mean time to recovery after stopping treatment.

	Cholestasis	Hapatocellular	Mixed
No of Patients	04	01	01
Hepatotoxic Grade	Grade 1	Grade 2	Grade 1
Mean Recovery Time	32 Days	39 Days	34 Days

Table IV: LFTs of One of the patients who was on Amoxiclav for two weeks

Weeks	ALT(U/L)	ALP(U/L)	Bil(mg/dl)	Jaundice
1st	35	85	0.9	Nil
2nd	55	95	1.2	Nil
3rd	150	119	3.6	Present
4th	180	130	3.8	Present
5th	140	122	3.2	Present
6th	110	111	2.8	Present
7th	90	103	2.1	Present
8th	67	93	1.4	Present

DISCUSSION

The combination of amoxicillin and clavulanate, a commonly used antibiotic which is active against many bacterial organisms that cause sinusitis, bronchitis, otitis media, skin and soft tissue infections and community acquired pneumonia. The combination consists of amoxicillin which is a semisynthetic, third generation penicillin and clavulanate which acts as an inhibitor of beta lactamase, the major bacterial enzyme responsible for penicillin resistance. This combination is provided in multiple dose combinations, typically as 250 to 875 mg amoxicillin with 125 mg of clavulanate, given two to three times daily for 7 to 10 days.

As with any medication there are some side effects, we conducted our study to find out how common they are with the Co-amoxiclav and our main focus was on the side effects related to the gastroinstestinal tract and Liver.

In our study, we found that 12% patients developed diarrhea and it was also found that these were mainly aged patients with higher doses, a fact which is comparable to the previous data.[5,12] In our study, we also noticed that diarrhea was more profuse in those taking extended release formulation in contrast to those put on immediate release tablets.[13] None of the patients had bloody diarrhea and the they improved on stopping the drug and by giving them metronidazole proving the fact that the diarrhea was probably due to pseudomembranous colitis rather than direct gut irritation.[14]

Our second and basic focus of interest was to list any hepatic side effects which are rarely mentioned in literature.[15] In our study, we found that they were not very common and only 3% of the patients had symptomatic or biochemical indication of hepatotoxicity. Cholestataic pattern of derangement of LFTs was the commonest type of reaction (4 out of 6 patients) in our study which is comparable to the previous studies while one patient showed hepatocellular and one showed a mixed pattern of deranged LFTs. All the six patients with hepatotoxicity have jaundice and their mean age was 55 years and majority of them were chronic smokers and their mean time of presentation was 16th day from the commencement of treatment. All these facts correlate to studies conducted in the past.[16,17]

Age appeared to be most important risk factor for hepatotoxicity with co-amoxiclav, though in our study smoking history was also notable in those developing hepatotoxicity. One study showed that, age was the most important determinant in the biochemical expression of hepatotoxicity; younger age is associated with cytolytic damage and shorter treatment duration, whereas cholestatic/mixed type of damage is related to older age and prolonged therapy".[18] Two of the patients in our study group who developed relatively severe hepatotoxicity were having past history of some bad experience and allergic type of reaction with co-amaxiclav. This may point some immune-allergic basis to hepatotoxic reactions in patients taking co-amoxiclav. Susceptibility to drug-induced hepatotoxicity is also influenced by genetic and environmental risk factors.[17,18] Co-amoxiclav associated hepatotoxicity may have a genetic basis and be delayed, severe, and prolonged, although complete recovery is usual. However, as the combination of amoxicillin and clavulanate[19] is more hepatotoxic than amoxicillin alone, and hepatotoxicity has been reported with clavulanate and ticarcillin,[20,21] it is possible that clavulanate is the hepatotoxic component of co-amoxiclav. Further studies of the genetic susceptibility to co-amoxiclav associated live disease are necessary to further elucidate the

mechanism of this disease, which is at least in part immune mediated. Unpredictable, low-frequency, idiosyncratic reactions often occur on a background of a higher rate of mild asymptomatic liver injury and, although difficult to predict, they may be detected by monitoring serum alanine aminotransferase levels.[19]

All the patients with hepatotoxicity in our study group were given supportive treatment. They all recovered within three to four weeks of stopping the drug and just one of them needed hospitalization. None of them showed signs of acute liver failure. Acute liver failure is a rare manifestation of amoxicillin and amoxicillin/clavulanate hepatotoxicity with no obvious clinical features at presentation. Early transfer of patients with severe drug-induced hepatotoxicity (i.e., encephalopathy or coagulopathy) to a transplant center is recommended due to their poor likelihood of recovery.[22]

CONCLUSION

From our study we conclude that co-amoxiclav is usually a well-tolerated antibiotic prescribed. However, diarrhea is the commonest adverse effect. Hepatotoxicity is very rare and if present is usually mild to moderate and its mean time of presentation is usually the third week from the commencement of treatment and usually resolves within 7-8 weeks with supportive measures and on stopping the drug and does not need hospitalization. It is recommended that further studies be done in this regard to understand the depths of hepatotoxic events secondary to the Co-Amoxiclav.

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