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The Action of Amoxicillin-Clavulanate on Hepatocytes

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Abstract The oral antibiotic amoxicillin is third generation penicillin combined to clavulanate, widely employed in medicine and dentistry for treatment of mild-to-moderate bacterial infections. Clavulanate is not indicated alone because it lacks antibacterial activity, so it is added to amoxicillin in order to inactivate beta-lactamse enzyme which is the major cause of penicillin resistance. Beta- lactamase is produced by many microorganisms, it destroys beta lactam ring of beta lactam antibiotics, therefore amoxicillin-clavulante is indicated as an extended antibiotic that covers many gram positive a and a significant number of gram negative microorganisms which produce beta-lactamse. This compound amoxicillin-clavulanate is available in multiple dose variations, typically as 250, 500 to 875 mg amoxicillin with 125 mg of clavulanate potassium, given two to three times daily for 7 to 10 days. The combination is provided in many trade formulation namely moclav and agumentin. Amoxicillin is in general use because it is the most effective and least toxic antibiotic, however it can cause some unwanted effects particularly allergic, GIT and renal effects. The purpose of recent study is to estimate possibility toxic effect of amoxicillin-clavulanate on hepatocytesand its revesibility, about 64 infectious patients of several ages were investigated, 35 of them are men and the 29 are women, for about 3 weeks. Complete blood count (CBC) and serum of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (AP) and gamma glutamyltranspeptidase (gamma-GT) are taken before, and after completion of treatment. The main finding of this research is that amoxicillin-clavulanate has a toxic effect on hepatocytes, represented mainly by reversible cholestatic hepatitis in patients older 50 years, who experience fatigue, GIT upset, prurituts and jaundice. The hepatic injury has occurred in elderly men more than in women.

Keywords: *amoxicillin, clavulanate, beta-lactamase, moclav, agumentin, alkaline phosphatase, gamma glutamyltranspeptidase, alanine transaminase, aspartate transaminase, prurituts, jaundice*

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1. Methodology

64 patients were included in the research study, patients were suffering from acute upper respiratory infections such as tonsillitis, laryngitis, nasopharyngitis as well as, sinusitis, gingivitis and periodontitis, both sexes of patients are divided into 3 groups according to severity and treatment period with amoxicillin-clavulanate, in each group are 22 patients aged from 20 to 60 years of old.

The patients of first group, treated by amoxicillin-clavulanate (625 mg 3 times daily) therapy for about 1 weeks.

The second group, patients medicated by amoxicillin-clavulante (625 mg 3 times daily) therapy for about 2 weeks.

The third group treated by amoxicillin-clavulante (625 mg 3 times daily) therapy for about 3 weeks,

All patients were examined to exclude hepatic, renal as well as cardiac impairments, CBC and hepatic enzymes are taken before and after treatment. The patients were asked after treatment about their complaints.

2. Methods of Investigation & Discussion

Investigations show that the first and second groups who were treated by amoxicillin-clavulante at a dose of 625 mg 3 times daily for 1and 2 weeks respectively have not significant deviation in their CBC, Gamma- GT, ALT, AST and AP enzymes, patients were asked if they have had GIT symptoms or other problems, they didn't demonstrate any complaints, pruritus and jaundice have not been noted.

The third group was treated for 3 weeks, because of their prolonged infectious process, that accompanies with many symptoms of intoxication syndrome, such as fever, arthragia, myalgia, coughing, nausea, vomiting and headache, in these patients systemic complications such as pneumonia, meningitis and endocarditis were excluded.

About 13 patients aged from 50-60 years of the third investigated group who were medicated by the same dose of amoxicillin- calvulanate for 3 weeks have eosinophilia, as well as patients experience fatigue, fever, skin rash and arthralgia, the mechanism of eosinophila and allergic symptoms mentioned above is unknown but it seems to be of immunologic origin.

Hepatic enzymes elevations above their normal values are also seen, in about 7 patients (5 of them are men) the AP and Gama- GT serum are markedly increased, indicating cholestatic hepatic injury, after excluding bone abnormalities in these patients, with a slight elevation of ALT and AST.

In 4 patients (3 of them are men) the serum of ALT and AST are significantly elevated, showing hepatocellular

injury, in these patients the AP serum is still around its normal range, but Gamma-GT is slightly increased.

In 2 male patients of this group high levels of all hepatic enzymes are noted (AP, Gamma-GT, ALT and AST), indicating that the hepatic injury in these two patients is mixed, The hepatic injury in this group is more common in elderly people, and in men rather than in women.

The remaining patients of the third group who are under 50 years of old didn't show any significant deviation. (see Table 1).

Additional analysis were taken from the third group one week after completion of amoxicillin-clavulanate therapy, including CBC and hepatic enzymes, to ensure reversibility of hepatic injury, the results shows that CBC and hepatic enzymes return to their normal values a week after treatment with amoxicillin-clavulanate therapy, indicating temporary hepatic injury caused by medication, (See Table 2).

According to the above data amoxicillin-calvulante does not produce hepatic injury in infectious patients treated for a period of either 1 or 2 weeks, but it is hepatotoxic in elderly people treated for 3 weeks, the mechanism of injury is not linked to amoxicillin by its self , but the hepatic cell injury here is associated with clavulanate, because other beta lactamase inhibitors (tazobactam and subactam) have not been reported to cause a similar hepatic injury, although it has been manifested with other penicillins when combined with clavulanate (ticarcillin/clavulanate).

The hepatic injury is reversible because hematologic and hepatic alterations normalize following a week after treatment.

3. Conclusion

1. Amoxicillin-clavulanate is a safe antibiotic in an infectious patients until 50 years in a period of 1- 2 weeks.
2. Amoxicillin-clavulanate is currently the most common cause of clinically apparent, drug induced acute hepatic injury in elderly patients treated at a dose of 625mg tid for 3 weeks.
3. The type of hepatic injury caused by amoxicillin-clavulanate is usually reversible cholestatic rather than hepatocellular or mixed character.
4. The mechanism by which amoxicillin-clavulanate induce eosinophilia is not well understood but it is thought to be of immunologic origin.
5. It is better to replace clavulanate by other beta lactamase inhibitors such as tazobactam to avoid hepatic injury caused by clavulanate in elderly patients.

Table 1. Analysis of Patients Treated With Amoxicillin-Clavulanate In A Period of 3 Weeks

Hematologic Tests	Normal Values	I Group B/T	I Group A/T	II Group B/T	II Group A/T	III Group B/T	*III group A/T*		
							5(M),2(F)	***3(M),1(F)***	***2 (M)***
Eosinophils	0-6%	0 -4 %	1-3%	2-5%	2-7%	1-6%	***1216%***	***10-14%***	***13-14%***
AST	8 to 48 U/L	9-32	10-41	11-39	16-38	8-43	***52-56***	***97-101***	***94-98***
ALT	7 to 55 U/L	8-46	8-34	8-52	12-40	10-50	***61-66***	***97-105***	***85-92***
AP	45 to 115 U/L	57-95	47-90	46-88	49-105	52-100	***143-152***	***49-113***	***141-146***
Gamma-GT	9 to 48 U/L	10-32	10-38	9-44	12-41	12-42	***79-84***	***54-59***	***72-87***

N.B
B/T= Before Treatment A/T= After Treatment
U/L= Units Per Liter M= Male
F= Female.

Table 2. Analysis of Patients of Third Group One Week After Completion of Treatment

Hematologic Tests	Normal Values	III Group (13 of 22 patients)
Eosinophils	0-6%	0 -5 %
AST	8 to 48 U/L	32-46
ALT	7 to 55 U/L	27-49
AP	45 to 115 U/L	53-101
Gamma-GT	9 to 48 U/L	14-39

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