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Drug Hepatitis At AINS

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ABSTRACT
Hepatic lesions induced by drugs include extremely diverse various clinical, biological and histological manifestations that can determine acute or chronic hepatobiliary disease. The term of hepatitis is recommended to be used when there is a histological confirmation. In the last decades a 11 time increase of the hepatic lesions induced by drugs is reported, due both to the increase of the number of used drugs but also by their more frequent recognition.
We carried out a combined retrospective study and longitudinally prospective study that included patients with drug hepatitis. In our study there were 83 cases of drug hepatitis at AINS, which represents 33.46 % of the total number of 248 patients with drug hepatitis. In our study the highest drug hepatitis at AINS were Nimesulid (24 cases), followed by Diclofenac (21 cases), and the fewest at Piroxicam (9 cases). All the cases from the study were symptomatic, showing the increase of the cytolysis enzymes and sometimes cholestasis enzymes (mainly GGT).
The average age at diagnosis was 60.1 years for the 248 patients, being lower for the male gender (57.47 years), compared to the female gender (61.26 years). Women were affected in the highest degree, 69.35% being women and 30.64% men. In our study drug hepatitis by hepatic cytolysis was dominant, more frequent than the cholestatic ones.

Keywords: drug hepatitis, non steroid anti-inflammatory drugs, liver

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Introduction

Hepatic lesions induced by drugs include extremely diverse various clinical, biological and histological manifestations that can determine acute or chronic hepatobiliary disease. The term of hepatitis is recommended to be used when there is a histological confirmation. In the last decades a 11 time increase of the hepatic lesions induced by drugs is reported, due both to the increase of the number of used drugs but also by their more frequent recognition. The clinical criteria are of practical utility because they draw attention on the drug etiology.

The clinical diagnosis is based on:

- disease occurrence chronology- includes the relation between the drug intake and the therapeutic accident occurrence;
- regression of the symptomatology on the interruption of the treatment

- reoccurrence after administration - the most certain criterion by which an isolated drug can be proven as cause of an adverse hepatic reaction
- the fostering field - hepatic lesions induced by drugs are more frequent in women and they usually occur after the age of 40 years;

Material and method

We carried out a combined retrospective study and longitudinally prospective study that included patients with drug hepatitis. In our study there were 83 cases of drug hepatitis at AINS, which represents 33.46 % of the total number of 248 patients with drug hepatitis.

Inclusion criteria:

- ALAT increase (alanine aminotransferase) > 2N and/or FAS increase > 2N
- AgHbs and Ac anti VHC negative
- Anamnestic denial of alcohol consumption

Results:

The distribution of the patients per decades of age and sex of the drug hepatitis cases are as follow:

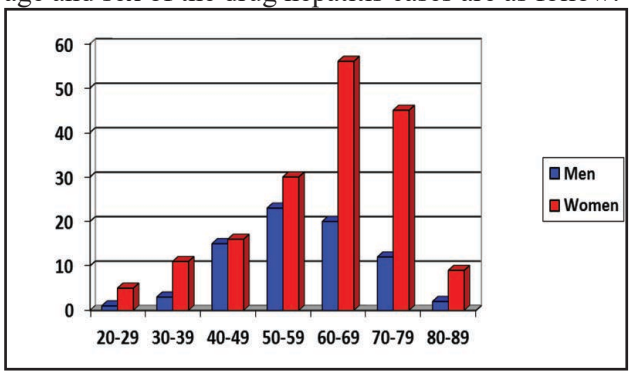


Figure 1 Distribution according to age

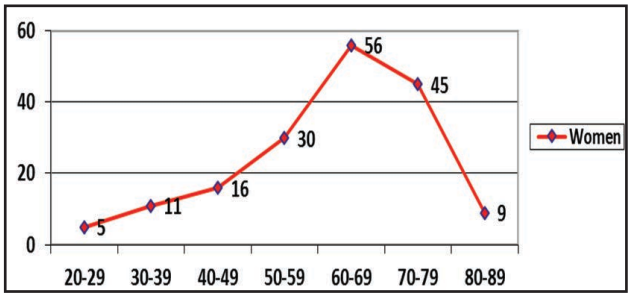


Figure 2 Distribution according to age groups for women

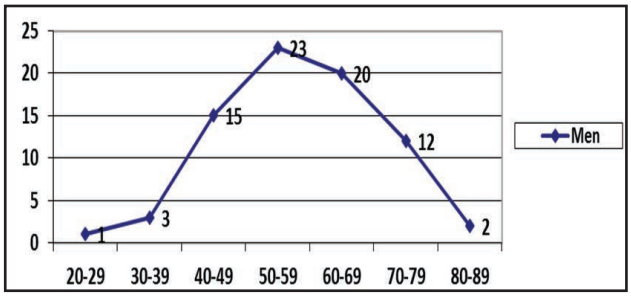
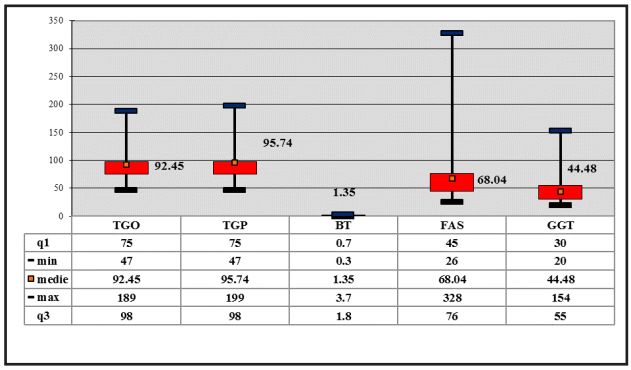


Figure 3 Distribution according to age groups for men

It can be noticed that the decade 60-69 was the most aff ected for the female gender and for the male gender the decade 50-59. There are some statistics that show that at the persons over 50 years the incidence of drug hepatitis increases.

The distribution of the patients with drug hepatitis according to the value of hepatic tests: for the 248 patients with drug hepatitis, the average value of the hepatic cytolysis tests were for TGO 92.45 ui and for TGP 95.74 ui. The colestatis tests had the following average values: total bilirubin of 1.35 mg/di, FAS of 68.04 ui and GGT of 44.48 UI (Figure 4).

In our study drug hepatits by hepatic cytolysis was dominant, more frequent than the cholestatic ones.



	TGO	TGP	BT	FAS	GGT
q1	75	75	0.7	45	30
min	47	47	0.3	26	20
medie	92.45	95.74	1.35	68.04	44.48
max	189	199	3.7	328	154
q3	98	98	1.8	76	55

Figure 4 Descriptive statistics for biological markers

With regard to AINS hepatotoxicity, FDA concluded that it is a class characteristic of AINS.

There are genetic risk factors for drug hepatitis which are involved in 20-95% [I] and non genetic risk factors represented by age (adults are more predisposed than children), gender (women are more predisposed than men), race, obesity, malnutrition, sugar diabetes, steatosis, alcoholism, pre-existing hepatic diseases, drug (its hepatotoxic potential, doses), associated drugs and certain diseases (PR, LES) [2].

Increases of transaminases are frequently associated with AINS utilization, yet hepatic failure is pretty rare [3-4]. The net hepatic risk was illustrated in a retrospective study on 625000 patients who received more than 2 million prescriptions for AINS and who were evaluated for drug hepatitis at AINS [4].

Diclofenac was reported to cause clinically manifest hepatitis, including ANA positivity and active chronic hepatitis histological evidence [5].

The most frequent adverse hepatic reactions were reported at Sulindac, Diclofenac [6-7] and at Nimesulid [8]. Ibuprofen is one of AINS that are least involved in the occurrence of hepatic lesions, but occasional cases of cytolythic or mixed cytolytic and cholestatic hepatic lesions were reported [9-10].

Piroxicam has a low incidence of drug hepatitis (1-2%) but cases of severe hepatitis were described fatal hepatic necrosis or that required transplant [11,12].

Conclusions:

The average age on diagnosis was 60,1 for the 248 patients, being lower for the male gender (57.47 years), against the female gender (61.26 years). Women were more affected, 69.35% being women and 30.64% men. In our study drug hepatitis by hepatic cytolysis was dominant, more frequent than the cholestatic ones.

In our study the highest number of drug hepatitis at AINS were Nimesulid (24 cases), followed by Diclofenac (21 cases), and the fewest at Piroxicam (9 cases). All the cases from the study were symptomatic, showing the increase of the cytolysis enzymes and sometimes cholestasis enzymes (mainly GGT).

Ketoprofen has a low incidence of adverse hepatic effects.

References:

1. Fernández-Villar, A., Sopeña, B., Vázquez, R., Ulloa, F., Fluiters, E., Mosteiro, M., César, M.-V. & Piñeiro, L. (2003). Isoniazid Hepatotoxicity among Drug Users: The Role of Hepatitis C. *Clinical Infectious Diseases*. *36*(3), 293-298. doi: 10.1086/345906.
2. Gronhagen-Riska, C., Hellstrom, P.E. & Froseth, B. (1978). Predisposing factors in hepatitis induced by isoniazid-rifampin treatment of tuberculosis. *Am Rev Respir Dis*. *118*(3), 461-466. doi: 10.1164/arrd.1978.118.3.461
3. Huang, Y.S., Chern, H.D., Su, W.J., Wu, J.C., Lai, S.L., Yang, S.Y., Chang, F.Y. & Lee, S.D. (2002). Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology*. *35*(4), 883-889. doi: 10.1053/jhep.2002.32102
4. Huang, Y.S., Chern, H.D., Su, W.J., Wu, J.C.,

Chang, S.C., Chiang, C.H., Chang, F.Y. & Lee, S.D. (2003). Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. *Hepatology*. *37*(4), 924-930. doi: 10.1053/jhep.2003.50144

5. Steele, M.A., Burk, R.F. & DesPrez, R.M. (1991). Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest*. *99*(2), 465-471.
6. Yew, W.W. & Leung, C.C. (2007). Antituberculosis Drugs anbd Hepatotoxicity. *Hong Kong Medical Diary*, *12*(1), 7-9
7. de Abajo, F.J., Montero, D., Madurga, M. & Garcia Rodriguez, L.A. (2004). Acute and clinically relevant drug-induced liver injury: a population based case-control study. *Br J Clin Pharmacol*. *58*(1), 71-80. doi: 10.1111/j.1365-2125.2004.02133.x
8. Jobanputra, P., Amarasena, R., Maggs, F., Homer, D., Bowman, S., Rankin, E., Filer, A., Raza, K. & Jubb, R. (2008). Hepatotoxicity associated with sulfasalazine in inflammatory arthritis: A case series from a local surveillance of serious adverse events. *BMC Musculoskelet Disord*. *9*, 48. doi: 10.1186/1471-2474-9-48
9. Emery, P., Breedveld, F.C., Lemmel, E.M., Kaltwasser, J.P., Dawes, P.T., Gomor, B., Van Den Bosch, F., Nordstrom, D., Bjorneboe, O., Dahl, R., Horslev-Petersen, K., Rodriguez De La Serna, A., Molloy, M., Tikly, M., Oed, C., Rosenburg, R. & Loew-Friedrich, I. (2000). A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)*. *39*(6), 655-665.
10. Matteson, E. & Cush, J.J. (2001). Reports of leflunomide hepatotoxicity in patients with rheumatoid arthritis. *ACR Hotline*
11. Cohen, S.B. & Iqbal, I. (2003). Leflunomide. *Int J Clin Pract*. *57*(2), 115-120.
12. Strand, V., Cohen, S., Schiff, M., Weaver, A., Fleischmann, R., Cannon, G., Fox, R., Moreland, L., Olsen, N., Furst, D., Caldwell, J., Kaine, J., Sharp, J., Hurley, F. & Loew-Friedrich, I. (1999). Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. *Arch Intern Med*. *159*(21), 2542-2550.