The Effect of Long-term Neuroleptic Treatment on Liver Function Tests

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ÖZET

Uzun süreli nöroleptik tedavisinin karaciğer fonksiyonları üzerindeki etkisini incelemek üzere en az son beş yıldır sürekli nöroleptik almakta olan 100 kronik şizofrenik hasta grubu yanısıra yeni tanı almış, henüz tedavi uygulanmamış 40 şizofreni hastası karaciğer fonksiyon testleri ile değerlendirilmiştir. Kronik şizofrenik hastalara bir aylık ilaç tatili uygulanmış, hastaların %8'inde alevlenme gözlenmiştir. Uzun süre nöroleptik kullanımının karaciğer üzerine olumsuz etkisinin bulunmadığı ve ilaç tatillerinin gerekmediği gözlenmiştir.

Anahtar kelimeler: Nöroleptikler, Şizofreni, Karaciğer.

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SUMMARY

The liver function tests of 100 chronic schizoprenic patients who were taking neuroleptics for at least five years and 40 newly diagnosed schizoprenic patients before any treatment have been assessed. Also the chronic schizophrenic group had one month drug holiday and they have been followed for a possible relapse. The values for whole groups were within normal limits. Discontinuation of the treatment resulted a relapse in 8 of 100 chronic patients in one month. The reliability and safeness of neuroleptics in long-term treatment in aspect of hepatic effects and the useless of drug holidays have been confirmed.

Key words: Neuroleptics, Schizophrenia, Liver.

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INTRODUCTION

Neuroleptics show their effects by their pharmacological activities on various cholinergic, dopaminergic and adrenergic receptors. The effects on these receptors induce some side effects. Luckily, many of these side effects-except malignant neuroleptic syndrome- are not usually life threatining.

Neuroleptics effects almost all of the systems in the body. Most neuroleptic agents other than thioridazine have a marked interaction on CTZ (chemoreceptor trigger zone) in the medulla. Also the effects of neuroleptic drugs on hypothalamic regulatory hormones induce many changes, especially on gonadotropins and prolactin. Classically aside from the hypersensitivity reactions, neuroleptics have no characteristic hepatic side effects (7).

PATIENTS AND METHODS

In this controlled, retrospective and prospective study, we assessed the liver function tests of 100 chronic schizophrenics who taking neuroleptics for least 5 years and of a control group consisting from 40 newly diagnosed pre-treatment schizophrenics.

The analyses included the assessment of liver function tests: aminotransferases, alkaline phosphatases, albumin, globulin, bilirubins, prothrombin time. Also creatinine and urine analysis were performed. The patients in the chronic group had a "drug honeymoon" for one month. In this withdrawal period they were followed for a possible relapse.

RESULTS

Except psychiatric symptoms and features all of the patient had normal physical and ultrasonographic findings.

The mean SGOT level for the chronic schizoprenics was 28.3 ± 0.8 Ü, while the control group had 25.1 ± 1.0 Ü. Both values were within normal ranges, but statistically the difference between the averages was significant. ($p < 0.05$) The mean SGPT levels of chronic and control schizoprenics were 25.6 ± 1.03 U and 25.7 ± 1.07 U

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respectively. The SGOT levels were higher than the SGPT levels which showed a normal ratio.

Direct and indirect bilirubins showed normal values. For direct bilirubin, the averages were 0.19±0.1 mg/dl and 0.20±0.1 mg/dl respectively for the chronic and the control schizophrenics.

Alkaline Phosphatases levels were 34.7±1.2 U and 34.5±2.0 U respectively for chronic and control groups. The values were within normal ranges which is 15-69 U for our laboratory.

Gamma Glutamyl Transpeptidase which is one of the best indicator of cholestases has been assessed as 19.3±0.8 and 19.0±1.0 respectively. They were within 6-28 U/L which is the normal range of our laboratory. The mean levels for albumin were 3.6±0.03 and 3.8±0.05 gr/dl, respectively for the chronic and control groups. They were within the normal ranges. Prothrombin Time for chronic and control groups were 12.1±0.8 seconds and 10.1±0.3 seconds respectively. Creatinine levels were normal.

DISCUSSION

This study compared the liver functions of chronic schizophrenics taking neuroleptics for more than five years to a group of newly diagnosed pretreatment schizophrenics. The result concluded that long-term treatment with neuroleptics has no severe side effects on liver functions. 8% of the chronic group had a relapse within one month after stopping the drug. This was accepted as a reinforcing finding at disregard drug withdrawal periods aiming a washout period for probable hepatotoxicity.

The injury due to neuroleptics is usually cholestatic and appears within 1-5 weeks after the beginning of the drug.(2) The occurence rate of hepatic side effects is much higher in adults than in children. Serum Alkaline Phosphatase is greatly elevated and aminotransferases are only slightly increased. Eosinophilia occurs in most of the cases. On liver biopsy cholestasis is most pronounced around the terminal hepatic venule. (8, 5)

Usually neuroleptic induced cholestases gradually gets to normal over 1 to 2 months in majority of the cases. Some of them show a primary biliary cirrhosis symtoms as unresolving cholestatic jaundice, hypercholesterolemia and xantomas. (8, 9)

There are sporadic reports about cholestatic side effects.(6, 7) The mechanism of hepatic injury of neuroleptic induced hepatotoxicity is thought to be related to free radical toxic intermediates damaging by covalent binding. Chlorpromazine an its metabolites affect plasma membrane Na+-K+ ATPase and alter membrane fluidity. (2, 8)

Even to some reports about side effects of neuroleptics represent a valuable and effective agent in the treatment of schizophrenia. In a clinical pharmacological study (3) the polymorphism for a particular drug including neuroleptics was related to a difference in cytochrome p450 genes. In that study it was concluded that assessment of the patients phenotype would have a potential value.

In the studies with Clozapine, a slight rise in liver enzymes have been observed in short term trials. (10, 6) But the benefit/risk ratio was appeared to be high and acceptable.

In a review of 30 controlled prospective studies involving near 3500 schizophrenics, the mean overal relapse rate was 55% for the patients who were withdrawn from antipsychotic drugs and given a placebo, compared to only 17% of those who continued on drug therapy. (Davis, 1975, Baldesserini et al, 1980) In our study, the relapse in one month was 8%. As a conclusion, neuroleptics seem to be safe in long-term use in schizophrenia. Also the identification of the genetic status of the patients and follow up of aminotransferases, alkaline phosphatases and gamma glutamyl transpeptidases for the first few months seems to have a value.

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