Histopathologic examination of rat liver after experimental application of fluoxetine

Fluoksetinin deneysel verilmesinden sonra rat karaciğerinin histopatolojik incelenmesi

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Summary

Objective: To investigate the histopathological changes in the liver after experimental application of fluoxetine.

Materials and methods: Nineteen male and 24 female rats of Sprague-Dawley strain were used to study the effect of administration of fluoxetine over a period of 3 weeks. The rats were randomly divided into five groups. Groups A to group D, each consisting of 10,10, 10, 7 rats respectively, were for different tests, while 6 rats were used as normal controls (N). For group A,B,C,D fluoxetine was administered via intraperitoneal enjection at a dosage of 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 25 mg/kg, respectively. The experiment lasted 3 weeks. Hepatic tissue samples were extracted under anesthesia for histopathologic study. Liver tissues were fixed in 10% buffered formalin and embedded in paraffin. Histopathologic changes were evaluated on the H&E stained sections.

Results: The major histopathological changes in the liver after fluoxetine are hydropic degeneration, karyomegaly, steatosis, lobuler inflammation, focal necrosis, apoptosis, disruption, twinning cell plates, cholestasis, portal area inflammation, Kupffer cell hyperplasia and double nucleus *(P*<0.05*).*

Conclusion: Our results show that exposure of rats to fluoxetine leads to toxic effects. At the end of the exposure period, livers of all exposed rats, but no controls, showed hydropic degeneration, karyomegaly, steatosis, lobular inflammation, focal necrosis, apoptosis, disruption, twinning cell plates, cholestasis, portal area inflammation, Kupffer cell hyperplasia and double nucleus. The main histopathological changes in all exposed rats were hepatocellular hydropic vacuolar degeneration (%100).

Key words: rat liver, fluoxetine, hepatotoxicity, degeneration, antidepressants

Özet

Amaç: *Deneysel olarak fluoksetin verilmesinden sonra karaciğerdeki histopatolojik değişiklikleri araştırmak.*

Gereç ve yöntem: *Sprague-Dawley cinsinden 19 dişi ve 24 erkek rata 3 hafta süresince verilen fluoksetinin etkileri incelendi. Ratlar rastgele 5 gruba ayrıldı. Grup A'dan D'ye kadar her grupta sırasıyla 10, 10, 10, 7 rat vardı. Her gruba farklı test uygulandı ve 6 rat normal kontrol grubu olarak kullanıldı (N). A, B, C, D gruplarına sırasıyla intraperitoneal enjeksiyon yoluyla 5 mg/kg, 7,5 mg/kg, 10 mg/kg, 25 mg/kg fluoksetin verildi. Deneyden 3 hafta sonra karaciğer örnekleri histopatolojik inceleme için anestezi altında alındı. Karaciğer dokuları %10'luk buffer formalinde tespit ettikten sonra parafine gömüldü. Histopatolojik değişiklikler H+E boyalı kesitlerde değerlendirildi.*

Sonuç: *Fluoksetin verildikten sonra karaciğerdeki başlıca histopatolojik değişiklikler hidropik dejenerasyon, karyomegali, yağlanma, lobular inflamasyon, fokal nekroz, apopitoz, ayrışma, çift hücre kordonları, kolestaz, portal alanda inflamasyon, Kupffer hücrelerinde hiperplazi ve çift nukleusdu (p<0.05).*

Tartışma: *Sonuçlarımız da ratların fluoksetine maruz kalması toksik etkilere yol açtığı görülmüştür. Deney sonunda, kontrol grubu dışında bütün maruz kalan ratların karaciğerlerinde hidropik dejenerasyon, karyomegali, yağlanma, lobular inflamasyon, fokal nekroz, apopitoz, ayrışma, çift hücre kordonları, kolestaz, portal alanda inflamasyon, Kupffer hücrelerinde hiperplazi ve çift nukleus izlendi. Maruz kalan ratlardaki başlıca histopatolojik değişiklik hepatosellüler hidropik vakuoler dejenerasyondur (%100).*

Anahtar sözcükler: *Rat karaciğeri, fluoksetin, hepatotoksik, dejenerasyon, antidepresanlar.*

Fluoxetine hydrochloride (Prozac, Dista) is a new nontricyclic antidepressant that inhibits serotonin reuptake, has a long half-life, and is essentially metabolized in the liver. Fluoxetine hydrochloride is designated (α)-N-methyl-3-phenyl-3-(α-α-α-trifluoro-p-tolyloxy) propyl-amine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO,HCl$. Its chemical structure differs from that of the tricyclic antidepressant such as imipramine and its analogs, which are tertiary or secondary amines with a three-ring molecular core. Fluoxetine is a secondary amine with one phenyl and one tolyl group in the structure (1).

Fluoxetine, which was approved by the US Food and Drug Administration in December 1987 and introduced into clinical practice in January 1988, is now a common first-line agent in the treatment of depression. The safety of fluoxetine has been studied extensively. Millions of patients have received this medication, and many have taken the drug continuously for almost 10 years without severe adverse effects (2).

After oral administration, fluoxetine is almost completely absorbed and is metabolized to norfluoxetine in the liver. Fluoxetine has a half-life elimination of about 2-3 days and norfluoxetine of about 7-9 days. Norfluoxetine is the active metabolite of fluoxetine, which may contribute to the pharmacological and clinical effects of drug (3). As in human tissues, fluoxetine and norfluoxetine are extensively distributed in rat tissues (4). When fluoxetine is administered intraperitoneally the drug and its metabolite rapidly reach higher concentration in organs such as liver, lung and brain (5). Floxetine has proved clinically useful as an antidepressant and in the treatment of obsessive-compulsive disorder, bulimia, and obesity (6). Using fluoxetine in these indications includes the possibility that patients may have other diseases, such as renal impairment or hepatic dysfunction. It is essential to know the impact of the physiological changes associated with renal and hepatic disease on the dose requirements. Therapeutic dosing of fluoxetine causes significantly fewer anticholinergic side effects (7) and appears not to cause the cardiovascular side effects seen in therapy with tricyclic antidepressants (8).

The most common adverse events associated with fluoxetine are nervousness, insomnia, nause and sexual dysfunction (2, 9). Serum transaminase elevations due to fluoxetine have been previously reported (10). Animal models have shown hepatocytic changes in mice, with fatty change and hepatocytic enlargement (11). Fluoxetine-induced hepatotoxicity is generally considered of minimal clinical importance and not well recognized. Asymptomatic increases in liver enzyme values have been observed in %0,5 of patients who take long-term fluoxetine therapy. This report details 2 cases of acute hepatitis believed to be caused by fluoxetine. Three cases of acute hepatitis caused by fluoxetine have been reported previously (12). The mechanism of fluoxetine-induced hepatotoxicity is unknown, some investigators suspect a metabolic idiosyncratic reaction and possibly a genetic predisposition (12, 13).

The aim of this study was to investigate the effects of fluoxetine in liver morphology in rats.

Materials and methods

Approval for the study was granted by the Medical Surgical Research Center of Osmangazi University and the Committee on Animal Experiments of the Medical Faculty of Osmangazi University. All experimental procedures were performed in accordance with the National Institute of Health's Principles of Laboratory Animal Care.

Nineteen male and 24 female Sprague-Dawley rats weighting 200-220 g were used for this study. Animals were kept under standart laboratory conditions and allowed free access to food and water.

Rats were divided in to five groups: Group A (n= 10) : Fluoxetine was administered via intraperitoneal injection at a dosage of 5 mg/kg. Group B (n=10) : Fluoxetine was administered via intraperitoneal injection at a dosage of 7.5 mg/kg. Group C (n=10): Fluoxetine was administered via intraperitoneal injection at a dosage of 10 mg/kg. Group D (n=7): Fluoxetine was administered via intraperitoneal injection at a dosage of 25 mg/kg. Group N (n=6): Control group. Instead of fluoxetine, 0.9 % saline solution was given.

The experiment lasted 3 weeks. Hepatic tissue samples were extracted under anesthesia for histopathologic study. Liver tissues were fixed in 10% buffered formalin and embedded in paraffin. Pathologic changes were evaluated on the H&E stained sections.

Morphological examination: Fragments of the liver were fixed for 48 h in buffered 10 % formalin solution and the embedded in parafin, sectioned at 5 μm; the sections were stained with hematoxylin and eosin, coded, and examined by a pathologist (KB), who was unaware of the treatment received and sacrifice time.

Liver lesions involving disruption of hepatic cell cords and lobular architecture were quantified in the five groups. In three randomly selected fields (x100) disruption was graded as absent (0), mild, indicating occasional focal architectural disruption (1), moderate, involving about 50% of the lobule (2) or severe, in which no recognizable ordered structure remained (3). Karyomegaly was defined as the presence of a large irregular nucleus containing a big nucleolus or multiple nucleoli and prominent chromatin clumping in abnormal hepatocytes. Distribution of this nuclear pleomorphism within lobules was graded numerically as no atypia (0), occasional foci of karyomegaly comprising less than 25% of the lobule (1), involvement of 25-50% of the lobule (2) or involvement of the entire lobule (3). Bile-duct proliferation was diagnosed microscopically as the occurence of duct-like structures lined with plump cuboidal hyperplastic epithelial cells surrounding a lumen with minimal supporting connective tissue, and was graded as absent (0), three bile ducts per triad (1), four or five bile ducts per triad (2) or more than five bile ducts per triad (3). Piecemeal necrosis was graded numerically as none (0), mild (1), moderate (involves less than 50% of the circumference of most portal tracts) (2), marked (involves more than 50% of the circumference of most portal tracts) (3). Intralobuler degeneration hydropic and steatosis were graded none (0), mild (< 1/3 of lobules) (1), moderate (1/3-2/3 of lobules) (2), marked (> 1/3 of lobules) (3). Portal inflammation: no portal inflammation (0), mild (sprinkling of inflammatory cells in <1/3 of portal tracts) (1), moderate (increased inflammatory cells in 1/3-2/3 of portal tracts) (2), marked (dense packing of inflammatory cells in >2/3 of portal tracts) (3). Fibrosis was graded as no fibrosis (0), fibrous portal expansion (1), bridging fibrosis (2), cirrhosis (3). Acute cholangitis was defined as neutrophil infiltration into and around the lumen of the bile duct in the portal triad (14). Acute cholangitis and lobuler inflammation were graded as follows: marked (3), moderate (2), slight (1) and none or negligible (0). Focal hepatocyte necrosis was defined as an accumulation of neutrophils in an area where hepatocytes had vanished from liver cell plates [hepatocytolysis and cellular infiltration (15)]. Apopitotic hepatocytes were detectable by cytoplasmic acidophilia and hyalinization. Focal necrosis, diffuse necrosis, apopitosis, erosion of limiting plate, twinning cell plates, Kupffer cell hyperplasia, intranuclear glycogenosis, double nucleus, sinusoidal dilatation and congestion were evaluated as follows: positive (1) and negative (0). Cholestasis was evaluated as absent (0), intracytoplasmic (1), in the bile ductuli (2), in the Kupffer cell (3) and in the bile duct (4).

Statistical analysis: Differences among groups were evaluated using X^2 and Kruskal- Wallis tests. Results were considered significant when $p<0.05$. Calculations were performed with SSPS 10.0.

Results

No significant gross pathology was recorded in any of the rats at autopsy.

Livers of all control rats were histologically normal, however all fluoxetine-exposed rats exhibited hepatic injury.

The major histopathological changes in the liver after fluoxetine are hydropic degeneration, karyomegaly (Fig 1), steatosis (Fig 2), lobuler inflammation (Fig 3), focal necrosis (Fig 4), apoptosis, disruption (Fig 5), twinning cell plates, cholestasis, portal area inflammation (Fig 6), Kupffer cell hyperplasia and double nucleus ($p<0.05$) when compared with the control group. No significant difference was determined in terms of bile duct proliferation, diffuse necrosis, erosion of limiting plate, fibrosis, sinusoidal dilatation and congestion, piece-meal necrosis, intranuclear glycogenosis ($p>0.05$).

The liver tissues of the Group A were similar to a normal microscopic appearence but minimal histopathologic change were observed. Following 7.5 mg/kg, 10 mg/kg and 25 mg/kg dose of fluoxetine exposure of the animals hydropic degeneration, karyomegaly, steatosis, disruption, apoptosis, twinning cell plates, portal area inflammation, double nucleus in the liver tissue became more pronounced. Disruption and marked hydropic degeneration have been shown most pronounced in the Group D rats.

Histopathological change scores of study groups were shown Table I. The results of statistical analysis were summarized in Table II.

Discussion

Toxic damage to the liver is a common finding with many chemicals and drugs including mycotoxins, and the wide range of histological lesions. Although hyperchromasia, karyomegaly and bile duct proliferation represent significant hepatic damage, a direct relationship with preneoplastic or neoplastic change should not be inferred at this stage (16).

Table I. Histopathological change scores in all study groups.

Histopathological changes	Score	Grup A	Grup B	Grup C	Grup D	Grup N
Hydropic degeneration	0	-	-	-	-	-
	1	10 (100%)	3 (30%)	-	-	6(100%)
	2	-	6 (60%)	10 (100%)	-	-
	3	-	1 (10%)	-	7 (100%)	-
Karyomegaly	0	3 (30%)	-	-	-	3 (50%)
	1	7 (70%)	8 (80%)	1(10%)	-	3 (50%)
	2	-	1(10%)	9 (90%)	5 (71.4%)	-
	3	-	1(10%)	-	2(28.6%)	-
Steatosis	0	10 (100%)	10 (100%)	5 (50%)	6 (85.7%)	6 (100%)
	1	-	-	3 (30%)	-	-
	2	-	-	2 (20%)	1 (14.3%)	-
	3	-	-	-	-	-
Bile duct proliferation	0	10 (100%)	10 (100%)	8 (80%)	5 (71.4%)	6 (100%)
	1	-	-	2 (20%)	2 (28.6%)	-
Lobuler inflammation	0	1 (10%)	-	-	1 (14.3%)	6 (100%)
	1	9 (90%)	10 (100%)	10 (100%)	4 (57.1%)	-
	2	-	-	-	2 (28.6%)	-
Focal necrosis	0	-	-	-	-	6(100%)
	1	10 (100%)	10 (100%)	10 (100%)	7 (100%)	-
Diffuse necrosis	0	10 (100%)	10 (100%)	9 (90%)	6 (85.7%)	6 (100%)
	1	-	-	1 (10%)	1 (14.3%)	-
Apoptosis	0	4 (40%)	2 (20%)	-	-	6 (100%)
	1	6 (60%)	8 (80%)	10 (100%)	7 (100%)	-
Erosion of limiting plate	0	10 (100%)	9 (90%)	10 (100%)	6 (85.7%)	6 (100%)
	1	-	1 (10%)	-	1 (14.3%)	-
Acute cholangitis	0	10 (100%)	10 (100%)	10 (100%)	7 (100%)	6 (100%)
	1	-	-	-	-	-
Disruption	0	10 (100%)	10 (100%)	2 (20%)	-	6 (100%)
	1	-	-	8 (80%)	5 (71.4%)	-
	2	-	-	-	2 (28.6%)	-
	3	-	-	-	-	-
Twinning cell plates	0	10 (100%)	1 (10%)	-	-	6 (100%)
	1	-	9 (90%)	10 (100%)	7 (100%)	-
Cholestasis	0	2 (20%)	-	-	1 (14.3%)	6 (100%)
	1	8 (80%)	9 (90%)	7 (70%)	1 (14.3%)	-
	2	-	1 (10%)	3 (30%)	4 (57.1%)	-
	3	-	-	-	1 (14.3%)	-
	4	-	-	-	-	-
Fibrosis	0	10 (100%)	10 (100%)	10 (100%)	6 (85.7%)	6 (100%)
	1	-	-	-	1 (14.3%)	-
Portal area inflammation	0	5 (50%)	1 (10%)	-	-	6 (100%)
	1	5 (50%)	9 (90%)	10 (100%)	7 (100%)	-
Sinusoidal congestion	0	4 (40%)	1 (10%)	-	-	-
	1	6 (60%)	9 (90%)	10 (100%)	7 (100%)	6 (100%)
Sinusoidal dilatation	0	4 (40%)	1 (10%)	-	-	-
	1	6 (60%)	9 (90%)	10 (100%)	7 (100%)	6 (100%)
Kupffer cell hyperplasia	0	7 (70%)	1 (10%)	-	1 (14.3%)	6 (100%)
	1	3 (30%)	9 (90%)	10 (100%)	6 (85.7%)	-
Intranuclear glycogenosis	0	8 (80%)	10 (100%)	10 (100%)	6 (85.7%)	6 (100%)
	1	2 (20%)	-	-	1 (14.3%)	-
Double nucleus	0	6 (60%)	1 (10%)	-	1 (14.3%)	6 (100%)
	1	4 (40%)	9 (90%)	10 (100%)	6 (85.7%)	-
Piece-meal necrosis	0	10 (100%)	10 (100%)	10 (100%)	5 (71.4%)	6 (100%)
	1	-	-	-	2 (28.6%)	-

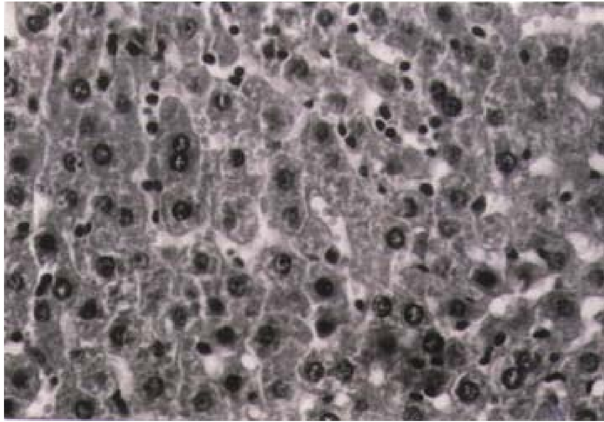

Figure 1. Note severe hydropic degeneration throughout the liver lobules, double nucleus and karyomegaly (H+E X200).

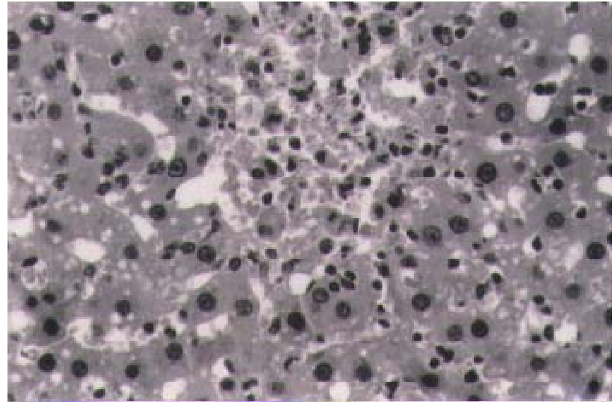

Figure 4. Focal necrosis (H+E X200).

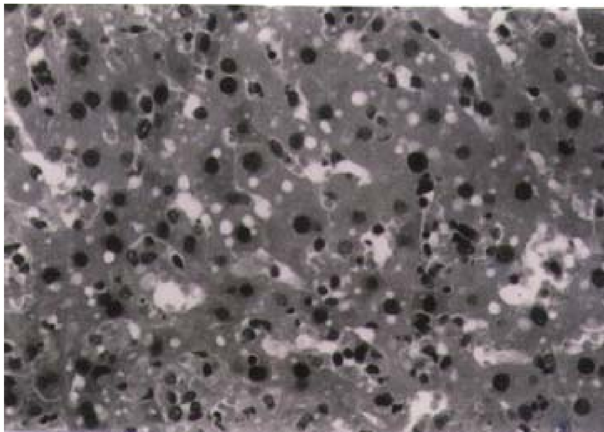

Figure 2. Fatty change and karyomegaly (H+E X200).

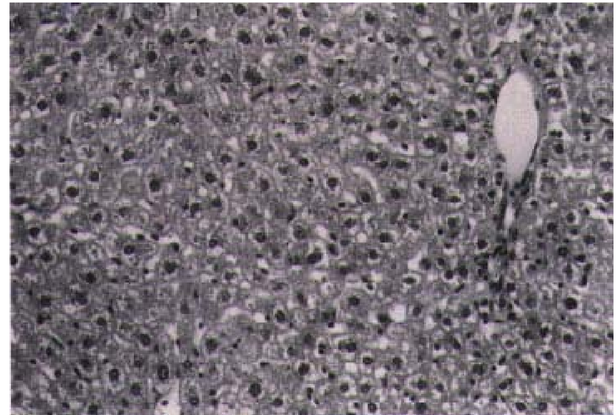

Figure 5. Disruption and severe hydropic degeneration (H+E X100).

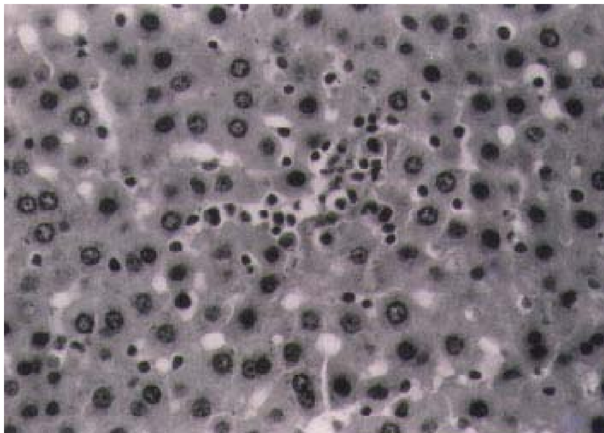

Figure 3. Lobuler inflammation (H+E X200).

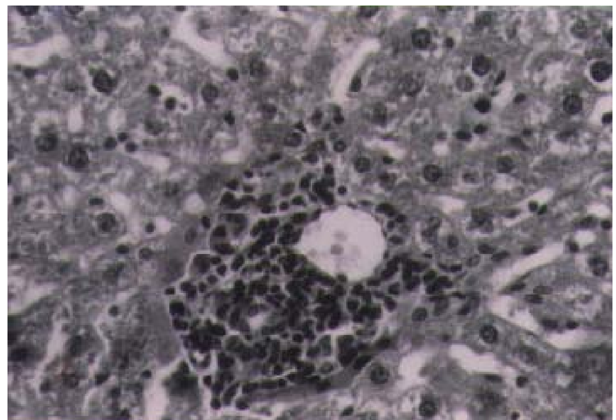

Figure 6. Portal area inflammation (H+E X200).

Table II. The results of statistical analysis.

Histopathological changes	P value
Hydropic degeneration	0.000**
Karyomegaly	0.000**
Steatosis	0.000**
Lobuler inflammation	0.015*
Disruption	0.000**
Twinning cell plates	0.000**
Cholestasis	0.045*
Apoptosis	0.049*
Focal necrosis	0.015*
Portal area inflammation	0.015*
Kupffer cell hyperplasia	0.001**
Double nucleus	0.004**

** $p<0.01$ *$p<0.05$

Fluoxetine is metabolized primarily in the liver. Evidence suggests that it is metabolized by 1 of the P-450 iso-enzymes, P-4502D6, in both saturable and nonsaturable pathways (2). During the CYP-450 mechanism, genetic polymorphism is an efficient factor in drug metabolism. Pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers and toxicity risk in these individuals might be increased. Although fluoxetine is a commonly used agent in treatment of depression, no data is present about the effect of it on DNA (2).

The mechanism of fluoxetine-induced hepatic injury is unclear. Whether the injury is caused by fluoxetine per se or by one or more of its metabolites is unknown. The low incidence of this toxicity, the variable latent period before onset of injury, the lack of hypersensitivity markers such as eosinophilia and rash, and the apparent lack of dose correlation suggest a metabolic idio-syncratic injury, as defined by Zimmerman (17). Whether fluoxetine-induced hepatoxicity is rare or is simply not well recognized is also unknown.

Among 3000 patients treated with fluoxetine in clinical trials, elevated aminotransferases developed in appro-ximately 0.5% (18). Despite the use of fluoxetine by some 10 to 15 million patients worlwide, the drug has been implicated as a cause of acute hepatitis in only two previous case reports, and no liver biopsies were done on these patients (10, 19). Johnston et al. (20) reported a case of serious chronic hepatitis related to use of fluoxetine. Cai et al. (1) reported two case of acute hepatitis due to fluoxetine therapy. Cosme et al. (21) described a case of acut cholestasis due to fluoxetine and confirmed by liver biopsy. In the present study, cholestasis (79.07%) and portal area inflammation (72.09%) were shown in our study groups.

The twinning of liver cell plates and the karyomegaly seen in the rats subjected to fluoxetine suggest increased proliferation of hepatocytes in response to fluoxetine (22). We observed karyomegaly (79.07%) and twinning of liver cell plates (60.5%) in the study grups.

The major finding in the presented study was the deve-lopment of hepatocellular hydropic vacuolar degene-ration (100%), which was most severe in Group D. What is the underlying mechanism of hepatocellular vacuolar degeneration? Results of Sudan III staining and assay of hepatic lipid contents confirmed that the vacuoles were not lipid accumulations. Similarly, PAS staining and assay of hepatic glycogen content confirmed that the vacuoles did not contain glycogen. Since hepatic protein contents decreased in parallel with the severity of hepatocellular vacuoler degeneration, the vacuoles were considered to be mainly associated with intracellular water accumulation (23). Insulin and glucagon were recently recognized as potent modulators of liver cell volume (24). In isolated perfused rat liver, insulin stimulates Na^+-H^+ exchange, Na^+-K^+-2Cl cotransport, and Na^+-K^+-ATPase, and the concerted action of these transporters lead to cellular accumulation of K^+, Na^+ and Cl^- and, consequently, cell swelling (25). In contrast, glucagon may lead to a depletion of cellular Na^+ , K^+, and probably Cl^- , resulting in cell shrinkage (26, 27). It is reported that both insulin and glucagon exert half-maximal effects on cell volume and cellular K^+ balance at hormone concertrations found physiologically in the portal vein (28).

Effect of fluoxetine on cell proliferation is not clear yet. Previous studies showed inhibitory effects on murine B and T cell proliferations but mechanism of its effects has not been well defined (28-30). Further experiments are needed to address these hypotheses.

In conclusion, we have demonstrated that fluoxetine can cause hepatotoxity. At the end of the exposure period, livers of all exposed rats, but no controls, showed hyd-ropic degeneration, karyomegaly, steatosis, lobuler inflam-mation, focal necrosis, apoptosis, disruption, twinning cell plates, cholestasis, portal area inflammation, Kupffer cell hyperplasia and double nucleus. The main histo-pathological changes in all exposed rats were hepato-celluler hydropic vacuolar degeneration (%100).

Further histopathologic and molecular experimental studies are reguired to elucidate the pathogenesis of fluoxetine induced hepatotoxicity in detail. Although routine monitoring of liver function may not be cost-effective, physicians should be alert to the possibility of fluoxetine associated hepatotoxicity and consider early discontinuation of the drug if this condition is suspected.

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