FACTA UNIVERSITATIS
Series: **Medicine and Biology** Vol.12, No 3, 2005, pp. 150 - 153 UC 616.36:613.83

CHRONIC INTRAVENOUS HEROIN ABUSE: IMPACT ON THE LIVER

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Summary. *Intravenous (i.v.) heroin intake leads to significant morphological changes in the liver tissue (vesicular changes, fat changes, chronic hepatitis, cirrhosis). The intensity of these changes increases with duration of heroin usage. Direct hepatoxic effects of heroin are vesicular changes in hepatocytes, fat changes are the result of chronic influence of alcohol, whereas the rest of the morphological lesions to the liver are the result of the interaction of heroin, viral infection and alcohol. We analyzed a total of 50 autopsies, 40 from the group of i.v. heroin users and 10 from the control group (dead bodies of young and healthy people with mechanical injuries that did not affect the liver). For ease of analysis, all autopsy cases of i.v. heroin abuse were divided into 4 groups according to the duration of intravenous heroin intake: 2 years, between 2 and 5 years, between 5 and 10 years, and longer than 10 years.*

Key words: *Heroin, liver, intravenous intake, morphological lesions*

Introduction

The liver is a very important organ in the human organism. It is the largest gland and plays a key role in the removal of lipophyllic material from the plasma, including morphine and its derivative heroin. Hepatocyte is the main locus of the bio-transformational systems which, through the action of the enzymes, enable the removal of the metabolites of these compounds from the organism. During these processes, ultrastructural hepatocyte changes and toxic liver damage occur, and intravenous intake of heroin leads to severe hepatic tissue infections (hepatitis, AIDS). The effects of heroin intake are most pronounced in the liver. The morphologic changes in the liver tissue are associated with its function disturbances, which results in the altered metabolism of heroin and other toxins taken simultaneously (alcohol, drugs) and, if these substances are abused, leads to the effects that are often surprising (1,2,3).

Heroin, diacetylmorphine, is produced through morphine acetylation at loci 3 and 6. Wright synthesized it in 1874, the event that was warmly welcomed by the medical profession due to the fact that heroin could be used as a possible substitute for morphine and codeine (4). This compound is converted *in vivo* in much more potent analgesics such as morphine and 6-acetyl morphine (5).

Liver insufficiency as a consequence of primary hepatocyte damage can develop gradually and take a chronic course, and it is caused by a diffuse pathologic process (diffuse hepatocyte necrosis, diffuse fibrosis with anarchic lobule regeneration and simultaneous hepatocyte ischaemia (6).

All liver diseases with a marked hepatocyte necrosis demonstrate a highly reduced activity of enzymes, specifically hydroxilases, due to which the inactivation of certain drugs (opiates, sedatives, hypnotics, etc.) is made difficult and their action on CNS increased and prolonged. There is no rule in this respect, as it is possible that some patients with more severe forms of hepatitis or cirrhosis metabolize drugs fasted than expected or that mild forms demonstrate a slower metabolism (7,8,9).

Hepatic encephalopathy (hyperamonianemia being the main culprit) develops as one of the manifestations of liver cell insufficiency. Cerebral disturbances are probably associated with the liver inability to provide all required metabolic substrates for cerebral functions, but the action of endogenous toxins on the brain tissue is also important (10). The functional disorder of the liver increases hemato-encephalic barrier permeability, thus enabling neuroactive substances to reach the brain cells in enormous amounts (10,11).

Aim of the Study

A micro-morphologic, histochemical, and immunohistochemical study of the liver, the organ most affected by heroin abuse, should provide a precise insight into the type and degree of liver damage induced by intravenous drug abuse, as well as determining whether the degree of these lesions depends on the duration of intravenous heroin abuse.

Patients and Methods

We analyzed a total of 50 autopsies, 40 from the group of i.v. heroin abusers and 10 control autopsies (corpses of young and healthy individuals who died of mechanical traumas not affecting the liver).

Out of 40 corpses of i.v. heroin abusers, there were 34 males and 6 females.

There were 5 corpses in the age group 15-20 years, 9 in the group 21-25 years, 12 in the group 26-30 years, 5 in the group 31-35, 6 in the group 36-40 years, and 3 in the group over 40 years of age.

Among controls, there were 8 male and 2 female corpses.

In this group, 1 person was below 15 years of age, 2 were in the age group 16-20 years, 5 were in the 21-25 years of age group, 1 was in the age group 26-30, and 1 in the group of 30-35 year-olds.

The autopsy served as proof of the status of i.v. heroin abusers (fresh and old injection scars), as well as for chemical-toxicological demonstration of heroin in the blood and organs. Evidence from the Registry of the Department for Addictions, Mental Health Center in Niš, and information from close relatives before autopsy at the Center for Forensic Medicine in Niš were provided. Similarly, data were obtained on the duration of i.v. heroin abuse, frequency of heroin abuse, possible abstinence periods, and alcohol intake and/or sedatives (benzodiazepine, etc.).

For the purpose of facilitating the investigation, all autopsies of i.v. heroin abusers were divided into 4 groups according to the duration of i.v. heroin intake: up to 2 years; 2-5 years; 5-10 years; and over 10 years.

During the autopsies, the livers were sampled (3-5 samples per autopsy), fixated in a 10% formaldehyde solution, and processed in an autotechnicon. Paraffin sections, 5 μm thick, were stained using the following methods:

1. Classical (HE) method to investigate histologic changes;
2. Histochemical methods to verify detected histologic lesions;
   - Van Gieson – to confirm collagen;
   - Gomori – to provide insight into reticulin skeleton (stroma) and membranes;
   - PAS – to stain deposited glycogen.
3. Immunohistochemical (PAP) method, using antibodies to "core" and "surface" antigens – to confirm viral B hepatitis.

Results and Discussion

Vesicular changes are second-degree milder degenerative changes. They are characterized by the presence of a large number of small vacuoles in the hepatocyte cytoplasm. These changes are collectively known as vacuolar degeneration.

The percentage of cases with panacinary distribution grows with duration of i.v. heroin abuse – there is none in the group of addicts with up to 2 years of heroin abuse; 25% in the group 2-5 years; 69% in the group 5-10 years; and 75% in the group over 10 years. Longer periods of i.v. heroin abuse lead to more serious hepatocyte damage in the form of vacuolar degeneration.

Fatty change is the most severe form of reversible cell damage. It is characterized by the presence of small and large vacuoles within hepatocytes. Droplets of fat press the nucleus and cytoplasm against the cell membrane.

In this study, fatty changes of various intensity were found, from focal, through multifocal, all the way to diffuse ones, within specific acinary zones and within all liver acini.

Panacinary presence of hepatocytic fatty changes was found at highest degree in the group of 5-10 years i.v. heroin abusers (61.5% of all cases with fatty changes with this degree of severity). It should be emphasized that, for this group, the most frequent were the data obtained on alcohol intake (10 out of 13 cases, or 77%), which may explain the presence of diffuse distribution of fatty change in most cases. In the group of over 10 years of i.v. heroin abuse, the data on significant alcohol intake were obtained in one case, so the percentage of fatty change is low (25%).

A highly common complication of i.v. heroin abuse is a chronic viral and primarily active hepatitis which induces a significant morphologic and functional liver damage. Its frequency increases with years of heroin abuse (by groups, 14.5%, 37%, 77%, 100%), which suggests a temporal correlation of i.v. heroin abuse and the degree of morphologic change of the liver. It is most probably the consequence of long-lasting heroin intake, which further compromises the immunologic status in heroin abusers, and it is considered the major pathophysiological mechanism of chronic viral infection (12,13,14,15). The parenteral mode of intake is the factor which promotes viral hepatitis and it is confirmed in all investigated cases (16).

In our study, cirrhosis was present in 30% of the analyzed cases (12 out of 40), and its frequency rises with years of i.v. heroin abuse (0%, 6%, 66%, 75%). The correlation was similar to that observed in chronic viral hepatitis.

Out of 12 cases with established cirrhosis, none was proven without the finding of HAH or alcoholic fatty degeneration, so cirrhotic liver changes are the consequence of viral infection and alcohol, rather than a result of direct heroin impact. The role of heroin most probably lies in enhancing viral infection via immuno-suppression; i.v. heroin abuse itself favours viral infection.

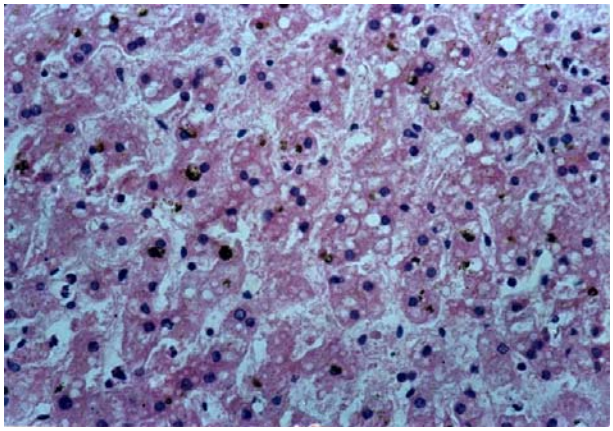

Fig. 1. Vesicular hepatocytic changes and cholestasis. PAS × 250

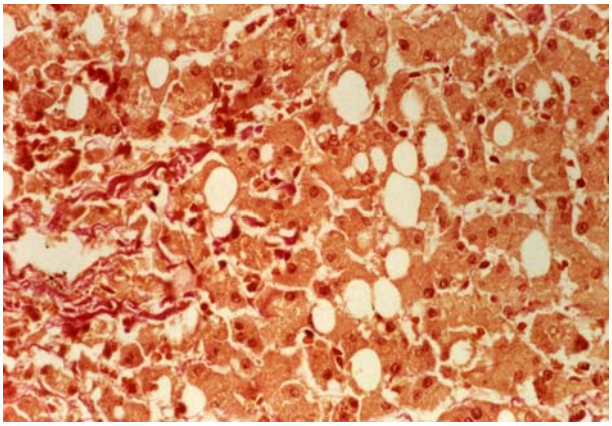

Fig. 2. Macro-droplet-like fatty change in hepatocytes and focal condensation of collagen in portal spaces. Van Gieson × 250

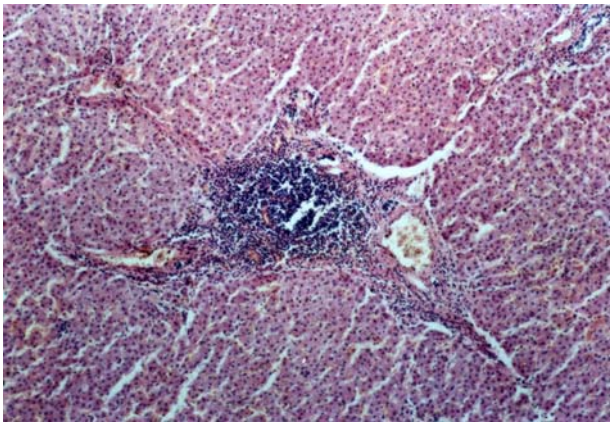

Fig. 3. Chronic persistent hepatitis: hyper-plastic lymph follicle in the portal space – characteristic of hepatitis C. HE × 200

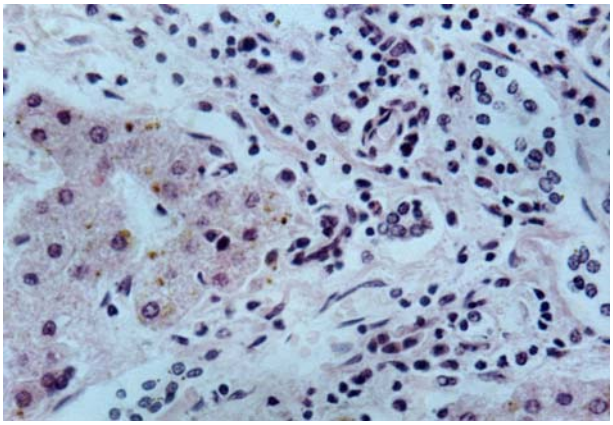

Fig. 4. Chronic active hepatitis: marked cholangiogenesis, with marked mononuclear infiltration, in the portal space. HE × 200

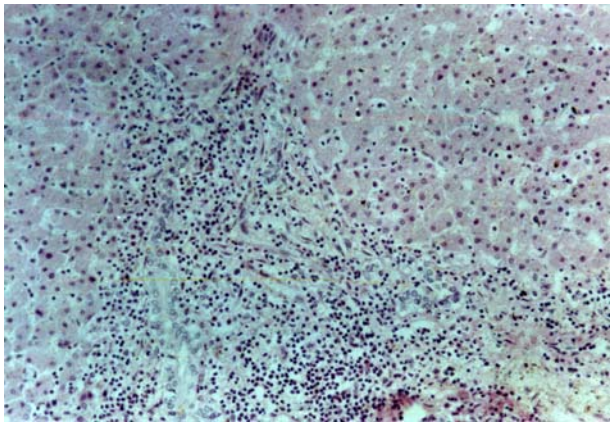

Fig. 5. Chronic active hepatitis: evident "bridging" necrosis. HE × 200

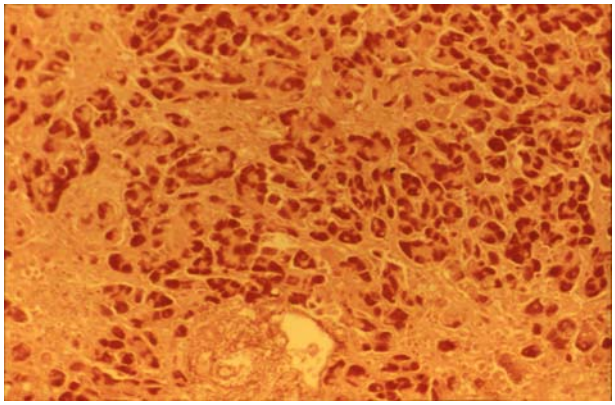

Fig. 6. Viral B hepatitis: "core" antigen within hepatocytes. PAP × 250

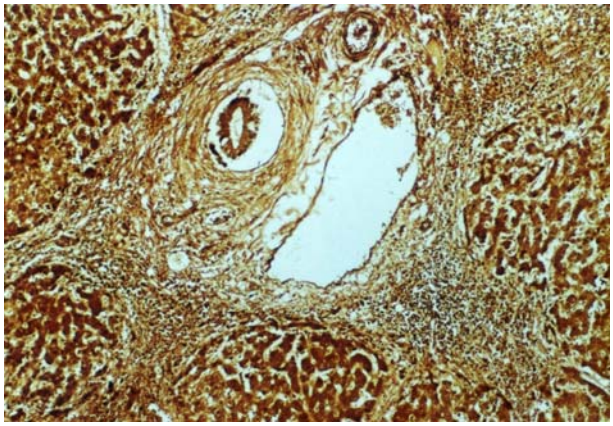

Fig. 7. Post-hepatic cirrhosis: pseudo-lobules surrounded by collagen fibers and dense lymphocytic infiltration, rupturing the border plate. Gomori × 200

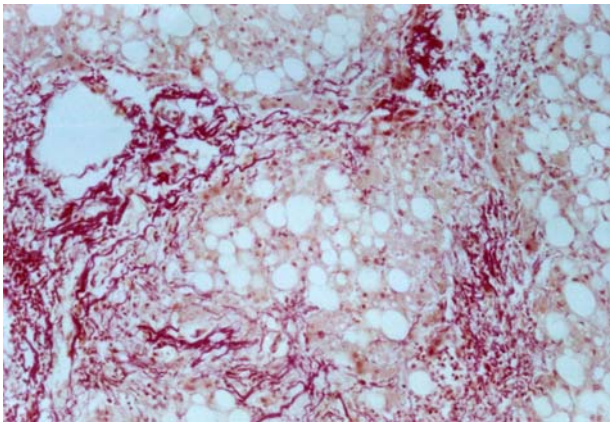

Fig. 8. Alcoholic cirrhosis: pseudo-lobule with macro- and micro-droplet-like fatty change surrounded by condensed collagen fibers. Van Gieson × 250

Conclusion

Direct hepatotoxic effects of heroin are vesicular hepatocytic changes, fatty changes are the consequence of chronic alcohol abuse, while other established morphologic liver lesions are the result of the interaction of heroin abuse, viral infections and alcohol.

Intravenous heroin abuse induces significant morphologic changes in the liver tissue (vesicular changes, fatty changes, chronic hepatitis, cirrhosis), and the severity of these changes increases with years of heroin abuse.

Significant morphologic changes in the liver the percentage of which increases with years of heroin abuse, most commonly cause a significantly reduced detoxification function of the liver, which further induces reduced heroin bio-transformation and development of increased sensitivity of the brain centers to the action of this drug and other toxins.

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UTICAJ HRONIČNE INTRAVENSKE ZLOUPOTREBE HEROINA NA JETRU

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Kratak sadržaj: *Intravensko unošenje heroina dovodi do značajnih morfoloških promena na tkivu jetre (vezikularne promene, masne promene, hronični hepatitis, ciroza), pri čemu je intenzitet ovih promena veći, što je duži vremenski period u kojem je zloupotrebljavan heroin.*

Direktni hepatotoksični efekti heroina su vezikularne promene na hepatocitima, masne promene su posledica hroničnog dejstva alkohola, dok su ostale utvrđene morfološke lezije jetre nastale u interakciji dejstava heroina, virusnih infekcija i alkohola.

Studija je obuhvatila analizu 50 autopsija i to 40 iz grupe intravenskih heroinomana, a 10 obdukcija je predstavljalo kontrolnu grupu (leševi mladih i zdravih osoba smrtno stradalih zbog mehaničkih trauma koje nisu zahvatile jetru). Radi lakšeg proučavanja svi obdukcijski slučajevi intravenskih heroinomana grupisani su po dužini vremenskog perioda intravenskog unošenja heroina u 4 grupe: sa stažom do 2 godine, između 2 i 5 godina, između 5 i 10 godina i sa stažom dužim od 10 godina.

Ključne reči: *Heroin, jetra, intravenska aplikacija, morfološka oštećenja*