Duration dependent effect of intravenous heroin intake on morphological changes in the liver

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Abstract: Intravenous heroin intake leads to significant morphological changes in the liver tissue (vesicular changes, fatty changes, chronic hepatitis and cirrhosis). The intensity of these changes increases with the duration of heroin use. Direct hepatotoxic effects of heroin are vesicular changes in hepatocytes, fatty changes are the result of chronic influence of alcohol, whereas the rest of the morphological liver lesions are the result of the interaction of heroin, viral infection and alcohol. In the present study, we analyzed a total of 50 autopsies, 40 from the group of intravenous 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 intravenous heroin abuse were divided into 4 groups according to the duration of intravenous heroin intake: up to 2 years, between 2 and 5 years, between 5 and 10 years, and longer than 10 years.

Key Words: heroin, liver, intravenous intake, morphological lesion

Heroin, diacetylmorphine, is produced through morphine acetylation at loci 3 and 6. It was first synthesized in 1874 by C. R. Alder Wright, and that event was warmly welcomed by the medical profession due to the fact that heroin could be used as a possible substitute for morphine and codeine. This compound is converted in vivo in much more potent analgesics such as morphine and 6-acetyl morphine [1]. The effects of heroin intake are most pronounced in the liver. Liver insufficiency presenting 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 ischemia) [2, 3, 4, 5, 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 in the human brain is 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 faster than expected or that mild forms demonstrate a slower metabolism [7, 8].

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. The functional disorder of the liver increases hemato-encephalic barrier permeability, thus enabling neuroactive substances to reach the brain cells in enormous amounts [9, 10].

A micro-morphologic, histochemical, and...
immuno-histochemical 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 whether the degree of these lesions depends on the duration of intravenous heroin abuse.

**Material and methods**

We analyzed a total of 50 autopsies, 40 from the group of IV 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 IV heroin abusers, 34 were males and 6 females (Graph 1). 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 (Graph 2). Among controls, there were 8 male and 2 female corpses (Graph 1). 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 (Graph 2).

The autopsy served as proof of the status of IV 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 Centre in Niš, and information from close relatives before autopsy at the Institute of Forensic Medicine in Niš were provided. Similarly, data were obtained on the duration of IV 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 IV heroin abusers were divided into 4 groups according to the duration of IV heroin intake: up to 2 years (7 autopsies); 2-5 years (16 autopsies); 5-10 years (13 autopsies); and over 10 years (4 autopsies). 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 histological changes;
2. Histochemical methods to verify detected histological 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.

The research on the human cadavers was approved by the Internal Ethic Committee and conducted at the Institute of Forensic Medicine of this Faculty.

**Results and discussion**

Vesicular changes 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 panacinar distribution grows with the duration of IV 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 IV 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. The investigation showed fatty changes of various intensity, from focal, through multifocal, all the way to diffuse ones, within specific acinar zones and within all liver acini (Figure 1).

Panacinary distribution of fatty changes were found at the highest degree in the group of 5-10 years of IV heroin abuse (61.5% of all cases with fatty changes in this degree of severity). It should be emphasized that in 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 IV heroin abuse, the data on significant alcohol intake were obtained in one case, so the percentage of fatty change is low (25%) (Graph 3). A highly common complication of IV heroin abuse is a chronic viral and primarily active hepatitis which induces a significant morphologic and functional liver damage (Figure 2, 3, 4). Its frequency increases with years of heroin abuse (by groups, 14.5%, 37%, 77%, 100%), which suggests a temporal correlation of IV heroin abuse and the degree of morphologic change in 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 [11, 12, 13, 14]. The parenteral mode of intake is the factor which promotes viral hepatitis and it is confirmed in all investigated cases [15].

The most important characteristic of chronic active hepatitis is the inflammatory destruction of the border plate marked as piecemeal necrosis. In this case, it is about a gradual inflammatory destruction of individual hepatocytes, or their groups in the periportal zone with a dense infiltration of lympho-plasmocytes and macrophages (Figure 5).

The remaining hepatocytes show degenerative changes of hydropic (lytic) and acidophilic type. With progression, there are lethal damages of individual hepatocytes of lytic or acidophilic type. The acidophilic type is characterized by dense eosinophilic bodies expelled from the normal plane, called Councilman's bodies (Figure 6). In our study, cirrhosis was present in 30% of the analyzed cases (12 out of 40), and its frequency rises with years of IV 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 chronic active hepatitis or alcoholic fatty degeneration (Figure 7), 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; IV heroin abuse itself favours viral infection. In the area of hepatocytes and stromal collapse (a consequence of necrosis) reticular network is dense (Figure 8). In portal areas, the condensation of fibres is pronounced in the case perportal piecemeal or bridging necrosis, as well as in the case of cirrhosis, regardless of its genesis.

Graph 3. Fatty changes of hepatocyte depending on the duration of IV heroin intake
Figure 1. Fatty changes in hepatocytes and focal condensation of collagen in portal space. Van-Gieson x 250.

Figure 2. Chronic persistent hepatitis: hyperplastic lymph follicle in the portal space – characteristic of hepatitis C. HE x 200.

Figure 3. B viral hepatitis: "core" antigen in hepatocytes. PAP x 250.

Figure 4. B viral hepatitis: "surface" antigen in hepatocytes. PAP x 250.
Figure 5. Chronic active hepatitis: "peacemeal" necrosis in border area of acinus. HE x 200.

Figure 6. Chronic active hepatitis: acidophilic necrosis (Councilman's body) with reactive inflammation PAS x 250.

Figure 7. Cirrhosis of combined origin: fatty changes in hepatocytes and dense mononuclear infiltrate in expanded portal space with a pronounced piecemeal necrosis (active septa). HE x 200.

Figure 8. Focal condensation of reticular fibres. Gomori x 200.
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 (chronic hepatitis, cirrhosis) 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 detoxifying function of the liver, which further induces reduced heroin bio-transformation and development of increased sensitivity of the brain centres to the action of this drug and other toxins.

List of abbreviations:
intravenous – IV
intravenous heroin addicts - ivH

References