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Research Article

Effects of Deferiprone and Deferasirox on Liver and Duodenum Histology in an Iron-Overloaded Rat (*Rattus norvegicus*) Model

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Abstract | Iron is an essential micronutrient for the human body, but excessive iron can trigger reactive reactions leading to oxidative stress, which may damage cells, tissues, and organs, particularly the liver and duodenum. Iron overload can be treated with iron chelation therapy, such as Deferiprone (DFP) and Deferasirox (DFX). This study aims to determine the more effective and safer iron chelator for preventing histological damage to the liver and duodenum in iron-overloaded rats. This experimental study was conducted over 46 days using a completely randomized design (CRD) with four test groups, consisting of 24 male Wistar rats (*Rattus norvegicus*). Iron dextran (120 mg/kg BW) was administered intravenously for the first 18 days at 3-day intervals, while DFP and DFX were given orally for 28 consecutive days. The treatment groups received DFP (100 mg/kg BW) or DFX (30 mg/kg BW). The observed parameters included relative liver weight and histological structure of the liver and duodenum. The results showed that DFP and DFX reduced relative liver weight (by 17.3% and 11.4%, respectively), hepatocyte necrosis (by 49% and 33.1%, respectively), and duodenal villi damage score (by 88.3% and 47%, respectively) compared to the negative control. These effects were achieved through the binding of free iron in plasma, which was subsequently excreted via urine or feces. Based on these findings, DFP 100 mg/kg BW was more effective and safer than DFX 30 mg/kg BW.

Keywords | Deferasirox, Deferiprone, Duodenum, Histology, Iron overload, Liver

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INTRODUCTION

Iron (Fe) is an essential micronutrient needed in the process of blood formation in the synthesis of hemoglobin (Hb). Iron plays a role in oxygen transportation and oxidative phosphorylation (Milic *et al*., 2016), but excess iron in the body can trigger reactive reactions that can lead to oxidative stress (Sousa *et al*., 2020). This oxidative stress has the potential to damage cells, tissues, and organs (Aldi *et al*., 2019) such as the liver and duodenum.

The liver plays a role in iron metabolism, namely iron absorption and storage (Perdana and Jacobus, 2015). Continued iron deposition in the body can cause transferrin in the plasma to become saturated with iron, so the free iron that is not bound by transferrin is called Non-Transferrin Bound Iron (NTBI) (Vogt *et al*., 2021). This NTBI is then rapidly bound by hepatocyte cells in the liver. The binding process under iron-depositing conditions plays a role in liver damage such as hepatocyte cell death (ferroptosis). NTBI has toxic properties due to the formation of reactive oxygen substances it produces (Yutarti and Susilowati, 2023).

The duodenum plays a role in iron absorption through enterocyte cells, which is very important for maintaining iron balance in the body (Piskin *et al*., 2022). Excess iron accumulation can cause loosening to the intestinal mucosa, which can damage the epithelial tight junctions and increase the permeability of the small intestinal lining. This causes patients with iron overload to develop gastrointestinal complications, such as diarrhea, vomiting, and gastrointestinal tract injury (Huo *et al*., 2022). Therefore, iron chelation therapy such as Deferiprone and Deferasirox is required (Chaudhary and Pullarkat, 2013; Morales *et al*., 2022).

Deferiprone is an orally administered bidentate iron chelator (Whiteside *et al*., 2007). Deferiprone helps to reduce the accumulation of iron in the body by excreting it through the urine (Morales *et al*., 2022), but Deferiprone has side effects such as agranulocytosis, mild neutropenia, abdominal discomfort, erosive arthritis (Neufeld, 2006), and causes an increase in Alanine Aminotransferase (ALT) or Serum Glutamic Piruvic Transaminase (SGPT) levels which can cause liver damage (Yosia and Wahidiyat, 2018). Deferasirox is a new orally administered tridentate iron chelator. Deferasirox helps to reduce the accumulation of iron in the body by excreting it through the feces (Chaudhary and Pullarkat, 2013) but Deferasirox has side effects such as abdominal discomfort, rash or mild diarrhea after starting therapy, and increased creatinine levels (Neufeld, 2006).

No studies have compared the effects of Deferiprone and Deferasirox on liver and duodenum histology. Therefore, this study aims to determine the more effective and safer iron chelator for preventing histological damage to the liver and duodenum in iron-overloaded rats (*Rattus norvegicus*).

MATERIALS AND METHODS

Animal Treatment

This research was approved by the Research Ethics Committee of Padjadjaran University (No. 75/UN6.KEP/EC/2023) and conducted experimentally using the Completely Randomized Design (CRD) method. A total of 24 male rats (*Rattus norvegicus*) Wistar strain, 7 weeks old, average body weight 200-300 grams were used in this study. The test animals were acclimatized for 7 days at room temperature with 12 hours of light and dark (OECD, 2008). Every day, the rats were given food and water ad libitum and grouped into 4 treatment levels, namely Normal (aquadest) (N); Negative Control (NC) (Iron Dextran (ID) (Hemadex, Sanbe, Bandung, Indonesia) 120 mg/kg BW); Treatment 1 (T1) (ID 120 mg/kg BW and Deferiprone (DFP) 100 mg/kg BW); and Treatment 2 (T2) (ID 120 mg/kg BW and Deferasirox (DFX) 30 mg/kg BW). The accumulated dose of iron dextran 120 mg/kg BW was given intravenously for 18 days with a 3-days interval, while DFP and DFX were given orally every day for 28 days. Furthermore, all rats were sacrificed one day after the treatment period was completed and had been fasted for 16 hours.

Organ Sampling

Rats that had previously been fasted for 16 hours were sacrificed by being anesthetized using Ketamine Xylazine 0.2 ml intramuscularly on day 47. Then the rats were placed on a surgical board or paraffin tray on their backs and dissected starting from the abdomen to the thorax (BPOM, 2021 with modifications), then the liver and duodenum were sampled. The organs were then put into a film bottle containing 10% Neutral Buffered Formalin (NBF) fixative solution, and then paraffin blocks were made.

Relative Organ Weight Calculation

The absolute organ weight that has been weighed is then calculated for the relative organ weight. According to Alipin and Azizah (2021), relative organ weight can be obtained with the following formula:

$$Relative\ Organ\ Weight = \frac{Absolute\ Organ\ Weight\ (g)}{Rat\ Body\ Weight\ (g)} \times 100\%$$

Histological Preparation with Hematoxylin-Eosin (HE) Staining

Organ specimens fixed in 10% NBF solution were placed into tissue cassettes, dehydrated with ascending alcohol (70%, 80%, 90%, and absolute), cleared with xylol, and infiltrated with paraffin before embedding in basemolds to form paraffin blocks. This block was then cooled and cut to 5 µm thick, immersed in a waterbath, and attached to a glass slide coated with Meyer's albumin before drying on a heating plate. Staining was done by Hematoxylin-Eosin method after deparaffinization using xylol and rehydration with alcohol series down (absolute, 90%, 80%, and 70%). After immersion in Harris Hematoxylin and Eosin, the preparations were dried with alcohol series up, dipped in xylol, and mounted before being observed using a light microscope (Januar *et al*., 2014; Yulianti, 2017).

Histological Structure Observation of Liver and Duodenum

Histological structure observations were made on liver and duodenal organ samples by comparing histological slides of treated rats with normal rats using a light microscope. The parameters of the observation of the histological structure of the liver and duodenum, namely the number of hepatocyte cell necrosis and damage to the mucosal layer of the duodenum (epithelial layer on the villi) were assessed using the scoring method according to Chiu et al. (1970). Each slide was observed in 5 fields of view with 400x magnification (El-Sheikh *et al.*, 2018; Imamah *et al.*, 2016). In histological observation of the liver, 20 hepatocyte cells were randomly counted in each field of view so that 100 hepatocyte cells were observed in 1 slide (Prasetiawan *et al.*, 2012). The number of hepatocyte cell necrosis can be calculated using the percentage formula (Januar *et al.*, 2014).

$$Percentage\ of\ cell\ damage\ (\%) = \frac{Number\ of\ damage\ cells}{Total\ number\ of\ cells} \times 100\%$$

Statistical Analysis

The data were tested with the normality test, followed by one-way analysis of variance (ANOVA) and Duncan post hoc test to evaluate significant differences when they are normal. Meanwhile, when the data is not normal, the Kruskal-Wallis and Mann Whitney U tests were performed. The analysis was carried out at a 95% confidence level ($p < 0.05$). Statistical analysis was carried out with the help of SPSS 26 for windows software.

RESULTS AND DISCUSSION

Relative Weight of Liver Organs

The results of the study groups were weighed relative weight of liver organs to see the presence of macroscopic damage. The results of descriptive tests and analysis of t-tests on the relative organ weight seen in the study groups are shown in Table 1.

Table 1: Average relative weight of liver organs.

Treatment	Relative liver Weight ($\bar{x}$ ± SD%)
N (Normal)	3,35 ± 0,37[a]
NC (Iron Dextran 120 mg/kg BW)	4,23 ± 0,36[b]
T1 (Iron Dextran 120 mg/kg BW + Deferiprone 100 mg/kg BW)	3,50 ± 0,33[a]
T2 (Iron Dextran 120 mg/kg BW + Deferasirox 30 mg/kg BW)	3,75 ± 0,64[ab]

Note: Different letters in the column indicate significant differences between treatments based on Duncan post hoc test at the 95% confidence level (α = 0.05).

The relative liver weight in the Deferiprone 100 mg/kg BW (T1) and Deferasirox 30 mg/kg BW (T2) groups was not significantly different ($p > 0.05$) from the Normal (N) group. However, T1 showed a significant difference ($p < 0.05$) from the Iron Dextran 120 mg/kg BW (NC) group, while T2 did not ($p > 0.05$). T1 and T2 reduced relative liver weight by 17.3% and 11.4%, respectively, compared to the NC, indicating that Deferiprone is more effective in reducing liver weight in iron-overloaded rats. Based on this analysis, all treatments influenced relative liver weight.

Iron Dextran 120 mg/kg BW can cause iron overload conditions (Maskoen *et al.*, 2016). Excessive iron levels in plasma can cause tissue damage due to the presence of hydroxyl free radicals (Kurniati *et al.*, 2020). The presence of free radicals can cause test animals to lose weight along with an increase in the absolute weight of the liver organ, causing an increase in relative organ weight (Soliman, 2002). This is caused by the disruption of K^+ transport activity out of the cell and the entry of Ca^{2+} and water, causing cell swelling (Putri *et al.*, 2018).

Deferiprone 100 mg/kg BW (T1) and Deferasirox 30 mg/kg BW (T2) can reduce the relative weight of the liver organs of iron overload model rats. Deferiprone is a bidentate iron chelator (3:1) (Morales *et al.*, 2022), while Deferasirox is a tridentate iron chelator (2:1) (Chaudhary and Pullarkat, 2013). Both chelators have a different number of binding sites. Deferiprone chelates redox-active iron using two binding sites, preventing oxidative damage. Its small size (139 g/mol) allows it to cross cell membranes, mobilize excess iron, and facilitate excretion through urine (Morales *et al.*, 2022). Deferasirox is metabolized in the liver and then the binding of free iron ions, especially redox active iron using three binding sites at the same time to form a soluble complex, then eliminated through bile into the intestine, and excreted from the body through feces (Chaudhary and Pullarkat, 2013).

Hepatocyte Cell Necrosis on Liver Histology

The mean number of necrotic hepatocytes in the Iron Dextran 120 mg/kg BW (NC), Deferiprone 100 mg/kg BW (T1), and Deferasirox 30 mg/kg BW (T2) groups were significantly different ($p \leq 0.05$) from the Normal (N) group. T1 and T2 were significantly different ($p \leq 0.05$) from NC, while T1 was not significantly different ($p > 0.05$) from T2. This indicates that all treatments influenced hepatocyte cell necrosis (Figure 1 and Table 2).

Deferiprone 100 mg/kg BW (T1) and Deferasirox 30 mg/kg BW (T2) can reduce the number of hepatocyte cell necrosis in iron-overloaded model rats, even though it has not reached normal conditions, with T1 and T2 reducing necrosis by 49% and 33.1%, respectively, compared to the NC. This is supported by research conducted by Taher *et al.* (2005), namely Deferiprone 100 mg/kg BW can effectively reduce serum ferritin levels and liver iron levels less

than 15 mg/g dry weight. This is also in line with research conducted by Arfie *et al.* (2022) which states that the administration of Deferasirox 30 mg/kg BW can reduce iron in the body as indicated by a significant decrease in LIC (Liver Iron concentration) and a decrease in serum ferritin levels. Decreased iron levels in the body can prevent organ damage (Safitri *et al.*, 2017). Deferiprone and Deferasirox are iron chelators that bind to NTBI in plasma and reduce excess iron in the body (Supriatna *et al.*, 2020), thus reducing the amount of hepatocyte cell necrosis.

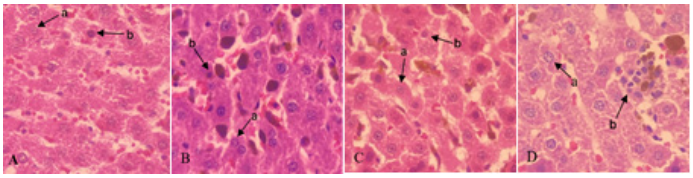

Figure 1: Histopathological features of rat liver. **(A)** N = Normal, **(B)** NC = Iron Dextran (ID) Dose 120 mg/kg BW, **(C)** T1 = ID 120 mg/kg BW + Deferiprone (DFP) 100 mg/kg BW, **(D)** T2 = ID 120 mg/kg BW + Deferasirox (DFX) 30 mg/kg BW, (a) Normal Hepatocyte Cells, (b) Hepatocyte Cell Necrosis, Hematoxylin-Eosin Staining, Magnification 400x.

Table 2: Average hepatocyte cell necrosis.

Treatment	Hepatocyte Cell Necrosis ($\bar{x}$ ± SD%)
N (Normal)	2,17 ± 1,17[a]
NC (Iron Dextran 120 mg/kg BW)	24,17 ± 8,13[c]
T1 (Iron Dextran 120 mg/kg BW + Deferiprone 100 mg/kg BW)	12,33 ± 2,73[b]
T2 (Iron Dextran 120 mg/kg BW + Deferasirox 30 mg/kg BW)	16,17 ± 3,31[b]

Note: Different letters in the column indicate significant differences between treatments based on Duncan post hoc test at the 95% confidence level (α = 0.05).

Villi Damage Score on Duodenal Histology

These pathological changes in the duodenum caused by iron overload may be associated with the immune system and intestinal homeostasis through oxidative stress or inflammation (El-Sheikh *et al.*, 2018).

Based on the Mann-Whitney U test (Table 3), villous damage scores in the Deferiprone 100 mg/kg BW (T1) and Deferasirox 30 mg/kg BW (T2) groups were not significantly different from the Normal (N) group ($p > 0.05$). However, the T1 group showed a significant difference ($p \leq 0.05$) compared to the Iron Dextran 120 mg/kg BW (NC) group, while T2 did not ($p > 0.05$). There was no significant difference between the T1 and T2 groups ($p > 0.05$). T1 and T2 reduced the duodenal villi damage score by 88.3% and 47%, respectively, compared to the NC, indicating that all treatments influenced villous damage scores.

Table 3: Average duodenal villi damage score.

Treatment	Villi Damage Score ($\bar{x}$ ± SD)
N (Normal)	0,00 ± 0,00[a]
NC (Iron Dextran 120 mg/kg BW)	2,83 ± 1,47[b]
T1 (Iron Dextran 120 mg/kg BW + Deferiprone 100 mg/kg BW)	0,33 ± 0,52[a]
T2 (Iron Dextran 120 mg/kg BW + Deferasirox 30 mg/kg BW)	1,50 ± 1,64[ab]

Note: Different letters in the column indicate significant differences between treatments based on Mann Whitney U test at the 95% confidence level (α = 0.05).

Iron Dextran 120 mg/kg BW can cause iron overload conditions (Maskoen *et al.*, 2016). Excessive iron levels in plasma can cause tissue damage due to the presence of hydroxyl free radicals that can cause oxidative stress (Kurniati *et al.*, 2020). This is in line with research conducted by Yi-Chen *et al.* (2017) which states that excess iron in rats triggers small intestinal inflammation, marked by abnormal villi morphology and mucosal necrosis. Cellular iron overload increases villous permeability, allowing antigens and pathogens to enter the bloodstream, activating immune cells like macrophages and lymphocytes. This immune response leads to inflammation and tissue damage (El-Sheikh *et al.*, 2018).

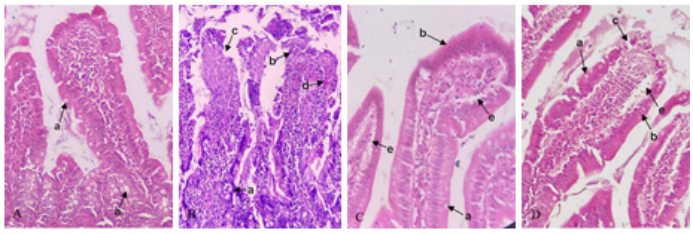

Figure 2: Histopathological features of rat duodenum; **(A)** N = Normal; **(B)** NC = Iron Dextran (ID) Dose 120 mg/kg BW; **(C)** T1 = ID 120 mg/kg BW + Deferiprone (DFP) 100 mg/kg BW; **(D)** T2 = ID 120 mg/kg BW + Deferasirox (DFX) 30 mg/kg BW, (a) Goblet Cells, (b) Intraepithelial Lymphocytes, (c) Part of the Epithelial Layer that Disappears, (d) Blood Vessels, (e) Sub-Epithelial Space, Hematoxylin-Eosin Staining, 400x Magnification.

Deferiprone 100 mg / kg BW (T1) and Deferasirox 30 mg / kg BW (T2) can reduce the damage score of the duodenum villi of iron overload model rats. This is because Deferiprone and Deferasirox are iron chelators that bind free iron (Fe^{2+}) in plasma and reduce excess iron in the body (Supriatna *et al.*, 2020). Reducing iron levels in the body can prevent organ damage (Safitri *et al.*, 2017).

Deferiprone 100 mg/kg BW (T1) is more effective in reducing the duodenum villi damage score compared with Deferasirox 30 mg/kg BW (T2). This is indicated by a

significant difference in the mean score of villous damage (P 0.05) between Deferiprone 100 mg/kg BW (T1) with Iron Dextran 120 mg/kg BW (NC). This is supported by research conducted by Timoshnikov *et al.* (2021), which states that Deferiprone exhibits stronger antioxidant activity than Deferasirox, particularly in inhibiting linoleic acid peroxidation in micelles, a key process in cellular lipid peroxidation. Micelles are lipid molecules that organize themselves into spheres when in an aqueous environment (Datta, 2023). This antioxidant activity can prevent the formation of oxidants and lipid peroxidation and can repair damage caused by exposure to free radicals (Simanjuntak, 2011).

CONCLUSIONS AND RECOMMENDATIONS

Deferiprone and Deferasirox can prevent damage to the histological structure of the liver and duodenum in iron-overloaded rats (*Rattus norvegicus*) by reducing relative liver weight, hepatocyte cell necrosis, and duodenal villi damage scores. These effects occur through the binding of free iron in plasma, which is then excreted through urine or feces. Deferiprone 100 mg/kg BW is more effective and safer than Deferasirox 30 mg/kg BW.

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NOVELITY STATEMENT

No studies have compared the effects of Deferiprone and Deferasirox on liver and duodenum histology. Therefore, this study aims to determine the more effective and safer iron chelator for preventing histological damage to the liver and duodenum in iron overloaded rats (*Rattus norvegicus*).

AUTHOR'S CONTRIBUTIONS

All authors contributed equally to the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest in this study.

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