

ORIGINAL ARTICLE

Histopathological study of the hepatic and renal toxicity associated with the co-administration of Imatinib and Acetaminophen in a preclinical mouse model

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Abstract

Imatinib, a selective tyrosine kinase inhibitor, is the first line treatment against chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumors (GIST). Several fatal cases have been associated with imatinib hepatotoxicity. Acetaminophen, an over-the-counter analgesic, anti-pyretic drug, which can cause hepatotoxicity, is commonly used in cancer pain management. We assessed renal and hepatic toxicity after imatinib and acetaminophen co-administration in a preclinical model. Four groups of male ICR mice (30-35 g) were fasted overnight and administered either saline solution orally (baseline control), imatinib 100 mg/kg orally (control), acetaminophen 700 mg/kg intraperitoneally (positive control) or co-administered imatinib 100 mg/kg orally and acetaminophen 700 mg/kg intraperitoneally (study group), and sacrificed at 15 min, 30 min, 1 h, 2 h, 4 h and 6 h post-administration (n=4 per time point). The liver and kidneys were harvested for histopathology assessment. The liver showed reversible cell damage like feathery degeneration, microvesicular fatty change, sinusoidal congestion and pyknosis, when imatinib or acetaminophen were administered separately. The damage increased gradually with time, peaked at 2 h but resolved by 4 h. When both drugs were administered concurrently, the liver showed irreversible damage (cytolysis, karyolysis and karyorrhexis) which did not resolve by 6 h. Very minor renal changes were observed. Acetaminophen and imatinib co-administration increased hepatotoxicity which become irreversible, probably due to shared P450 biotransformation pathways and transporters in the liver.

Keywords: Imatinib, acetaminophen, histopathology, drug-drug interaction, hepatotoxicity, renal toxicity

INTRODUCTION

Imatinib (Gleevec® or Glivec® Novartis, NJ), is a specifically rationally designed drug for the treatment of chronic myeloid leukaemia (CML). Imatinib selectively inhibits BCR-ABL gene¹ which has been identified as the cause of CML and was approved by the USA FDA as a first line treatment for CML.^{1,2} Currently it is the treatment of choice for the management of the chronic and accelerated phases of CML with an overall survival rate of 89% after 5 years.^{3,4}

Besides the BCR-ABL kinase, imatinib also inhibits the expression of c-Kit tyrosine kinase receptor in the gastrointestinal tract⁵ which is involved in the pathogenesis of gastrointestinal

stromal tumours (GIST).⁶ Imatinib has been also approved for the treatment of unresectable GIST.⁷ In addition, imatinib inhibits the platelet-derived growth factor (PDGF) receptor⁵ which may allow further therapeutic applications including dermatofibrosarcoma protuberans,⁸ glioblastoma,⁹ and non-cancer related pathologies like rheumatoid arthritis¹⁰ and atherosclerosis.¹¹

In humans, imatinib presents complete absorption¹² but large patient AUC variability.¹³ It is highly bound to α -1-acid glycoprotein,¹⁴ has an elimination half-life around 13 hours² and its tissue distribution is limited by the P-glycoprotein efflux pump.¹⁵ Imatinib undergoes P450 mediated metabolism mainly via CYP3A4 and CYP3A5, and CYP1A2, CYP2D6, CYP2C9 and CYP2C19

which play a minor role.¹⁶ The main metabolite, CGP 74588 presents equivalent activity to that of the parent drug and longer elimination half-life (40 h). Imatinib and metabolites are excreted in the bile¹⁷ and only around 5% is excreted unchanged in urine.²

The main adverse effects include severe neutropenia and thrombocytopenia, oedema, fluid retention, nausea, mild diarrhoea, skin rashes, arthralgia, myalgia, bone pain, acute renal failure^{18,19} and hepatotoxicity.²⁰ Hepatotoxicity has been observed in 5% of CML patients which show elevated levels of AST, ALT and bilirubin²¹ as well as hepatic necrosis,²² acute hepatitis, cytolytic hepatitis including spotty and piecemeal necrosis.^{23,24}

Although in most cases, hepatotoxicity (Table 1) resolved after imatinib discontinuation and steroids administration,²¹ in some patients, the hepatic condition further deteriorated leading to fatal liver failure.²⁰ Histopathological analyses revealed severe necrosis, cellular canalicular cholestasis, submassive acute hepatic necrosis²⁵ and multiacinar hepatocellular necrosis.²⁶ Research on the pathogenic mechanisms of imatinib-induced hepatotoxicity or renal toxicity suggests that toxicity may be related to the P450 mediated metabolic pathway or idiosyncratic reactions in susceptible individuals.⁴

Acetaminophen is a commonly used over-the-counter analgesic and antipyretic drug that the WHO recommends as a first-line, non-opioid co-adjuvant analgesic for the relief of persistent pain affecting cancer patients,²⁷ even with an established opioid regime.²⁸ Acetaminophen presents drug-drug interactions with a variety of drugs including imatinib²⁹ and may also cause hepatotoxicity at high doses.³⁰ Severe hepatotoxicity associated with acetaminophen coadministration has been suggested previously in CML patients who developed fatal liver failure.^{31,32}

The current study evaluates the histopathological changes that occur in the liver and kidneys when imatinib and acetaminophen are co-administered and whether a drug-drug interaction exists in a preclinical mouse model.

MATERIALS AND METHODS

Experimental animals and procedures

Prior to initiation of the study, the Institutional Animal Use Ethics Committee reviewed and approved all the experimental protocols. Male

ICR mice, 12–14 weeks, ~30 g weight (Institute for Medical Research, Kuala Lumpur, Malaysia) were housed in the animal holding facility at $20 \pm 2^\circ\text{C}$ and a 12-hour light/dark cycle, let to acclimatize for a week before any experiment was performed and provided feed and water *ad libitum*.

The mice were randomly assigned to the experimental groups and fasted overnight. Group 1 did not receive any drug and was designated as the control for the histopathological analysis. Group 2 was dosed 100 mg/kg imatinib orally (in acidified saline solution) using a 24G feeding needle and a 1 ml syringe (Terumo Corporation, Philippines). Group 3 received 700 mg/kg acetaminophen intraperitoneally (water) using a 26G needle with a 1 ml syringe. Lastly, Group 4 was dosed 100 mg/kg imatinib PO and 700 mg/kg acetaminophen IP. Imatinib was given first immediately followed by acetaminophen.

Mice (n=4 per time point) were euthanized at 15 min, 30 min, 1h, 2h, 4h and 6h by cervical dislocation and exsanguination performed via cardiac puncture with a 23G needle and a 1 mL syringe containing EDTA (Merck, Malaysia). The liver and the kidneys were harvested, rinsed twice in 0.9% saline solution, a piece cut and stored in 10% neutral buffered formalin solution (Richard-Allan Scientific, Malaysia) at room temperature. The remaining tissue was stored at -30°C .

Preparation of histological sections

The tissue samples were grossed and transferred into Histosette® cassettes, placed in an automatic tissue processor (Leica, Japan) and processed as follows: (1) 10% neutral buffered formalin – two consecutive changes of 1 h and 1.5 h; (2) 85% alcohol – 1.5 h; (3) 95% alcohol – 1.5 h; (4) 100% Alcohol – three consecutive changes of 1.5 h each; (5) xylene (Fisher Scientific, Malaysia) – three consecutive changes of 1.5 h each; and (6) paraffin (Richard-Allan Scientific) bath at 55°C – two changes of 1.5 h each. Upon completion, the tissues were placed in 1.5x2 cm moulds lined with molten paraffin wax at 65°C . The mould was transferred to a cold plate at -5°C , the tissue adjusted to the desired orientation and the cassette base placed on top of the mould, filled with molten wax and let to solidify for 1 h, removed and stored at -20°C until sectioning.

The frozen embedded wax blocks were sectioned at 3 μm thickness, placed on frosted glass slides and dried overnight at 37°C . Prior

to modified Harris Haematoxylin and Eosin (Richard & Allan Scientific) staining, the samples were washed in xylene twice (3 min each), hydrated in five sequential changes of alcohol 100%, 100%, 95%, 80% and 70% for 3 min each, rinsed with water for 3 min and stained. Finally, the stained slides were dehydrated in three sequential 1-min changes of alcohol 70%, 80% and 95% and two changes of 100% alcohol for three minutes each. The sections were then dried and mounted onto the slide for analysis.

Histopathological analysis

Two stained slides for each mouse tissue samples were observed at 100x and 400x magnification using a Nikon’s Brightfield Compound Nikon microscope (model YS100). Changes in lobular architecture, fatty changes, nuclear alterations and congestion of the sinusoids were evaluated in liver samples. Similarly, changes in cyto-architecture of the glomeruli, proximal and distal convoluted tubules and interstitium were assessed in the kidney samples.

A semi-quantitative analysis was done to assess the extent of the histopathological changes. Photomicrographs of representative changes were also taken using a Nikon (Japan) camera attached to the microscope.

RESULTS

Histopathology in liver tissue

Histological examination of the liver tissues showed varied damage when compared with the baseline-control group (Figure 1). Experimental groups 2 and 3 showed signs of reversible damage, which were different from the results in

group 4 which showed irreversible damage.

Mice dosed 100 mg/kg imatinib orally (group 2) showed feathery degeneration, microvesicular fatty change and very mild sinusoidal congestion (Figure 2). Toxicokinetic assessment revealed no effect at the earliest time point: the hepatocytes were normal with intact cell margins and normal nucleus. The lobular architecture and sinusoids appeared normal and no congestion of sinusoids was seen (Figure 2). The first signs of toxicity appeared at 30 min when zones 1 and 2 showed feathery degeneration and loss of cellular outlines. By 1 h, the feathery degeneration extended to zone 3 and fatty change became diffuse at microvesicular level. This condition remained at 2 h but the histological signs of toxicity resolved by 4 h when all cells appeared normal, as was observed at 6 h.

On the other hand, 700 mg/kg IP acetaminophen administration (group 3) caused reversible toxicity: sinusoidal congestion and centrilobular cell damage (Figure 3). Initial toxicity was observed 15 min after IP administration, when sinusoidal prominence and mild congestion was noted. Toxicity progressed to focal damage around the central vein and congestion at 30 min, which evolved to diffuse damage, poorly defined cellular outlines, loss of lobular architecture and congestion of the sinusoids at 1 h after administration. Nuclear clumping (pyknosis), further loss of lobular architecture and congestion of the sinusoids were clearly visible at 2 h post administration. These signs remained at 4 h with some microvesicular and macrovesicular fatty change, congestion and pyknosis. The toxicity was resolved at 6 h when no cellular damage and very minimal congestion were observed, and the cells were fully normal looking.

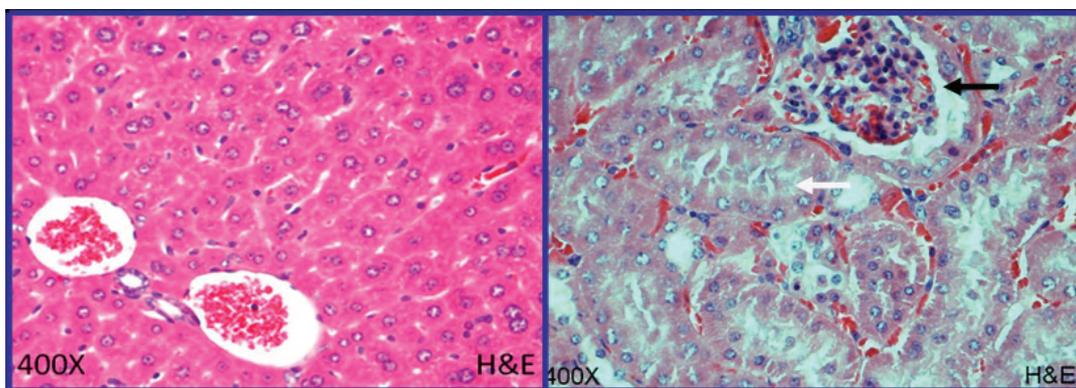


FIG. 1: Photomicrographs of liver and kidney after administration of 0.9 % saline solution (400x). (A) normal hepatocytic outlines and (B) normal glomerulus (black arrow) and proximal and distal convoluted tubules (white arrow).

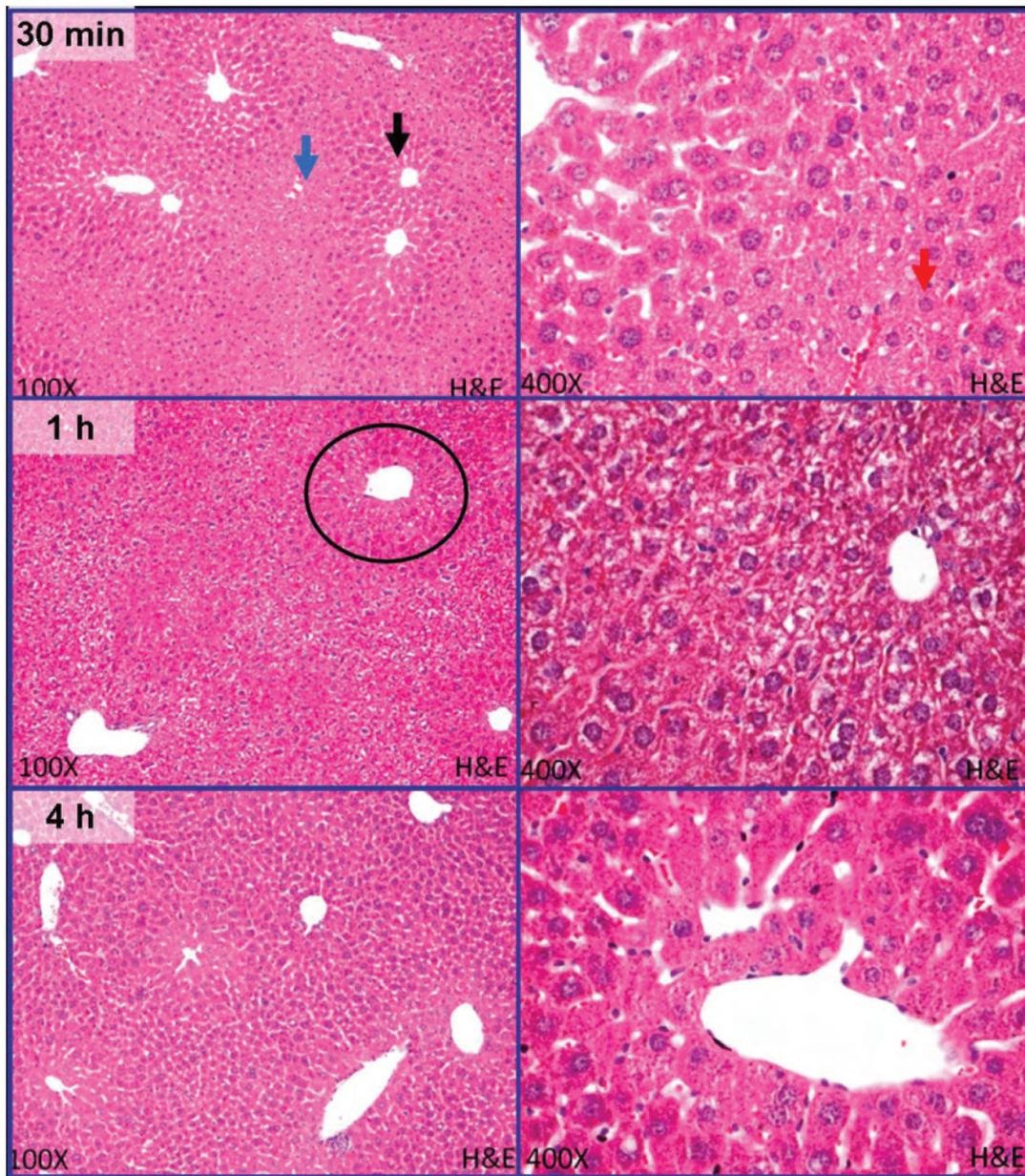


FIG. 2: Photomicrographs of liver after 100 mg/kg imatinib PO administration (group 2). Feathery degeneration (blue arrow), lost of cellular outlines (red arrow) at zones 1 and 2 and normal centrilobular zone (black arrow) is seen at 30 min. These changes extended to zone 3 (circled) at 1 h. By 4 h the cell damage was resolved and the lobular architecture restored.

Mice that were treated with 100 mg/kg imatinib PO and 700 mg/kg acetaminophen IP (group 4) experienced the greatest damage which was mainly irreversible and included nuclear changes (pyknosis, karyolysis and karyorrhexis), cytolysis and massive congestion (Figure 4). At 30 min there were clear signs of toxicity: the hepatocytes appeared swollen, their nuclei enlarged and there was microvesicular

fatty change although minimal congestion. Progression of toxicity was clear at 1 h when macrovesicular fatty change, loss of cellular outline and lobular architecture and nuclear damage (pyknosis) were observed. Toxicity increased at 2 h with greater loss of lobular architecture, cellular outlines became completely indistinct and macrovesicular fatty change visible at zones 1 and 2. Nuclear damage progressed

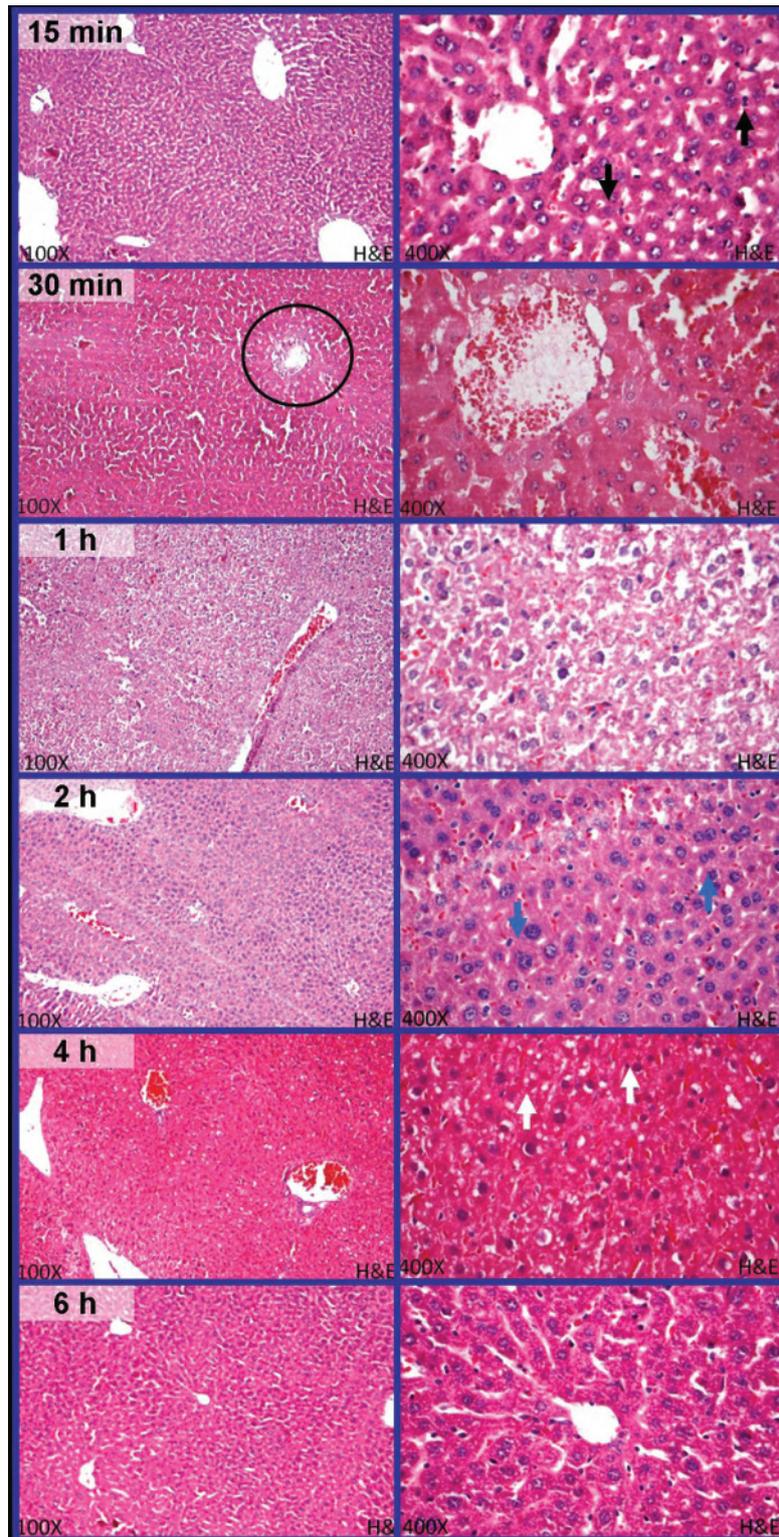


FIG. 3: Photomicrographs of the liver after administration of 700 mg/kg IP acetaminophen. Mild sinusoidal congestion (black arrows), focal damage around the central vein (circled), feathery degeneration, loss of lobular architecture with damaged cellular outlines and congestion are seen at 1 h. By 2 h, nuclei have become condensed and pyknotic (blue arrow) which intensified at 4 h with microvesicular fatty change (white arrows). By 6 h the damage has been reverted.

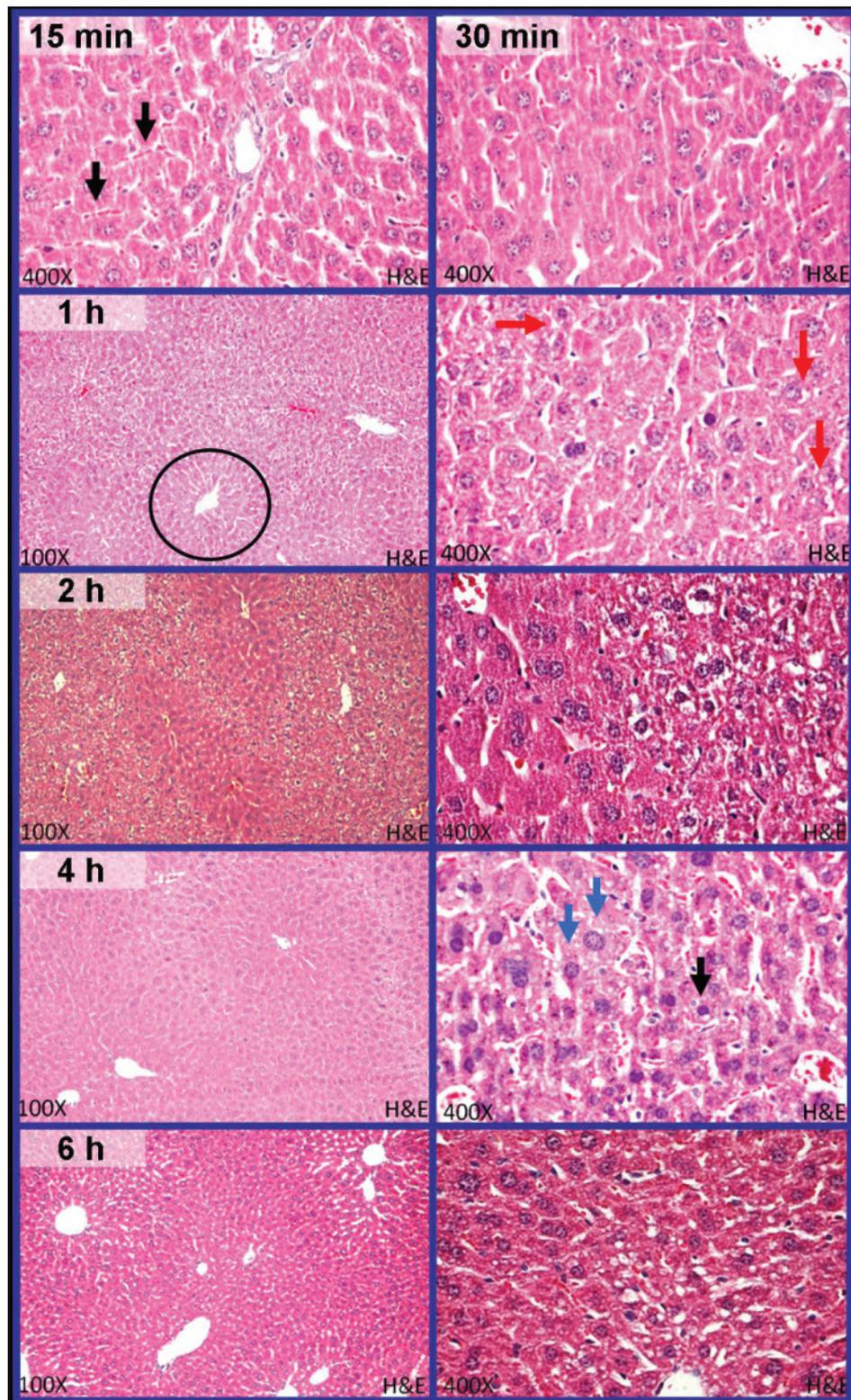


FIG. 4: Photomicrographs of liver after administration of 700 mg/kg IP acetaminophen and 100 mg/kg PO imatinib. Mild sinusoidal congestion (black arrows), swollen hepatocytes and nuclei was seen within 30 min, by feathery degeneration (encircled), macrovesicular fatty change (black arrow) and pyknosis. The nuclear damage progressed with pyknosis (black arrow) and karyolysis (blue arrow) present at 6 h.

to pyknosis and karyolysis and unlike the other two groups that recovered by 4 h, the combined administration of imatinib and acetaminophen led to further toxicity at 6 h: uniform macrovesicular fatty change, massive congestion and nuclear pyknosis, karyolysis and karyorrhexis. Moreover, cytolysis and loss of lobular architecture were still apparent.

Histopathology in renal tissue

Qualitative assessment of tissue sections of the kidney showed no damage in the experimental groups that received either imatinib or acetaminophen. This was consistent with other studies where no histopathological changes were observed in the kidney after an overdose of acetaminophen.³³ Group 4 (combination treatment) revealed mild cloudy degeneration of the kidney tubules at 6 h time point, which is a reversible change (Figure 5).

DISCUSSION

Although imatinib is well tolerated it may lead to hepatotoxicity. Mice treated with 100 mg/

kg imatinib orally showed mild liver damage with the peak cell damage at 1 hour but with clear signs of restoration at 4 h and complete restoration by 6 h. This level of toxicity is in agreement with the overall findings in other preclinical studies or in clinical trials. Studies in dogs showed hepatotoxicity 2 weeks after imatinib administration. The histological assessment revealed mild focal hepatocellular necrosis, single cell bile duct necrosis and bile duct hyperplasia (associated with peribiliary fibrosis) and elevation of liver enzymes.³ In humans, signs of liver dysfunction were found in CML patients with grade 3 AST abnormalities in 2%, AST in 3% and 2% in bilirubin as well as hepatobiliary disorders (Budd-Chiari syndrome and hepatotoxicity).²⁷ Similar signs of hepatotoxicity were found in other human studies involving CML patients where grade 3 or 4 increased ALT and AST levels in ~5% of them.³⁴ Discontinuation of treatment and initiation of steroids usually stopped and reverted toxicity progression.²⁰ However in several cases, fatal liver failure occurred^{24,26} (Table 1). Our histological findings in mice show lesser

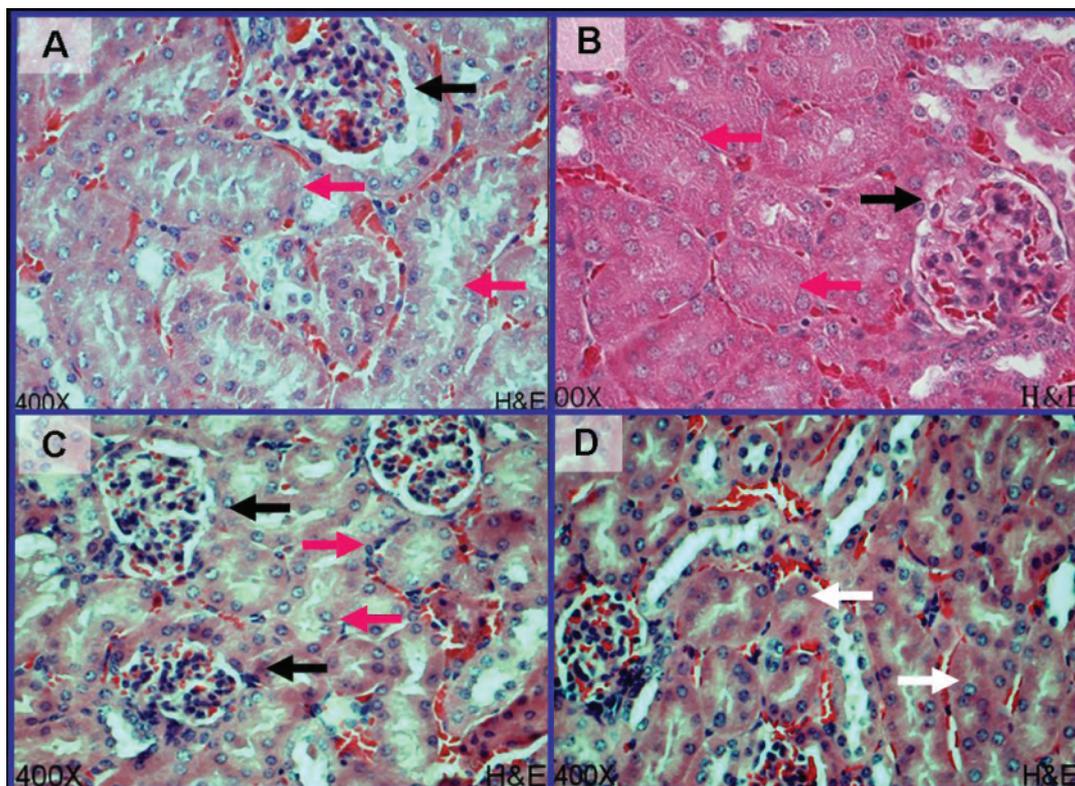


FIG. 5: Photomicrographs (400x) of kidney 6 h after administration of (A) vehicle control; (B) 100 mg/kg oral imatinib; (C) 700 mg/kg IP acetaminophen and (D) combination treatment of 100 mg/kg PO imatinib and 700 mg/kg IP acetaminophen.

degree of toxicity which may be anticipated since we used a single oral dose of imatinib (100 mg/kg); while the greater toxicity observed in the reported cases may be contributed by imatinib accumulation due to the multiple dosage administration.³

Acetaminophen toxicity at high doses is well known.³⁰ Our dose of 700 mg/kg IP was established after initial studies showed dose dependent hepatotoxicity. After acetaminophen IP administration, we observed congestion of the sinusoids and centrilobular necrosis (Figure 3) which extended around the central vein which are hallmark signs of acetaminophen toxicity.³⁰ Pyknotic nuclear change and microvesicular fatty change observed are consistent with findings from other studies as well as the reversible nature of the toxicity.³⁵

Coadministration of acetaminophen with imatinib changed the hepatotoxicity from reversible to irreversible and increased its intensity and extent (Figure 4). After co-administration, we

observed initial mild congestion of sinusoids progressing to loss of lobular architecture, macrovesicular fatty change and pyknosis was not restored at 6 hours (Figure 4). In fact, pyknosis and karyolysis in the nuclei together with cytolysis mark irreversible toxicity suggesting synergistic toxicity associated with both drugs coadministration. As shown in the toxicokinetic comparative time profile in Figure 6, imatinib seems to prevent hepatocyte recovery from the damage caused, probably via the acetaminophen metabolite, NAPQI. While there are clear signs of restoration at 4 h in the control groups, the toxicity signs in the combination treatment further intensified and progressed without recovery by 6 hours. This toxicokinetic profile suggests that the presence of imatinib leads to a 'perpetuation' of acetaminophen toxicity. This appears similar to cases of acetaminophen coadministration with imatinib in cancer patients leading to irreversible fatal liver failure.^{27,28}

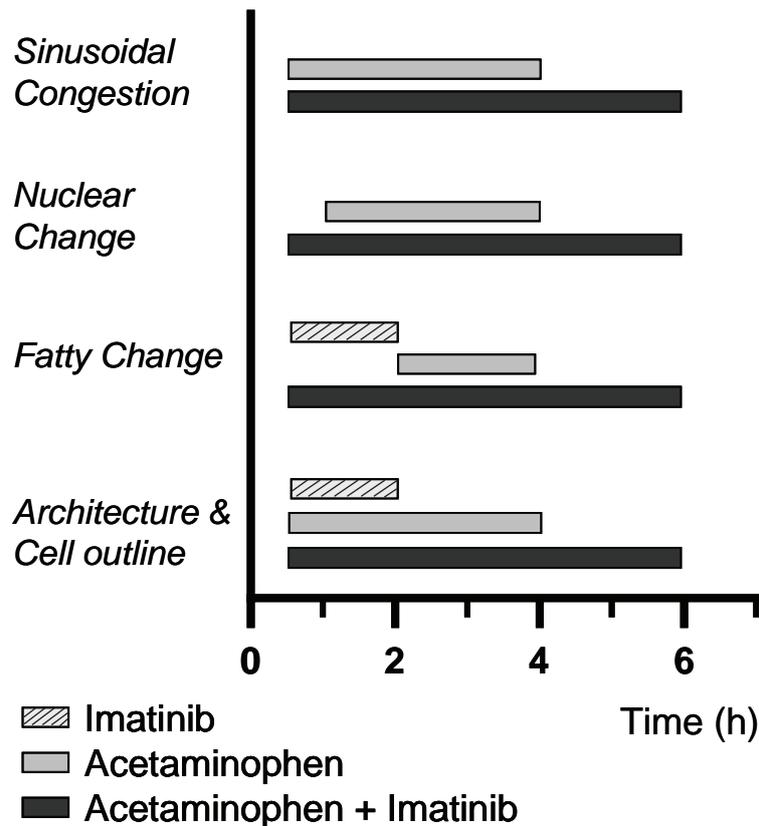


FIG. 6: Comparative toxicokinetic assessment of main histopathological findings in liver for control and combination groups.

TABLE 1. Summary of selected cases of imatinib hepatotoxicity, including fatal outcome of six patients

Year	Imatinib dose (mg/d)	Time to liver dysfunction*	Concurrent medications	Toxicity Features	Outcome	Ref
2002	400	12 d	None	Focal necrosis resembling acute viral hepatitis.	Recovered upon discontinuation of treatment. [22]	
2002	600	2 w	Acetaminophen (3000-3500 mg/d)	Jaundice, elevated transaminases and bilirubin after 6 days of treatment.	The patient died on day 12 after beginning treatment. [31]	
2003	400	22 w	None	Acute hepatitis cytolysis.	Recovered upon discontinuation of treatment. [23]	
2003	250	1 y	Roxithromycin (300 mg for 5 d)	Jaundice, asthemia concomitant with major hepatic dysfunction.	Recovered after discontinuation of imatinib treatment. [23]	
2003	400	7 w	Phenytoin (subtherapeutic)	Submassive acute hepatic necrosis with microthrombi.	The patient died 6 days later of uncontrollable acidosis. [25]	
2004	400	2 y	None	Hepatitis. Increased AST, ALT, bilirubin 6 months after therapy.	Recovered upon discontinuation of treatment [24]	
2005	400	n/a	None	Severe hepatic injury with severe hyperbilirubinaemia.	Therapy continued with co-administration of prednisolone [37]	
2006	n/a	n/a	None	Fulminant hepatitis, reactivation of hepatitis B virus infection.	The patient died . [38]	
2006	400	72 w	None	Acute liver failure with severe hepatic necrosis after 18 months of treatment.	The patient died 3 days after liver transplantation. [20]	
2007	600	10 d	None	Skin rashes, portal track inflammation with cholestasis and hepatocyte acute injury.	Recovered upon discontinuation of treatment and administration of steroids. [39]	
2007	400	1 y	Acetaminophen (500-1000 mg/d)	Severe hepatitis with coagulopathy 5 months after beginning of treatment. Grade III encephalopathy.	Died 48h after transplantation. [32]	
2008	600	20 w	None	Multiacinar hepatic necrosis with hepatitis B virus infection reactivation	Died after 6 days of HBV reactivation. [26]	

* Legend: d (days), w (weeks), y (years); n/a = not available

Working hypothesis

The pathogenic mechanisms of imatinib-induced hepatotoxicity are unknown. How imatinib may interfere in the pharmacokinetics of acetaminophen remains to be clarified.²⁹ Imatinib presents numerous drug-drug interactions which involve P450 mediated metabolism and efflux transporters (e.g. P-glycoprotein).² The change from reversible to irreversible toxicity suggests that the interaction may be synergistic in nature. The extensive and sustained damage to hepatocytes in group 4 compared to groups 2 and 3 may reflect the inability of hepatocytes to eliminate acetaminophen and its metabolites. Imatinib may interfere with transporter-mediated removal mechanisms of acetaminophen or its metabolites. *In vitro* evaluation of the role of P-glycoprotein in acetaminophen toxicity showed that the presence of verapamil (a P-glycoprotein and CYP3A4 substrate) significantly increased acetaminophen induced cell damage, even at non toxic doses of acetaminophen.³⁶ The results of our study *in vivo* are consistent with that finding. It is plausible that imatinib, which shares the same transporters and cytochrome P450 may be affecting the ability of the efflux pumps to reduce acetaminophen-induced hepatotoxicity.

Conclusion

Liver histopathological changes observed after coadministration of imatinib and acetaminophen show an increase of acetaminophen toxicity and a change from reversible to irreversible. This finding may have deep consequences in the clinical management of cancer related pain. The fact that several deaths associated with acetaminophen-imatinib coadministration have occurred, clearly points to the need for close monitoring of liver function in cancer patients receiving imatinib treatment and acetaminophen for pain management. No significant renal toxicity was observed in the study.

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