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Therapeutic dose of acetaminophen may induce fulminant hepatitis in the presence of risk factors: a report of two cases

Editor—The safety profile of acetaminophen (*N*-acetyl-*para*-aminophenol) makes it one of the most widely prescribed analgesics.[1] Acute liver failure due to therapeutic doses of acetaminophen is controversial.[1 2] Some clinicians encourage regular postoperative administration of acetaminophen 4–5 g day^{-1}.[3] However, liver injury with therapeutic doses cannot be excluded.[4] We report two cases of postoperative acute liver failure attributed to therapeutic doses of acetaminophen.

Case 1: A 43-yr-old female (70 kg, 166 cm, BMI 25) was re-operated on for laparoscopic readjustment of her gastric band. Anaesthesia was induced with propofol followed by desflurane, sufentanil, and rocuronium. The surgery was uncomplicated. She received a dose of ketorolac i.v. (30 mg) and acetaminophen 1 g four times a day. On the third day, after a total intake of acetaminophen 11 g, she presented with acute liver failure associated with multiple organ failure (factor V level 5% of normal, prothrombin time: 71 s, INR 12.9, liver cytolysis: ASAT: 5321 U litre^{-1}, ALAT: 3401 U litre^{-1}) (Table 1). Serum concentration of acetaminophen was 31.8 mg litre^{-1} (17 h after the last dose). She was treated with *N*-acetylcysteine (NAC) and supported by a Molecular Adsorbed Recirculation System (MARS). Two days later, an orthotopic liver transplantation (OLT) was successfully performed under desflurane-based anaesthesia. Histopathology of the liver showed generalized steatosis in the viable hepatocytes and major centrolobular necrosis (zone 3) highly suggestive of a toxic origin. The patient was discharged after 6 weeks at home.

Case 2: A 60-yr-old female (90 kg, 160 cm, BMI 35) with a chronic elevation of γ-glutamyl transpeptidase (γGT) (preoperative value: 217 U litre^{-1}) and seizures controlled with valproic acid and carbamazepine presented in acute liver failure 2 days after a re-intervention for a post-lumbar laminectomy dural leak. Anaesthesia, at that time, was induced with propofol followed by sevoflurane, sufentanil, and rocuronium. Analgesia included diclofenac and morphine (48 h). Acetaminophen 1 g four times daily had been given for 10 days before the intensive care unit (ICU) admission. The acute liver failure was associated with a severe coagulopathy and encephalopathy (prothrombin time: 41 s, INR: 2.0, cephalin activated time: 48.5 s, severe thrombocytopenia: 9000 plat μl^{-1}, liver cytolysis: ASAT: 9301 U litre^{-1}, ALAT: 5011 U litre^{-1}, renal insufficiency: serum creatinine 2.7 mg dl^{-1}) (Table 1). Serum concentration of acetaminophen was 10 mg litre^{-1} (48 h after the last dose). She was treated with NAC. Improvement of all parameters permitted discharge from the ICU after 48 h.

In the two cases, CT scan and abdominal ultrasound showed a highly hypodense and hyperechogenic, homogeneous and enlarged liver, clearly suggestive of chronic liver steatosis. In the two patients, serological investigations did not show evidence of viral hepatitis (A, B, or C).

Acetaminophen toxicity proposed in these cases because of well-known risk factors (antiepileptic drugs and liver steatosis), highly suggestive histopathology,

Table 1 Pre- and postoperative laboratory values in two cases of fulminant hepatitis due to acetaminophen. Day 1, day of admission to the ICU. For case 1, MARS started on D2 and OLT performed on D3

	Preop.	D1	D2	D3	D4	D5	D6	D7	D14
Case 1									
ALAT (U litre^{-1})	8	3401	3110	3280	1451	829	513	345	120
ASAT (U litre^{-1})	20	5321	4190	2532	916	261	124	81	61
INR (s)	1.1	12.9	3.14	2.85	2.37	1.09	0.97	0.89	1.11
LDH (U litre^{-1})	494	5481	3770	1090	1018	230	219	194	189
Bilirubin (mg dl^{-1})	0.5	4.5	5.7	7.5	3.9	1.7	1.9	1.4	1.4
γGT (U litre^{-1})	10	24	34	45	22	19	76	150	110
Case 2									
ALAT (U litre^{-1})	27	5011	2535	918	502	—	—	—	51
ASAT (U litre^{-1})	19	9301	5540	1816	493	—	—	—	30
INR (s)	1.0	2.0	1.33	1.23	1.17	—	—	—	1.1
LDH (U litre^{-1})	361	9376	4000	606	351	—	—	—	493
Bilirubin (mg dl^{-1})	0.5	0.9	1.5	2.4	1.9	—	—	—	0.9
γGT (U litre^{-1})	217	712	571	568	551	—	—	—	362

classical clinical course,[2] and exclusion of other causes. Non-steroidal anti-inflammatory drugs (NSAIDs) may cause idiosyncratic liver damage but typically, the onset of the NSAIDs-induced hepatic injury is delayed and follows long-term administration.[5] The clinical course did not suggest inhaled anaesthetic-induced liver failure.

Obesity and liver steatosis risk factors may be associated with depletion of glutathione (GSH) stores due to impaired hepatocellular function. The first patient was not overweight, but inter-individual variations of acetaminophen glucuronidation have been also suggested.[2]

Acetaminophen is conjugated in the liver by the UDP-glucuronosyl-transferase and by sulphotransferase.[6] Other metabolic enzyme system is cytochrome P450 (mainly CYP2E1 but also 1A2 and 3A4) resulting in production of NAPQI. NAPQI-mediated mitochondrial injury may be the source of the superoxide leading to hepatotoxicity.[6] Conditions leading to depletion of GSH stores (obesity, liver steatosis, starvation, and malnutrition) could be considered as risk factors for acetaminophen-induced hepatotoxicity along with CYP inducers (alcohol, antiepileptic drugs).[3 7 8]

We conclude that when prescribing acetaminophen after operation, particular attention must be paid to patients who are at risk of hepatotoxicity due to pre-existing liver steatosis or other risk factors of hepatotoxicity.

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Ultrasound-guided transversus abdominis plane block

Editor—We read the article by El-Dawlatly and colleagues[1] with great interest. We were very surprised that they have called their ultrasound-guided technique of performing the transversus abdominis plane (TAP) block 'a new technique'. As mentioned in their study, the block has been described using ultrasound guidance in several reports[2 3] and a cadaveric study.[4] We have certainly described the exact approach for laparoscopic surgery in our case series.[5]

There are also a few omissions we would like to highlight. We expected to find a comparison of pain scores at different times between both groups in the postoperative period which is a good indicator of the quality of the analgesia provided. There was also no mention of the impact the reduction in morphine consumption had on the side-effects associated with this particular surgery and augmented by the use of opioids, such as nausea and vomiting.

Our experience with the use of TAP blocks for laparoscopic cholecystectomy shows comparable opioid-sparing effects, although in our institution two of the ports used by the surgeons are placed in the supra-umbilical region which necessitates an additional subcostal injection to provide adequate analgesia.

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Editor—I thank Drs Mukhtar and Singh for their comments and agree that the technique of ultrasound TAP block has been described earlier; however, its use in laparoscopic cholecystectomy has not been reported. I also agree that scores for pain and nausea and vomiting assessment would be appropriate for our study. However, these are our initial results which address the efficacy of TAP block in laparoscopic surgery and we are involved in a subsequent large sample study which will address the issues raised. We believe that further studies are needed to evaluate optimal volumes for ultrasound-guided TAP block and pharmacokinetic data.

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