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TOXICOLOGY OBSERVATION

Unintentional Chronic Acetaminophen Poisoning During Pregnancy Resulting in Liver Transplantation

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Abstract
Introduction Acetaminophen (APAP) is a widely used medication in pregnancy and is considered safe. Unfortunately, APAP is also among the most commonly reported agents implicated in overdoses during pregnancy. We present a unique case of a pregnant patient with fulminant hepatic failure resulting in a liver transplant from repeated supratherapeutic ingestions of APAP.
Case Report A 22 year pregnant female presented with abdominal pain and hepatotoxicity after taking supratherapeutic amounts of APAP to treat dental pain. The patient denied intentional or acute ingestion of APAP but did admit to taking approximately 8-9 grams of APAP per day for 10-14 days for dental pain. Other cause of hepatotoxicity, including acute fatty liver of pregnancy, were evaluated for and ruled out. She developed fulminant hepatic failure and required liver transplantation which was successful. The pregnancy remained viable through the operation but intrauterine fetal demise occurred 2 weeks later. An MRI of the fetus showed extensive peri-cerebral and intraventricular hemorrhage with extensive periventricular leukomalacia.
Discussion The degree of morbidity from repeated supratherapeutic ingestions of APAP seen in this case is rare and poorly described in a pregnant patient. There are no prior reports describing the need for liver transplant after repeated supratherapeutic ingestions of APAP during pregnancy. Along with the typical cause of hepatotoxicy several unique pregnancy-related causes also had to be evaluated for. This case highlights the significant morbidity that can occur with even unintentional APAP toxicity and the need to educate patients, especially pregnant patients, of the risk of excessive APAP use.

Keywords Acetaminophen · Pregnancy · Hepatotoxicity · Hepatic failure · Liver transplant

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Introduction

Acetaminophen (APAP) is one of the most widely used medications in pregnancy and is generally considered safe [1]. Unfortunately, APAP is also among the most commonly reported agents implicated in overdoses during pregnancy [2]. We present a unique case of a pregnant patient with fulminant hepatic failure resulting in a liver transplant from repeated supratherapeutic ingestions of APAP.

Case Report

A 22-year-old G2P1A0 female with no past medical history presented to the emergency department complaining of abdominal pain. She also complained of dental pain for several weeks and endorsed using APAP 500 mg and Tylenol #3 (APAP 300 mg with codeine 30 mg) tablets for it. Other than a prenatal vitamin, she denied taking any other prescription, herbal or OTC medications. Vital signs were: heart rate of 104 beats per minute (bpm), blood pressure of 122/60 mmHg, a respiratory rate of 26 with a SaO_2 of 100% and a temperature of 35.4°C. An estimated gestational age (EGA) by last menstrual period was 19 weeks and 5 days. The physical exam was notable for tenderness in the right upper quadrant, tachypnea and scleral icterus. Her uterus was nontender with a fundal height consistent with dates.

The remainder of her exam including mental status was normal. Initial pertinent laboratory values are shown in Table 1. Review of her medical record showed she had been evaluated 5 days earlier for chest pain. Laboratory results from this visit are listed in Table 1. The patient was further questioned about her APAP use and admitted to taking approximately 12 APAP 500 mg tablets and six to eight tablets of Tylenol #3 per day for the last ten to 14 days. She states she did so because she was told she could not take any other pain medications due to her being pregnant. She and her family adamantly denied suicidality or intentional ingestion. Resuscitation with intravenous (IV) fluids, dextrose and sodium bicarbonate was started. IV phytonadione was given and IV *N*-acetylcysteine (NAC) was started according to package insert dosing recommendations. She was admitted to the intensive care unit with presumed hepatotoxicity from unintentional chronic APAP overdose. In the ICU, a pelvic ultrasound showed a single intrauterine pregnancy dated at 20 weeks and 2 days weighing 423 g with fetal heart motion (FHM) of 126 bpm. An abdominal ultrasound was interpreted as normal. Despite resuscitation, her metabolic acidosis persisted, liver function continued to deteriorate and she became somnolent. She was then transferred to a tertiary care hospital for possible liver transplant approximately 24 h after admission. There, an extensive evaluation for other liver failure etiologies was undertaken. Serum iron levels, Hepatitis A IgM/IgG, Hepatitis B serologies, HBV DNA, HCV PCR, CMV PCR, EBV PCR, HSV PCR, HIV PCR, ceruloplasmin, ANA and F-actin IgG were all unremarkable. Her repeat labs are shown in Table 1. Though the patient's clinical condition continued to decline with worsening coagulopathy, jaundice and hepatic encephalopathy, the patient and her family expressed a desire that all measures be taken to preserve fetal viability. Approximately 48 h from her presentation, she was intubated for airway protection due to declining mental status. A CT of her head prior to intubation was interpreted as normal. She was listed for liver transplant with a MELD score of 27. She had stage IV hepatic encephalopathy but did not meet any other King's College Critera. Seventy-two hours from her initial presentation, she underwent successful orthotopic liver transplant. Intraoperative ultrasound at the end of the case documented FHM. The pathology result on her native liver was consistent with fulminant liver failure due to APAP toxicity. On the evening of postop day 0, she developed an anastomotic bleed which was successfully repaired. She subsequently did well and was extubated on postop day 3. Laboratory results immediately before and 30 h after her transplant are detailed in Table 1. She was started on tacrolimus, but not mycophenolate, due to concerns for teratogenicity. On postop day 4, a pelvic ultrasound demonstrated FHM of 124 bmp with appropriate interval fetal growth. However, fluid was noted within the fetal peritoneal cavity consistent with hydrops. A pelvic ultrasound done on postop day 13 showed FHM of 132 with resolving fetal intraperitoneal fluid but was concerning for bilateral ventriculomegaly. A

Table 1 Laboratory date from prior ED visit and hospital course

Laboratory	Date and time				
	04/29[a] 05:07	05/03 10:05	05/04 20:30	05/07[b] 02:30	05/08[c] 20:00
WBC (normal 3.8–11.0 K/μl)	10.8	24.9	24.9	19.1	16.7
Bicarbonate (normal 22–32 mmol/l	27	8	13	20	32
Blood glucose (normal 60–120 mg/dl)	86	30	87	103	143
AST (normal 14–36 U/l)	34	1,064	6,148	959	295
ALT (normal 9–52 U/l)	21	1,436	7,540	3,023	347
Total bilirubin (normal 0.1–1.2 mg/dl)	0.4	2.8	4.1	6.5	1.1
Serum ammonia (normal 11–47 μmol/l)		101	143		
PT		16.6	29.1[d]	35.6	13.7
INR		1.6	2.6[d]	3.2	1.2
pH (normal 7.37–7.43)		6.99	7.41	7.46	7.55
Serum APAP (normal 0–20 μg/ml)		31.5	6.0		
Lactate (normal 0.4–0.9 mmol/l)		11.9	3.97	4.59	2.0
Serum βHCG (normal < 5 mIU/ml)	5,865.03 mIU/ml	9,109.80 mIU/mL			

[a] Prior ED visit

[b] Prior to liver transplant

[c] 30 h after liver transplant

[d] After FFP given

repeat pelvic ultrasound on postop day 16 showed progressive ventriculomegaly and irreversible brain damage. On postop day 17, the patient underwent an induction termination of pregnancy with misoprostol for intrauterine fetal demise. No fetal autopsy was performed but a MRI of the fetal brain demonstrated extensive pericerebral and intraventricular hemorrhage with extensive periventricular leukomalacia.

Discussion

APAP is the most common drug implicated in overdoses during pregnancy [2]. The vast majority of the reported cases of APAP toxicity during pregnancy involve single, large acute ingestions and the reported outcomes are usually favorable if NAC therapy is initiated in a timely fashion [3]. However, with delays in treatment, fetal demise and maternal death have been reported [4]. In contrast, our case demonstrates the potential for severe morbidity with repeated supratherapeutic ingestions of APAP. Compared to acute, intentional APAP poisoning, unintentional APAP poisoning in pregnancy is poorly described. Horowitz et al. comment on the normal recovery of two women who ingested "repetitive, supratherapeutic (>4 g/day) doses" of APAP [5]. Haibach et al. reported on a 24-year-old at 27–28 weeks EGA who ingested 29 g of APAP over less than 24 h resulting in hepatotoxicity, fetal demise and eventual maternal recovery with NAC therapy [6]. Stokes et al. reported on a 17-year-old at 21 weeks EGA who ingested 25 g of paracetamol in two doses of 10 and 15 g, 18 and 8 h before admission who developed hepatotoxicity but recovered with NAC therapy to have a normal pregnancy [7]. Kurzel et al. attributed maternal hepatotoxicity and neonatal intraventricular hemorrhage to chronic APAP ingestion but were unable to confirm the amount of APAP ingested and coingestants complicated the case [8]. None of these previous cases demonstrated the severe morbidity seen with our case. To our knowledge, this is the first report of repeated supratherapeutic ingestions of APAP during pregnancy resulting in liver transplantation.

While the risk to the mother from APAP poisoning is paramount, there is concern that because APAP crosses the placenta and fetal livers demonstrate mixed-function oxidase activity by 14 weeks gestational age, fetal liver damage may occur [5, 9]. We were unable to document this in our case. Fortunately, NAC appears to readily cross the placenta [5].

While APAP was considered to be the most likely cause of hepatotoxicity and liver failure in this case, other causes were evaluated for. Viral, autoimmune and metabolic etiologies (i.e., Wilson's disease) were ruled out with laboratory testing. Unusual toxicological causes of liver failure such as pennyroyal or comfrey were considered but patient denied any herbal or OTC medications. Unique pregnancy-related causes of liver failure such as pre-eclampsia/eclampsia, HELLP syndrome and acute fatty liver of pregnancy (AFLP) were strongly considered. They were ruled out by history, exam and imaging studies. Concern was highest for AFLP which is a microvesicular steatotosis caused by a defect in mitochondrial β-oxidation leading to hepatotoxicity and liver failure usually in the third trimester [10]. The final pathology report proved to be inconsistent with AFLP.

Conclusion

This case of repeated supratherapeutic ingestions of APAP during pregnancy resulted in fulminant liver failure, liver transplantation and fetal demise. It highlights the significant morbidity that can occur with unintentional excessive ingestions of APAP and emphasizes the importance of educating both physicians and pregnant patients of the potential danger supratherapeutic APAP use poses to both the mother and the fetus.

Conflict of interest There are no conflicts of interest to announce.

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