Outcomes In Suspected "Missed" Acetaminophen Overdose

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Background

Acetaminophen (APAP) has a short half-life and may not be detected in some patients with ongoing APAP-induced liver injury manifested by rising aminotransferases (AT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In such "missed APAP overdose" cases, hepatotoxicity (HT) may continue to worsen despite undetectable APAP. Peak liver injury is typically seen 72-96 hours after APAP ingestion, though some AT elevation is usually evident by 24 hours in patients who develop HT (1-3). The aim of this study was to determine outcome in patients with suspected missed APAP overdose.

Methods

This prospective study of suspected overdose patients (age ≥12 years) at a regional poison center (RPC) over an 18 month period was undertaken to determine how many developed HT defined as AT ≥1,000 U/L. Entry criteria were: 1) undetectable APAP, 2) AST and/or AST >100 U/L or above normal range for health care facility (HCF). Cases were excluded if subsequent AT values were unavailable. During follow up calls, HCFs were queried about repeat AT values, N-acetylcysteine (NAC) treatment, international normalized ratio (INR), other causes of abnormal AT (ethanol abuse, elevated creatinine kinase (CK), hypotension), as well as medical outcome. The RPC recommended NAC treatment and INR determination for patients with AT ≥100.

Case	Initial AST/ALT (U/L)	Peak AST/ALT (U/L)	Peak INR	Peak CK (U/L)	NAC given	Ingestants by History
1	990/1312	990/1312	1.2	ND	Yes	Quetiapine, sertraline
2*	137/267	1689/6498	1.49	ND	Yes	Duloxetine, lithium, recent APAP misuse
3	2481/5286	3381/5286	1.45	ND	Yes	APAP/opioid misuse
4^	10003/5830	10003/5830	4.1	36,000	Yes	Lamotrigine, methocarbamol, orphenadrine
5	433/1225	433/1225	1.01	ND	Yes	Promethazine, history of APAP misuse
6*	117/85	1070/983	1.1	ND	Yes	Unknown
7	6500/8900	6500/8900	2.19	ND	Yes	APAP
8*	149/266	1660/907	ND	365,000	No	Designer stimulant abuse
9	~2000/2000	4000/2300	1.4	ND	Yes	Unknown
10	1189/1085	1189/1085	0.89	270	Yes	APAP/oxycodone
11	1164/395	1164/395	1.23	283	No	Pregabalin, bupropion, aspirin
12	1271/398	1271/398	ND	ND	Yes	APAP misuse
13	764/1085	764/1085	"Normal"	ND	Yes	APAP misuse
14	9755/11000	9755/11000	2.62	ND	Yes	Recent acute APAP overdose
15^	1388/737	3075/940	1.8	>168,000	Yes	Opioid abuse

Table. Cases with ALT and/or AST ≥1000 either initially or by hospital day 3
*Presented with both AT <1000 ^Hypotension documented ND = No data

Results

From 1/17/13 through 8/1/14 a total of a 148 cases met inclusion criteria. 70 (47.3%) were female. Mean age was 38.3 years (range 13-79); median age was 37. The most common reason for HCFs contacting the RPC was suspected suicide attempt (72.3%) followed by abuse (11.5%), misuse (5.4%), adverse drug event (2%), and unknown (8.8%).

AT ≥1000 was reported in 15 (10.1%) cases (Table). AST or ALT reached 1000 in 12 and 10 patients, respectively. Both AST and ALT were ≥1000 in 7 patients. Nine (6.1%) presented with AST, 9 with ALT ≥1000. Only 3 (2.0%, 95% confidence interval 0.4 to 6.0) began with both ALT and AST <1000 and subsequently developed AT ≥1000. 21 had CK >1000 U/L, although most patients did not have a CK determination. Among patients with AT ≥1000, 4 had peak INR >1.5 (4.1, 2.1, 2.62, 1.8), all of whom presented with AT ≥1000. INR was not reported in 2 patients with AT ≥1000, one of whom had a peak CK of 365,000 U/L suggesting AT elevation was due to rhabdomyolysis. One case had a blood pressure of 80/44 recorded and another had pre-hospital CPR; neither had vasopressor administration documented. NAC was given in 48 cases (12/14 with AT ≥1000). There were no fatalities and no patients underwent liver transplant.

Discussion

NAC has been shown to improve survival in patients with APAP-induced liver failure after APAP has cleared, though the mechanism is not well defined (4). The rationale for starting NAC in patients presenting with undetectable APAP and and mild AT elevation is that some may progress to liver failure. In 148 suspected overdose patients with undetectable APAP and initially elevated AT, 10.1% had AT ≥1000 U/L either at presentation or by day 3. Only 3 patients (2.0%) began with mild AT elevation that subsequently rose to ≥1000. None of these 3 developed coagulopathy with INR >1.5, though only 2 had INR reported. In the third case (#8), massive rhabdomyolysis rather than liver injury likely accounted for most of the AT elevation.

Conclusions

Suspected overdose patients with undetectable APAP and mild AT elevation may benefit from NAC treatment until AT can be trended, as a small proportion will develop significant hepatotoxicity. In patients with AT <1000 U/L at presentation, the risk of progression to liver failure appears to be low.

References

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