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Acetaminophen (APAP) hepatotoxicity—Isn't it time for APAP to go away?

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Summary

Acetaminophen (APAP) is the most commonly used drug for the treatment of pain and fever around the world. At the same time, APAP can cause dose-related hepatocellular necrosis, responsible for nearly 500 deaths annually in the United States (US) alone, as well as 100,000 calls to US Poison Control Centers, 50,000 emergency room visits and 10,000 hospitalisations per year. As an over-the-counter and prescription product (with opioids), APAP toxicity dwarfs all other prescription drugs as a cause of acute liver failure in the US and Europe, but it is not regulated in any significant way. In this review the ongoing controversy surrounding the proper role for this ubiquitous pain reliever: its history, pathogenesis, clinical challenges in recognition and management, and current regulatory status are highlighted. A new solution to a 50-year-old problem is proposed.

Key point

APAP is uniquely situated within over the counter drugs: a dose-related toxin, that is readily available and can be lethal.

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Introduction

Acetaminophen (N-acetyl-p-aminophenol, APAP, paracetamol, Tylenol®) is a ubiquitous and highly utilised over-the-counter medication for the relief of pain and fever that is also a dose-related toxin.[1] APAP toxicity accounts for 46% of all acute liver failure (ALF) in the United States (US)[2] and between 40 and 70% of all cases in the United Kingdom (UK) and Europe.[3] APAP toxicity accounts for several-fold more deaths related to acute liver failure (ALF) than all prescription drugs combined (Fig. 1). It has been the subject of two US Food and Drug Administration (FDA) Advisory Committee meetings in the past 15 years.

APAP is very safe when used in limited doses but the margin of safety is relatively narrow, leading to dose-dependent liver injury in all mammalian species. The opioid combination medications containing hydrocodone/APAP (Vicodin®, Norco®, *etc.*) represent the most frequently prescribed generic in the U.S. with 139 million prescriptions written in 2012.[4] Overall, APAP represents a multi-billion-dollar product and Tylenol®, a well-protected brand. Coupled with its reputation as being extremely safe, the public and regulatory authorities are faced with an unusual situation: over-the-counter, yet deadly. Meanwhile, APAP remains a vital tool for basic scientists seeking to better understand hepatic metabolism and mechanisms of liver injury.[5,6] Thus, for researchers and clinicians alike, APAP currently provides indefinite job security. How did a ubiquitous pain reliever achieve this unusual status? What can be done to better understand the risk and avoid the consequences of APAP overdosing? Is there a long-term solution here?

History

As early as 1960, APAP, or paracetamol as it is referred to in Europe and the UK, had become a popular analgesic for the treatment of headache and mild pain, possessing few of the side effects associated with aspirin (acetylsalicylic acid [ASA]). By 1966, reports began to appear concerning its association with liver injury resulting in fatal outcomes. By the 1970s, APAP was the most frequently used suicidal agent[7] in the UK; in 1972, the Liver Unit at Kings College Hospital London set up the first 2-bed Liver Failure Intensive Care Unit, typically filled with young women on life support following attempts at self-harm. A single-timepoint APAP overdose of 12–15 grams (24–30 'extra strength' (500 mg) tablets), is associated with a mortality rate of approximately 50%.[8] By 1973, Mitchell and Jollow at the US National Institutes of Health (NIH) had delineated the APAP metabolic pathway,[9] and suggested that *N*-acetylcysteine (NAC) was a suitable antidote. Oral NAC (Mucomyst®) came into common

Table 1. Parkland Hospital study of acetaminophen overdoses.[19] Over a 40-month period, in an urban county hospital, 71 cases were identified without confounding features that qualified as acetaminophen toxicity. The features of the intentional and unintentional cases were clearly different. While there were fewer unintentional cases identified, they had poorer outcomes, likely the result of late presentations.

Suicidal (n = 50)	Unintentional (n = 21)
• Suicide admitted	• Suicide denied
• Single time point	• Several days' use
• No cause of pain	• Reason for pain
• Early presentation	• Late presentation
• 20% ALT >1,000	• Virtually all high ALT
• 1 ALF/death in 50 (2%)	• 8 ALF; 6 (29%) died

usage within a few years and intravenous NAC shortly thereafter, although considerably later in the US, in 2004.[10]

Acetaminophen crosses the Atlantic

APAP was virtually non-existent in the US until the early 1980s when, after the association of aspirin with Reyes syndrome in children was recognised,[11] APAP was seen as a suitable substitute and became marketed actively as Tylenol®, as well as other brands. This was followed by development of convenience combinations such as APAP/diphenhydramine (Tylenol PM®, Nyquil®, others), as well as opioid/APAP combinations. APAP's popularity rose dramatically, even though virtually all Reyes cases were confined to children, not adults.[12] In the late 1970s and early 1980s, numerous reports surfaced regarding severe liver injury associated not with suicide attempts, but with so-called 'therapeutic misadventures'.[13–15] These represented inadvertent overdoses in the setting of acute or chronic pain, often accompanied by alcohol use and without suicidal intent. Over the next decade, US hepatologists became increasingly aware of this entity. Zimmerman and Maddrey published a comprehensive article in 1995, describing 67 cases of inadvertent toxicity, in patients who had ingested therapeutic or supra-therapeutic doses, often accompanied by alcohol use/abuse, without evident suicidal intent. These cases were associated with worse clinical outcomes than suicide attempts.[16]

A review of acute liver failure (ALF) in 1993 included mention that APAP was fast becoming the most frequent cause of ALF in the US.[17] While not substantiated with specifics, a subsequent article provided results of a comprehensive review of APAP-related toxicity at a large urban hospital: 71 hospital admissions for APAP toxicity (not necessarily ALF) were identified over a 40-month period.[18] Criteria were established to distinguish the intentional (suicide) from the unintentional (therapeutic misadventure) phenotype (Table 1).

The unique features of the two groups were evident. The intentional suicides typically occurred in young people with relationship problems, taking between 12 and 50 g at one timepoint, but once they admitted to having overdosed they were brought to the Emergency Department quickly (within 4–6 h), and, for the most part, received NAC promptly, precluding serious injury. Use of the NAC antidote within 12–18 h precludes the most severe liver injury, whereas later presentations demonstrate massive liver injury roughly proportional to the dose taken. By contrast, unintentional overdoses typically involved ingestion of 6–10 g/day over several days for postoperative pain, pancreatitis, low back pain, frequently involving opioid combinations, with denial of suicidal intent. Patients unaware of having done something risky presented late, after symptoms (nausea, vomiting, abdominal pain and eventually drowsiness) had developed and had worse outcomes.

Key point

For nearly 50 years, APAP hepatotoxicity has been recognised, its metabolism understood and an excellent antidote is available.

Unique pattern of toxicity

APAP toxicity has a characteristic 'hyperacute' evolutionary pattern, reproducible in virtually all subjects regardless of intentionality. After an APAP overdose at a single time point, there is no immediate sedative effect, and few symptoms initially, until abdominal pain and nausea develop between 12 and 24 h later. In the following 24 h, symptoms may appear to improve but aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and an international normalized ratio (INR) rise abruptly to very high levels, frequently above 10,000 U/L, normal (<40 U/L), with INR ≥4.0, respectively. By 72–96 h, biochemical elevation will

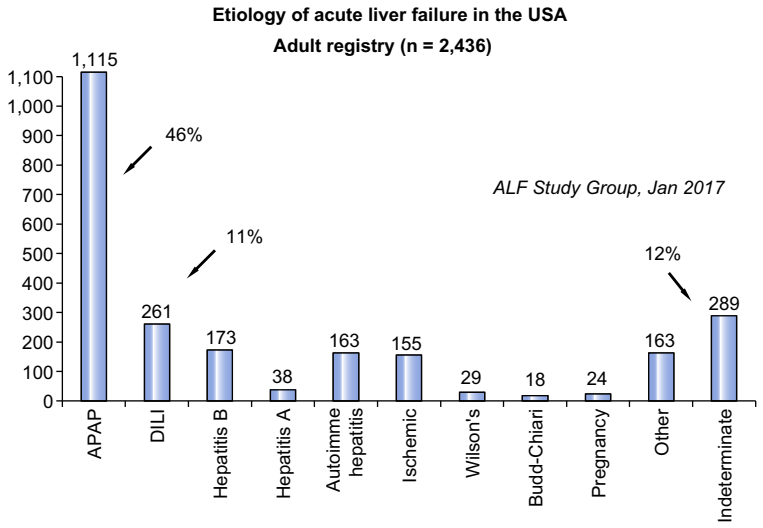

Fig. 1. Bar graph showing breakdown by percentage or actual number of cases enrolled for each of the major ALF aetiologies over 18 years. Over this period, there has been little change in the percentages for each aetiology, save a decline in hepatitis A and B.

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Key point

APAP toxicity follows a uniquely uniform pattern, such that the damage is either fatal or requires a liver transplant or recovery ensues within 4–5 days.

Key point

The number of deaths in North America and Europe shows no sign of decreasing, despite some efforts to limit package size in the United Kingdom.

have peaked along with hyperammonemia, somnolence, stupor and coma, accompanied by lactic acidosis, cerebral oedema, brain stem herniation and vascular collapse.[7,8] Concomitant acute (tubular) kidney injury (AKI) has been shown to occur in 70% of patients with ALF, alongside varying degrees of skeletal muscle cytolysis.[19] If the multi-organ failure syndrome does not evolve by this juncture, then recovery ensues equally quickly, with rapid resolution of AST, ALT and INR. Virtually no permanent injury has been identified after severe overdoses or long-term chronic use. The kidney injury resolves in a week or two, although occasionally dialysis is required for up to a month or more.[20] By comparison, idiosyncratic drug-induced liver injury (DILI), and most other forms of acute liver injury leading to ALF, except ischaemic hepatic injury, have a subacute course, which evolves over 1–4 weeks and features lower aminotransferase and higher bilirubin levels, with poorer overall outcomes, fewer spontaneous recoveries, but more time to await a liver graft and undergo transplantation (Table 2).

Centri-lobular hepatocellular necrosis, the hallmark lesion of APAP injury is indistinguishable from ischaemic necrosis by routine light microscopy, since both affect zone three of the hepatic lobule, where oxygen tension is lowest.[20] The metabolic pathway outlined indicates that the parent compound is readily esterified to glucuronides and/or sulfates unless the capacity for esterification is saturated, in which case the secondary pathway via cytochrome P450 enzymes comes into play, principally CYP2E1, leading to formation of a highly reactive and toxic intermediate metabolite, *N*-acetyl-p-benzoquinone imine (NAPQI) (Fig. 2).[9] NAPQI can be readily de-toxified via glutathione to mercapturic acid that is water soluble, harmless and readily excreted in urine. However, once glutathione is depleted, NAPQI binds directly to cell proteins via cysteine residues, disrupting cellular integrity and yielding hepatocyte necrosis. This injury likely takes place very rapidly once glutathione depletion is accomplished, leading to the extraordinary levels of aminotransferases, but also a very rapid decline upon cessation of liver injury. However, given the relatively long half-life of both AST and ALT, enzyme levels only resolve fully after 3–9 days, depending on the severity of the injury. The injury is so uniform in nature that a mathematical model has been created to predict outcome, using only the AST, ALT and INR values at one-time point.[21]

Between 1990 and 1998, the percentage of cases of ALF related to APAP in the US rose from ca. 20%[22,23] to its current 46%,[24] where it has remained with no evident decline for nearly two decades. There has been no decline in other aetiologies, save perhaps a small drop in hepatitis A and B.[24] (Very recently, the hepatitis B percentage has begun to increase once again, likely because of the opioid drug use epidemic.)

Beginning of regulatory action

Although first used in ca. 1966, the dangers of APAP had been recognised in case reports from as early as 1970, at least in the UK.[25] An unsigned editorial in *The Lancet* 1975 stated: "Surely the time has come to replace paracetamol with an effective analogue which cannot cause liver damage." [26] How ironic to read this 42 years later!

Professor Keith Hawton, a suicidologist at Oxford University, has chronicled the situation over the past 40 years.[27,28] Initially, little was known about APAP's toxicity as a suicidal agent, patients who had overdosed were not necessarily aware that it had risks.[29] Two decades later, this had evolved so that it was understood, at least in the UK, that APAP was responsible for a rising number of deaths, with extensive media publicity describing the problem.[30] Efforts to curb package size were encouraged by the Hawton group, based on surveys of overdose patients conducted in the 1990s that suggested that impulsive behaviour was responsible for most

Table 2. Comparison of different acute liver failure (ALF) aetiology groups. ALF study group data summary between January 1998 and December 2016. The APAP group is younger than the DILI, more likely to have advanced coma grade but shorter duration of jaundice to coma, much higher aminotransferases and lower bilirubin levels than the DILI case or most other groups. There are significant differences in outcomes as well. N = 2,436.

	APAP, n = 1,115	Drug, n = 261	Indeterminate, n = 289	HepA/HepB, n = 38/173	All Others, n = 560
Age (median)	37	46	40	50/43	45
Sex (% F)	76	69	61	45/46	70
Jaundice to coma (Days)	1	12	10	4/8	7
Coma ≥3 (%)	53	36	47	53/50	40
ALT (median IU)	3,798.5	648	870	2,316.5/1,415	774
Bili (median)	4.3	19.2	20.1	12.3/18.8	12.7
Tx (%)	8.6	38	42	34/39	29
Spontaneous survival (%)	64.4	25	23	50/19	31
Overall survival (%)	71.5	59	61	74/53	55

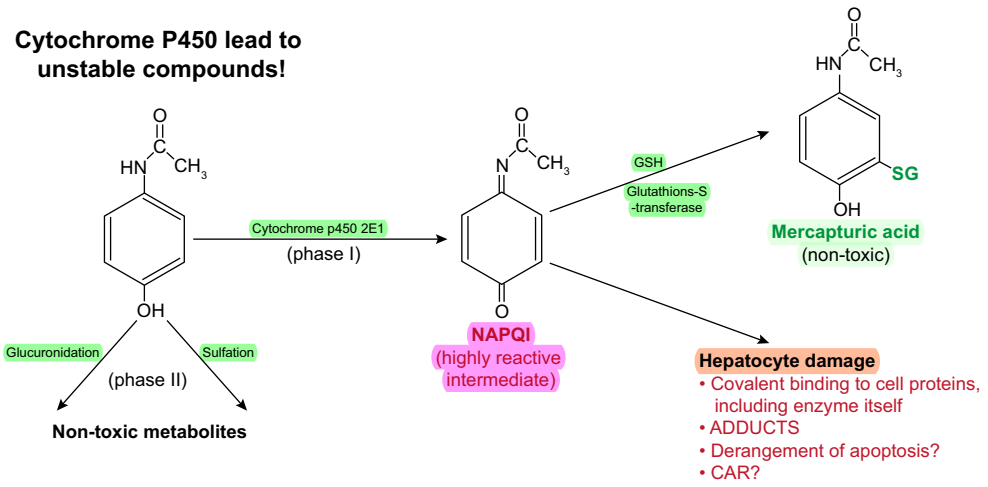

Fig. 2. Biochemical pathways of acetaminophen metabolism. Only small amounts of *N*-acetyl-p-benzoquinone imine (NAPQI) are formed unless the capacity for glucuronidation and sulfation is exceeded. Even then, glutathione supplies sulfhydryl groups that detoxify NAPQI to mercapturic acid, which is excreted in the urine. When glutathione is exhausted, then NAPQI binds to cell proteins disrupting cell function, the full details of which remain poorly understood.

suicides, involving utilisation of whatever was readily available in the home. These initiatives culminated in Parliament passing legislation in 1998 limiting the package size to 16 in convenience stores and 32 in pharmacies, and a requirement for blister packing to further inhibit the likelihood of impulsive behaviour. Whether these measures have been effective has been debated over the following two decades.[31–34] Most evidence suggests that the number of deaths, and number of registered self-harm incidents has declined considerably, while the number of liver transplants has declined more modestly, and there has been no evident change in Scotland for unclear reasons. If the anticipated results were somewhat limited, this is likely due to enforcement limitations—those intending to garner large numbers of tablets can readily do so, since the chemist (pharmacy) or store cashier serves, in effect, as the only gatekeeper. The original intent, of course, was to limit quantities found around the home that might then be used impulsively. Perhaps the modest diminution in incident cases reflects a decline in 'impulsive' cases with no diminution in those where more planning is involved.

Intentional *vs.* Unintentional overdoses

While most APAP overdoses were assumed to be attempts at self-harm as studied by the University of Oxford Centre for Suicide Research, when the problem of APAP overdoses emigrated to the US in the 1980s, it became apparent that most of the severe injuries were not related to intentional self-harm, perhaps casting the whole overdose conundrum in a different light: if one dies after inadvertently overdosing, does this carry a different significance compared to self-inflicted cases? In short, should the public care more or differently about unintentional overdoses? Do the different clinical phenotypes differ in other ways such as outcomes? The US FDA certainly considered the unintentional cases a more compelling argument toward regulatory oversight than intentional overdoses, discussed later.

Despite the seemingly contrasting clinical scenarios associated with unintentional and suicidal APAP ingestions, patients who develop ALF due to either phenotype resemble each other in many ways. In an early descriptive study of 662 patients enrolled by the US ALF Study Group, 275 (41.5%) were found to have APAP overdoses, all meeting ALF criteria: coagulopathy (prolonged INR ≥1.5) and encephalopathy.[35] In nearly all patients, the intentionality could be discerned; more were found to have unintentional than intentional overdoses. Seven percent gave a history of taking less than 4 g, suggesting that certain patients might have increased sensitivity to APAP's toxic effects, perhaps enhanced by alcohol or starvation, both known to deplete glutathione. Conversely, in Europe the unintentional overdose remained relatively unrecognised, or was thought to constitute very few instances of ALF, until 2010[36] when a report focused on outcomes of intentional *vs.* unintentional overdoses, suggesting that unintentional overdoses constituted a significant number (16.6%), still lower than the US reports. The term 'staggered overdose' was used, indicating that no longer were single time point ingestions the rule. Although seemingly unintentional, since toxicity occurred only after repeat sub-toxic ingestions over several days, the intentionality of staggered overdoses has remained somewhat ambiguous.[37] Some have questioned whether

a staggered overdose might simply be another form of suicidal behaviour.[37] Clinically, both forms are associated with nearly equally high aminotransferases and similar frequency of anti-depressant and other substance use (Table 3).[35] Unintentional overdose patients with chronic pain may be given anti-depressants as part of pain management, since several have been granted chronic pain indications, Duloxetine® being an example. More frequently, two thirds of unintentional patients reported taking high doses of hydrocodone/APAP products because of habituation/addiction to the opioid; others (roughly one third of unintentional patients) ingest more than one APAP-containing 'convenience' medication, such as Nyquil® along with Tylenol PM®, or plain Tylenol® alongside a hydrocodone/APAP combination (Table 3), unaware that they are overdosing by not reading labels carefully.[35] As previously stated, the damage is uniquely sudden and severe, resolving in an equally rapid fashion once APAP has been metabolised. APAP has a relatively short half-life of about 2–3 h (although it is somewhat prolonged in patients with significant liver injury).[38]

Further characterising the unintentional patient

Originally called the therapeutic misadventure or the 'alcohol/Tylenol® syndrome', unintentional overdose patients have long been recognised as having substance use issues.[13–16] This has been underlined in recent studies showing high rates of polysubstance abuse, including cocaine and benzodiazepines, in addition to alcohol and opioids.[39] Again, there are similarities between intentional and unintentional groups as a recent questionnaire study showed: the incidence of depressive disorder at any time, use of SSRI and SNRI medication, as well as the use of alcohol were similar between the two groups, although opioid use was more prevalent in the unintentional group (Table 3).[35] Long term outcomes for patients surviving all forms of APAP overdoses are poorer than for other forms of ALF; they tend to have lower socio-economic status, less education and are less likely to be married, with no differences apparent between the two phenotypes.[40]

Outcomes in APAP ALF

While spontaneous resolution of liver injury occurs with or without NAC in nearly two thirds of cases, many die or require transplantation (Table 2). There is little difference in transplant selection or

Table 3. Comparison of the acetaminophen (APAP) phenotypes. Acute liver failure study group data summary between January 1998 and December 2008.[35] Most APAP overdoses are women, and many features between the two phenotypes are similar although the percentage with opioid use or that used multiple preparations is higher in the unintentional group.

N = 603 (56 = unknown)	Intentional (n = 251)	Unintentional (n = 296)	*p* value
Female (%)	77	71	n.s.
Age	35	39	<0.001
ACM dose (g)	38/38	47/7.5	n.s.
Coma (% ≥3)	39	55	<0.026
ALT (IU/L)	6,053	4,207	<0.0001
Alcohol use/abuse (%)	50/18	50/17	n.s.
Antidepressant (%)	59	34	n.s.
History of depression (%)	45	24	<0.001
Opioid cpd (%)	18	63	<0.001
Multiple preps (%)	5	38	<0.001
Spont surv (%)	70	65	n.s.

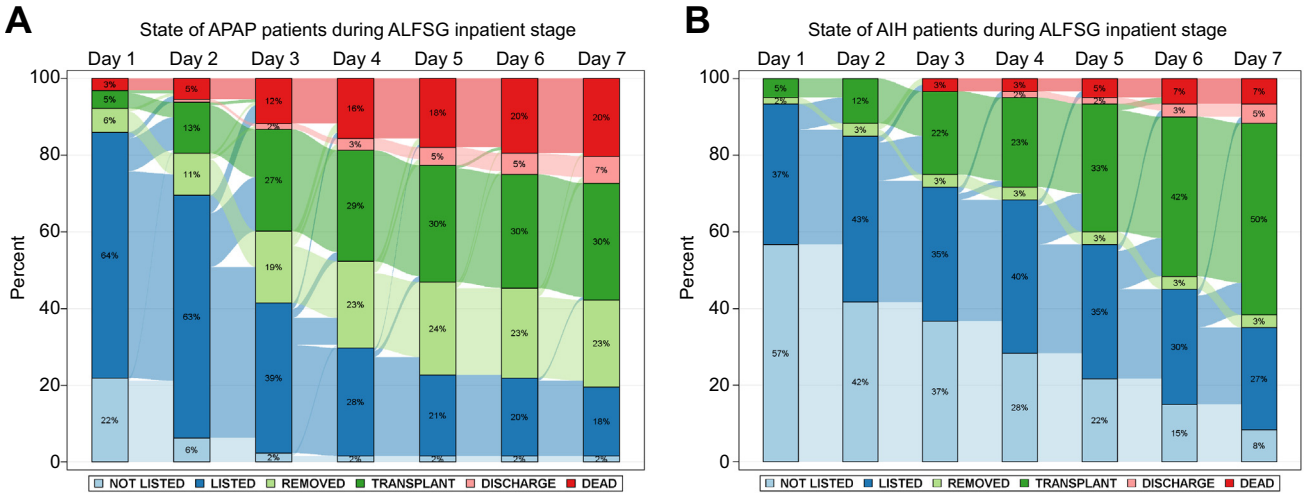

Fig. 3. Diagrammatic representation of events by day (Sankey plot), after registry enrollment/listing for transplantation, according to aetiology groups. (A) acetaminophen (APAP), and (B) Drug-induced liver injury (DILI). Most of the deaths and transplants in the APAP group (3a) took place within the first 48–72 h, while both deaths and transplants evolved more slowly in the non-APAP categories such as DILI (3 b).

outcomes between intentional and unintentional phenotype, and all progress to death, transplant or recovery in a similarly short time interval. In the ALF Study Group experience, virtually all APAP patients reached an endpoint four days after admission to the study, while DILI patients continued to die or receive liver grafts over the ensuing 7–10 days (Fig. 3).[41] Overall, 36% of patients with ALF were listed for transplantation, only 22% of those with APAP ALF were listed *vs.* 56% of those with non-APAP ALF. While this might suggest better outcomes in patients with APAP ALF, the listed patients taking APAP were actually more ill in terms of clinical and biochemical features. Only 36% of those listed received a graft *vs.* 74% of patients in the non-APAP group. The very sick patients with APAP ALF often die because a liver cannot be found in time – favourably impacting the death rate for APAP ALF cases remains extremely challenging. It will require more rapid evaluation for transplantation and quicker organ availability as well.[42]

FDA responses

In 2002 and 2009, the FDA held advisory committee meetings with the goal of tackling the issue of APAP hepatotoxicity. It should be noted that the FDA has little authority to act regarding over-the-counter medications, in comparison with its authority over prescription drugs. However, data regarding APAP toxicity had been presented at an FDA-sponsored educational meeting in 2001.[43] The 2002 FDA meeting principally dealt with package labelling:[44] were the cautions about use with alcohol and other products plain enough and was the full name appropriately placed on the front of the package? By 2009, the FDA had formed an internal group to review the ongoing problem.[45] This second advisory committee addressed more cogent issues (Table 4).[39] Was 4 g/day too large a dose? Should the hydrocodone/APAP combinations be unbundled? Were convenience medications (TylenolPM®, Dayquil®, other cough syrups) a significant problem? While the committee did in fact vote to lower the daily dose recommendation, a specific amount was not given; the committee also voted to unbundle the opioid/APAP combinations, but did not believe that convenience medications needed additional regulation.[45]

Following the 2009 Advisory Committee meeting, the FDA issued a mandate (in January 2011)[46] that any prescription form of APAP (basically oxycodone- or hydrocodone/APAP) combinations sold after January 2014 should only contain 325 mg per tablet as opposed to the prior combinations that were 500, 650 or even 750 mg per tablet. This rule is now in place in the US. Current package labelling mentions severe liver injury as a possible outcome if one takes more than 4,000 mg in 24 h or with other APAP-containing compounds or with alcohol. While there has been a certain degree of public outcry regarding the problem, further efforts to fully apply the committee's recommendations have not occurred.

Criticism of the FDA has been moderate.[47] In 2013, the problems surrounding APAP toxicity were featured by Propublica,[48] a U.S. public interest journalist website, and subsequently in an hour-long radio show, This American Life. In addition, a large class action lawsuit with over 100 plaintiffs was settled in June 2016 by McNeil, until recently the over-the-counter arm of Johnson & Johnson, who are responsible for Tylenol® and its many related products.[49] Thus far, any increased visibility afforded to the problem has appeared to have little impact. There is no apparent slowing of cases, although very recent data, other than ALF Study Group annual snapshots, has been somewhat sparse.[50,51] The blame has variously been laid at the slowness of the FDA and to the opioid combination products, for unintentional cases. All this has been dwarfed by the larger problem of the opioid epidemic.[52] Further regulation at

Key point

Efforts to manage toxicity once it develops require very rapid assessment. Prognostic indexes, including an 'app', are available.

Key point

Regulatory efforts by the U.S. Food and Drug Administration (and worldwide) have been ineffective thus far and are likely to remain so.

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Table 4. Summary of the questions and votes posed at the FDA Advisory Committee meeting in 2009 concerning acetaminophen toxicity. A, B and C refer to preferences. A, strongly in favour; B, in favour; C, against. Vote tallies follow each letter, and the final tally is indicated as yes or no: A + B *vs.* C. OTC, over the counter.

Reduce current dosage strengths for OTC: maximum total daily dose, maximum adult single dose, maximum strength.
1. Maximum dose per day: less than 4 g, exact amount unspecified. A 11, B 10, C 16. (Yes)
2. Maximum single dose: 650 mg (2 × 325 mg). A 12, B 12, C 13. (Yes)
If the above is approved, should 500 mg tablet, 1,000 mg, and/or 4 g/day dosing be prescription only?
3. Maximum dose of 500 mg × 2 should be prescription only. A 8, B 18, C 11. (Yes)
Establish pack size limits for OTC acetaminophen products?
4. Pack size limits? A 2, B 15, C 20. (No)
Eliminate non-prescription combination products (*e.g.* Nyquil™, Dayquil™)?
5. Eliminate these products? A 2, B 11, C 24. (No)
Limit formulations of liquids to only one concentration (this has to do with paediatric dosing)?
6.Do you recommend that only one non-prescription concentration of liquid be available? A 19, B 17, C 1. (Yes)
Eliminate prescription combination products (opioid/acetaminophen compounds)?
7. Do you recommend eliminating the prescription combination products? A 10, B 10, C 17. (Yes)
If not eliminated, should prescription combinations be sold in "unit of use" packaging or with additional warning labels?
8. Do you recommend "unit of use" packaging? A 5, B 22, C 10. (Yes)
9. Do you recommend box warning? A 25, B 11, C 1. (Yes)
10. What of the above is your highest priority? [These last two questions required subjective answers from the panellists.]
11. Discuss other options you would suggest.

this point seems unlikely since it is very difficult to accomplish for over-the-counter products, particularly for successful brands. Thus, 42 years after the call for its replacement in *The Lancet*, APAP remains the most commonly taken analgesic and there is no relief in sight.

Regulation will never solve this problem

Regulation of APAP to bring about a reduction in the number of intentional or unintentional cases appears impossible, given a highly successful product in a very cautious regulatory environment. Beyond further regulation, which seems highly unlikely, what might be done to diminish the overall cost in money and lives? Efforts to combine APAP with an antidote that would preclude toxicity began more than 30 years ago but have never gained traction. Compounds such as cysteamine,[53] methionine and cimetidine,[54] were considered. They would compete for CYP2E1 with APAP blocking NAPQI accumulation, while allowing continued detoxification via glucuronidation and sulfation to occur at a slower pace. The challenge with this approach would be to find a compound that has no intrinsic effects except protecting against APAP, and it would have to be very safe. It is likely that the cost of developing such a product is outweighed by the pressure to continue what is currently the standard, APAP as we currently know it.

What about a totally new pain pill?

Key point

What is needed is a new paradigm: development of a totally safe congener of acetaminophen that would provide effective analgesia with no risk of toxicity.

The most promising strategy would be to find a new analgesic that had the same properties as APAP but without the toxicity. If we can design biologics that interact with specific cell-surface receptors, why can't we apply some basic pharmacologic chemistry to analgesic development? APAP has a central CNS effect that is presumed related to the benzene ring structure, and although classed as a non-steroidal anti-inflammatory drug (NSAID), it does not share ulcerogenic or cardiac toxicity with other NSAID compounds. Other benzene ring structures should be explored. There has not been a new class of analgesics since the arrival of COX-2 inhibitors 15 years ago, and these were not really new, but simply an improvement on existing drugs.[55] The rewards for the company identifying such a new analgesic would be tremendous!

Challenges to implementation of a new safer product would also be enormous, but challenging APAP's popularity could be worth it. Pushback from existing analgesic providers would be formidable, particularly when marketing something unknown as being safer than APAP, as APAP maintains a reputation for safety though not well-deserved. It would be up to the FDA and a grateful (educated) public to embrace a truly safe and effective analgesic that is not saddled with the baggage of opioids (habituation, constipation, somnolence) or NSAIDs (gastrointestinal bleeding) or APAP (deaths from acute liver failure). One parallel that comes to mind is the barbiturate class of sleeping pills that were highly popular in the 1960s and '70s but caused innumerable overdose deaths. Once benzodiazepines came along, barbiturates disappeared with remarkable rapidity. The question is: who will come forth and make this happen for APAP?

Conflict of interest

WL has received research support from Gilead, Merck, BMS, Conatus, Ocera, Exalenz; provided consulting to Novartis, Repros, Lilly, Sanofi.

WL has no conflict of interests related to the manuscript.

Please refer to the accompanying ICMJE disclosure form for further details.

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References

[1] Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of acetaminophen (Paracetamol)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf 2006;15:398–405.
[2] Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SBH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947–954.
[3] Bernal W, Auzinger G, Dhawan A, et al. Acute liver failure. Lancet 2010;376:190–201.
[4] http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012, accessed May 10, 2016.
[5] Kon K, Kim JS, Jaeschke H, Lemasters JJ. Mitochondrial permeability transition in acetaminophen-induced necrosis and apoptosis of cultured mouse hepatocytes. Hepatology 2004;40:1170–1179.
[6] Fujimoto K, Kumagai K, Ito K, Arakawa S, Ando Y, Oda S, et al. Sensitivity of liver injury in heterozygous Sod2 knockout mice treated with troglitazone or acetaminophen. Toxicol Pathol 2009;37:193–200.
[7] Proudfoot AT, Wright N. Acute paracetamol poisoning. Br Med J 1970;3:557–558.
[8] Rumack BH, Peterson RC, Koch GG, Amara IA. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. Arch Intern Med 1981;141:380–385.
[9] Mitchell JR, Thorgeirsson SS, Potter WZ, Jollow DJ, Keiser H. Acetaminophen-induced hepatic injury: protective role of glutathione in man and rationale for therapy. Clin Pharmacol Therap 1974;16:676–684.
[10] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-539_Acetadote.cfm, accessed on June 26, 2017.
[11] Federal Register 1982: Labeling for Salicylate Compounds http://cdn.loc.gov/service/ll/fedreg/fr047/fr047249/fr047249.pdf#page=214, accessed on June 15, 2017.
[12] http://cdn.loc.gov/service/ll/fedreg/fr047/fr047249/fr047249.pdf#page=214 FDA monograph suggesting a warning to be put on aspirin in regard to use in children under 16 for influenza symptoms—1982.
[13] McClain CJ, Kromhout JP, Peterson FJ, Holtzman JL. Potentiation of acetaminophen hepatotoxicity by alcohol. JAMA 1980;244:251–253.
[14] Seeff LB, Cuccherini BA, Zimmerman HJ, Adler E, Benjamin SB. Acetaminophen toxicity in alcoholics. Ann Intern Med 1986;104:399–404.
[15] Wootton FT, Lee WM. Acetaminophen hepatotoxicity in the alcoholic. Southern Med J 1990;83:1047–1049.
[16] Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. Hepatology 1995;22:767–773.
[17] Lee WM. Medical progress: acute liver failure. N Engl J Med 1993;329:1862–1872.
[18] Schiødt FV, Rochling FJ, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. N Engl J Med 1997;337:1112–1117.
[19] Tujios SR, Hynan LS, Vazquez MA, Larson AM, Seremba E, Sanders CM, et al. Risk factors and outcomes of acute kidney injury in patients with acute liver failure. Clin Gastroenterol Hepatol 2015;13:352–359.
[20] James LP. Acetaminophen: Pathology and clinical presentation of hepatotoxicity, in Kaplowitz N, Deleve LD. Drug-Induced Liver Disease (Third Edition) Amsterdam 2013, pp. 331–341.
[21] Remien CH, Adler FR, Waddoups L, Box TD, Sussman NL. Mathematical modeling of liver injury and dysfunction after acetaminophen overdose: Early discrimination between survival and death. Hepatology 2012;56:727–734.
[22] Shakil AO, Kramer D, Mazariegos GV, Fung JJ, Rakela J. Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. Liver Transpl 2000;6:163–169.
[23] Schiødt FV, Atillasoy E, Shakil O, Lee WM, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. Liver Transplant Surg 1999;5:29–34.
[24] Reuben A, Tillman H, Fontana RJ, Davern T, McGuire B, Stravitz RT, et al. Outcomes in adults with acute liver failure (ALF) from 1998–2013: An observational cohort study. Ann Intern Med 2016;164:724–732.
[25] Proudfoot AT, Wright N. Acute paracetamol poisoning. BMJ 1970;3:557–558.
[26] Lancet Editorial (unsigned), December 13 1975, p. 1189.
[27] Hawton K, Fagg J. Deliberate self-poisoning and self-injury in adolescents. A study of characteristics and trends in Oxford, 1976–89. Br J Psychiatry 1992;161:816–823.
[28] Hawton K, Ware C, Mistry H, Hewitt J, Kingsbury S, Roberts D, et al. Paracetamol self-poisoning. characteristics, prevention and harm reduction. Br J Psych 1996;168:43–48.
[29] Gazzard BG, Davis M, Spooner J, Williams R. Why do people use paracetamol for suicide? BMJ 1976;i:212–215.
[30] Hawton K, Bergen H, Casey D, Simkin S, Palmer B, Cooper J, et al. Self-harm in England: a tale of three cities. Soc Psychiatr Epidemiol 2007;42:513–521.
[31] Hawton K, Bergen H, Simkin S, Dodd S, Pocock P, Bernal W, et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. BMJ 2013;346:403–410.
[32] Bateman DN. Limiting paracetamol pack size: has it worked in the UK? Clin Toxicol 2009;47:536–541.
[33] Morgan O, Hawkins L, Edwards N, Dargan P. Paracetamol (acetaminophen) pack size restrictions and poisoning severity: time trends in enquiries to a UK poisons centre. J Clin Pharm Ther 2007;32:449–455.
[34] Hawton K, Simkin S, Deeks J, Cooper J, Johnston A, Waters K, et al. UK legislation on analgesic packs: before and after study of long term effect on poisonings. BMJ 2004;329:1076–1082.
[35] Larson AM, Fontana RJ, Davern TJ, Polson J, Lalani EK, Hynan LS, et al. Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. Hepatology 2005;42:1367–1372.
[36] Craig DGN, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. Br J Clin Pharm 2010;71:273–282.
[37] Craig DGN, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. Br J Clin Pharmacol 2012;73:285–294.
[38] Schiødt FV, Ott P, Christensen E, Bondesen S. The value of plasma acetaminophen half-life in antidote-treated acetaminophen overdose. Clin Pharmacol Ther 2002;71:221–225.
[39] Lee WM. Point-counterpoint: The case for limiting acetaminophen-related deaths: Smaller doses and unbundling the opioid-acetaminophen compounds. Clin Pharm Ther 2010;88:289–292.
[40] Fontana RJ, Ellerbe C, Durkalski VE, Rangnekar A, Reddy KR, Stravitz T, et al. Two-year outcomes in initial survivors with acute liver failure: Results from a prospective, multicenter study. Liver Int 2015;35:370–380.
[41] Reddy KR, Ellerbe C, Schilsky M, Stravitz RT, Fontana RJ, Durkalski V, et al. Determinants of outcome among patients with acute liver failure listed for liver transplantation in the US. Liver Transpl 2015;22:505–515.
[42] Simpson KJ, Bates CM, Henderson NC, Wigmore SJ, Garden OJ, Lee A, et al. The utilisation of liver transplantation in the management of acute liver failure: Comparison between acetaminophen and non-acetaminophen etiologies. Liver Transplant 2009;15:600–609.
[43] https://wayback.archive-it.org/7993/20161022165242/http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm091365.htm, accessed June 14, 2017.
[44] www.fda.gov/ohrms/dockets/ac/02/slides/3882s1_01_ganley.pdf, accessed June 14, 2017.
[45] https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM174699.pdf dated January 13, 2011, accessed June 14, 2017.
[46] https://www.fda.gov/Drugs/DrugSafety/ucm239821.htm, accessed June 19, 2017.
[47] Graham GG, Day RO, Graudins A, Mohamudally A. FDA proposals to limit the hepatotoxicity of paracetamol (acetaminophen): are they reasonable? Inflammopharmacol 2010;18:47–55.
[48] https://www.propublica.org/article/tylenol-mcneil-fda-use-only-as-directed, accessed June 19, 2017.
[49] https://www.propublica.org/article/johnson-johnson-emerges-victorious-in-lawsuit-on-tylenols-risks, accessed June 19, 2017.
[50] Bronstein AC, Spyker DA, Cantilena L, Rumack BH, Dart RC. 2011 annual report of the american association of poison control centers' national poison data system. Clin Toxicol 2012;50:911–1164.
[51] Bond GR, Ho M, Woodward RW. Trends in hepatic injury associated with unintentional overdose of paracetamol (acetaminophen) with or without opioid. Drug Saf 2012;35:149–157.
[52] Rudd RA, Seth P, David F, Scholl L. Increases in drug and opioid-involved overdose deaths — United States, 2010–2015. MMWR 2016;65:1445–1452.
[53] Miller MG, Jollow DJ. Acetaminophen hepatotoxicity: studies on the mechanism of cysteamine protection. Toxicol Appl Pharmacol 1986;83:115–125.
[54] Jackson JE. Cimetidine protects against acetaminophen hepatoxicity. Vet Hum Toxicol 1981;23:7–9.
[55] Brune K. Next generation of everyday analgesics. Am J Ther 2002;9:215–223.