Concomitant overdosing of other drugs in patients with paracetamol poisoning

Lars E. Schmidt[1] & Kim Dalhoff[2]

Departments of [1]Hepatology A and [2]Clinical Pharmacology Q, Rigshospitalet, Copenhagen, Denmark

Aims Paracetamol is frequently involved in intended self-poisoning, and concomitant overdosing of other drugs is commonly reported. The purpose of the study was to investigate further concomitant drug overdose in patients with paracetamol poisoning and to evaluate its effects on the outcome of the paracetamol intoxication.

Methods Six hundred and seventy-one consecutive patients admitted with paracetamol poisoning were studied and concomitant drug intake was recorded. The relative risk of hepatic encephalopathy, death or liver transplantation, hepatic dysfunction, liver cell damage, and renal dysfunction associated with concomitant overdosing of other drugs was evaluated by multivariate analysis.

Results Concomitant drug overdose was found in 207 patients (31%, 95% confidence interval [CI] 27, 34%). Concomitant overdosing of benzodiazepines (99 cases), opioid analgesics (38 cases), acetylsalicylic acid (33 cases), and NSAID (32 cases) predominated. Concomitant benzodiazepine overdose was an independent risk factor in the development of hepatic encephalopathy (odds ratio [OR] 1.91; CI 1.00, 3.65) and renal dysfunction (OR 1.81; CI 1.00, 3.22). Concomitant overdosing of opioid analgesics was a protective factor in the development of hepatic encephalopathy (OR 0.26; CI 0.07, 0.96). Concomitant acetylsalicylic acid overdose was a risk factor in the development of hepatic encephalopathy (OR 4.87; CI 1.52, 15.7) and death or liver transplantation (OR 6.04; CI 1.69, 21.6). A tendency towards a more favourable outcome was observed in patients with concomitant NSAID overdose.

Conclusions Concomitant overdosing of benzodiazepines or analgesics is frequent in patients admitted with paracetamol poisoning. Concomitant benzodiazepine or acetylsalicylic acid overdose was associated with more severe toxicity, whereas concomitant overdosing of opioid analgesics was associated with less toxicity.

Keywords: acetaminophen, acetylsalicylic acid, benzodiazepines, cointoxication, drug interaction, liver failure, NSAID, opioid analgesics, paracetamol, poisoning

Introduction

Paracetamol (acetaminophen) is the drug most frequently involved in intended self-poisoning and the most common cause of acute liver failure in Denmark, the United Kingdom, and the United States [1–5]. In a substantial proportion of cases, the patient has concomitantly overdosed one or more other drugs in addition to paracetamol [2, 3, 6, 7]. Such drugs may affect the outcome of the paracetamol intoxication as a result of pharmacokinetic interaction with paracetamol or through independent toxic or hepato-protective properties [7–21]. Drug interactions with paracetamol may lead to reduced as well as enhanced hepatotoxicity. Suggested mechanisms of interaction include an increased or reduced rate of absorption of paracetamol, reduced conjugation of paracetamol, depletion of glutathione, and inhibition of cytochrome P450-mediated metabolism [9–16]. Independent hepatoprotective mechanisms may involve antioxidant, membrane stabilizing, or calcium channel blocking properties

Correspondence: Lars E. Schmidt, Department of Hepatology A. 2.12.1, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark. Tel.: (+45) 35 45 23 58; Fax: (+45) 35 45 29 13; E-mail: lars.schmidt@dadlnet.dk

Reprints available from: Kim Dalhoff, Department of Clinical Pharmacology Q. 7642, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark. Tel.: (+45) 35 45 75 25; Fax: (+45) 35 45 27 45; E-mail: dalhoff@rh.dk

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of drugs [17–21]. Thus, the same drug may have several and even opposing effects on the paracetamol intoxication [22]. In addition, the effects may vary with the timing and dosing of the drug [10, 17, 23]. Drugs with interactions leading to reduced hepatotoxicity may potentially be useful as antidotes in paracetamol poisoning [15].

Data on the effect of other drugs on paracetamol intoxication mainly result from animal studies [24], although interaction studies in humans receiving therapeutic doses of paracetamol have been performed and suggest a range of possible mechanisms [9, 10, 16, 22, 25–28]. In addition, a few observational studies have been made of the effect of concomitant medication or overdosing on paracetamol toxicity in humans [7, 29].

The aims of the present study were to document concomitant drug overdosing in patients with paracetamol poisoning in Denmark and to evaluate its effects on morbidity and mortality.

Methods

The charts of all patients admitted to Rigshospitalet, Copenhagen, Denmark, with paracetamol poisoning between January 1994 and December 2000 were reviewed. Patients admitted up to 1998 were studied retrospectively and those thereafter, prospectively. The former patients were identified by a computer search of the hospital registration of diagnoses. The following information was recorded for each case: age, sex, dose of paracetamol ingested, time from paracetamol ingestion to N-acetylcysteine (NAC) treatment ('time to NAC'), concomitant drugs ingested on an acute or regular basis with registration of the Anatomical Therapeutic Chemical Classification System (ATC) code, ingestion of alcohol on an acute or regular basis, nadir prothrombin index (pp), peak alanine transaminase (ALT) and creatinine, hepatic encephalopathy (HE) grade II–IV, orthotopic liver transplant (OLT) performed, and death/survival. Regular abuse of alcohol was defined as an excess of 14 units weekly for women and 21 units for men (1 unit equalling 10 g of ethanol). HE was graded according to the Fogarty criteria [30].

In accordance with the Danish recommendations, all patients with suspected paracetamol poisoning were immediately treated with NAC [31]. The standard regimen consists of an infusion of 150 mg kg^{-1} i.v. as a bolus, then 50 mg kg^{-1} over 4 h followed by repeated infusions of 100 mg kg^{-1} over 16 h until three consecutive recovering values of the prothrombin index have been demonstrated. The department of hepatology at the Copenhagen University Hospital is the tertiary care centre of liver disease in Denmark. The majority of the patients are transferred from other hospitals; however, some are admitted primarily from the local region, typically via the emergency room. Indications for considering transferral of a patient to the tertiary care centre are prothrombin index <0.40, creatinine >300 μmol l^{-1}, platelet count $<100\times10^{9}$ l^{-1}, arterial pH <7.30, or the development of HE. The department houses a specialized liver intensive care unit, where treatments such as dialysis, liver assist, mechanical ventilation, and liver transplantation may be employed. Patients fulfilling the King's College criteria are considered for orthotopic liver transplantation [32].

Statistics

For each drug group and outcome variable, a relative risk (RR) was calculated as the ratio between the observed frequencies of the variable in the patients who had taken the drug and those who had not. The RR was evaluated by univariate analysis (chi-square test with Yates' correction when appropriate). Based on the observed event incidences, a strength estimation showed that a minimum of 54 patients taking a drug was required to demonstrate a protective effect of the drug regarding survival and a minimum of 26 patients regarding HE. In order not to overlook minor effects, biochemical markers of paracetamol poisoning were included as outcome variables. For the multivariate analysis, a logistic regression analysis (STATISTICA (version 5.1, '97 Edition)) using known risk factors in paracetamol poisoning and drug groups involved in a minimum of 26 cases as independent variables was applied. Odds ratios (OR) are given with 95%-confidence intervals (CI) in parenthesis.

The Mann–Whitney test was used for the comparison of any two variables. The level of significance was set to $P<0.05$.

Results

A total of 671 patients were admitted with paracetamol overdose (101 in 1994; 90 in 1995; 74 in 1996; 99 in 1997; 109 in 1998; 108 in 1999; 90 in 2000). The charts of all patients identified by the computer search were complete. Information on medication, alcohol ingestion, biochemical and outcome parameters were available in all cases. Information on 'time to NAC' and self-reported paracetamol dose was available in 97 and 93% of cases, respectively, and in the remaining cases the charts explicitly stated that the information in question was unobtainable. All registration of data was performed by the principle author (L.S.), and no differences in the consistency or quality of data recorded retrospectively or prospectively were noticed.

The median age was 31 years (range 12–88 years). There were 448 women (67%) and 223 men. Four hundred and ninety-two patients (73%) with severe

paracetamol poisoning were transferred from other hospitals, whereas the remaining 179 patients from the local region all survived. The median paracetamol overdose was 25 g (interquartile range 16–50 g) and the median 'time to NAC' was 16 h (interquartile range 6–36 h). The self-poisoning was deliberate in 571 cases and accidental in the remaining 101 cases (15%). Alcohol was concomitantly ingested by 144 patients (21%), and 166 patients (25%) were regular abusers of alcohol. In 108 patients with HE, the maximum degree of HE was grade 2 in 5 patients, grade 3 in 26 patients, and grade 4 in 77 patients. The cause of death of the 46 patients who died without undergoing liver transplantation was liver failure or complications of liver failure ($n=44$), cardiac arrest due to severe hypothermia ($n=1$), and appendicitis with peritonitis ($n=1$). OLT was performed in seven patients with severe fulminant hepatic failure resulting in six total recoveries and one death due to postoperative complications.

Concomitant drug overdosing was registered in 207 patients (31%; 95% CI 27, 34%). In 144 cases, drugs from a single drug group were taken, whereas drugs from more than one drug group were taken in 63 cases (2 groups: 51 cases; >2 groups: 12 cases). Benzodiazepines, opioid analgesics, acetylsalicylic acid (ASA), and nonsteroid anti-inflammatory drugs (NSAID) predominated (Table 1). Co-intoxication with ASA was confirmed by blood testing. Illegal substances were registered in 11 patients (cocaine ($n=4$), cannabis ($n=4$), amphetamine ($n=2$), heroine ($n=1$)). Regular medication was registered in 294 patients (44%; 95% CI 40, 48%).

To estimate the risk of concomitant drug overdosing, HE, death or OLT, severe hepatic dysfunction (prothrombin index <0.20), liver cell damage (ALT >1000 U l^{-1}), and renal dysfunction (creatinine >200 μmol l^{-1}) were used as outcome variables. We have previously established age, dose of paracetamol, 'time to NAC', chronic alcohol abuse, and acute alcohol ingestion (Table 2) as independent risk factors in paracetamol poisoning (Schmidt *et al.* data not published). In a logistic regression analysis, using these known risk factors together with the number of drug groups taken concomitantly in overdose as independent variables, no excess risk of any outcome variable was associated with the presence of concomitant drug overdosing or with the number of drug groups involved.

In a separate analysis for each of the four predominant drug groups, an RR associated with the concomitant overdosing was calculated for each outcome variable using the background as controls (Table 3). In the logistic regression analysis, the above named known risk factors together with predominant regular medication (benzodiazepines, antidepressants, neuroleptics, paracetamol, oral contraceptives, β-adrenoceptor agonists, and opioid analgesics) and the four drug groups most frequently concomitantly overdosed were used as independent variables.

Concomitant benzodiazepine overdose was overall associated with a more severe outcome, which was partly explained by higher age, higher dose of paracetamol, and higher proportion of alcohol abusers. However, in the logistic regression analysis, concomitant benzodiazepine overdose was an independent risk factor in the development of HE (OR 1.91 (1.00, 3.65); $P<0.04$), renal dysfunction (OR 1.79 (1.00, 3.22); $P<0.05$), and marginally a risk factor for liver cell damage (OR 1.75 (0.91, 3.32); $P=0.09$).

Concomitant overdosing of opioid analgesics was an independent protective factor in the development of HE (OR 0.26 (0.07, 0.96); $P<0.05$). In 16 of the 38 cases overdosing opiates, a drug combination of ASA and codeine was ingested. This drug combination was involved in four of the five opiate related deaths.

Concomitant ASA overdose was associated with a markedly more severe outcome, despite a lower dose of paracetamol and a tendency towards reduced hepatotoxicity. In the logistic regression analysis, concomitant ASA overdose was an independent risk factor in the development of HE (OR 4.87 (1.52, 15.7); $P=0.008$) and death or OLT (OR 6.04 (1.69, 21.6); $P=0.006$), but was marginally protective against liver cell damage (OR 0.35 (0.10, 1.21); $P=0.09$). When the six ASA related deaths were reviewed, it was noticed that four of the patients presented with severe acidosis (pH 6.80, 6.90, 7.10, and 7.27, respectively), marked hypotension, and confusion or coma prior to the expected onset of hepatic failure. This is compatible with signs of severe ASA intoxication. However, the serum concentrations of ASA were only moderate (1.3, 2.0, 0.8, and 1.7 mmol l^{-1}, respectively), and well below the Danish recommended treatment threshold of 3.6 mmol l^{-1}.

Table 1 Drug groups most frequently taken in concomitant overdose with paracetamol.

Drug groups (ATC codes)	*Number of patients* (n = *671*)
Benzodiazepines (N05B + C)	99 (14.8%)
Opioid analgesics (N02A + R05D)	38 (5.7%)
Acetylsalicylic acid (N02B A)	33 (4.9%)
Non-steroid anti-inflammatory drugs (M01A)	32 (4.8%)
Neuroleptics (N05A excl. N05A N01)	18 (2.7%)
Antidepressants (N06A + N05A N01)	15 (2.2%)
Antibiotics (J01)	7 (1.0%)
Anticonvulsants (N03)	6 (0.9%)
Antihistamines (R06)	4 (0.6%)
Caffeine (A08A A56 + N02B A51)	4 (0.6%)

Table 2 Anamnestic data for patients with concomitant overdose of the most frequently taken drug groups with the background as controls. The variables (except sex) are known independent risk factors in paracetamol poisoning.

	Benzodiazepines			*Opioid analgesics*			*Acetylsalicylic acid*			*NSAID*		
	Cases (n = *99*)	*Controls* (n = *572*)	*RR*	*Cases* (n = *38*)	*Controls* (n = *633*)	*RR*	*Cases* (n = *33*)	*Controls* (n = *638*)	*RR*	*Cases* (n = *32*)	*Controls* (n = *693*)	*RR*
Age (years)	41 [34–54]	29 [21–43]⋆		35 [26–53]	31 [21–45]		29 [24–47]	31 [21–45]		29 [21–46]	31 [22–45]	
Sex (female)	71 (72%)	377 (66%)	1.09	25 (66%)	423 (67%)	0.98	23 (70%)	425 (67%)	1.05	24 (75%)	424 (66%)	1.17
Dose (g)	45 [25–50]	25 [15–50]⋆		25 [10–50]	25 [18–50]		15 [10–40]	25 [18–50]⋆		25 [13–45]	25 [18–50]	
Time to NAC (h)	16 [7–26]	17 [6–37]		19 [8–44]	16 [6–36]		14 [4–36]	17 [6–36]		8 [4–20]	17 [6–36]	
Chronic alcohol	34 (34%)	132 (23%)	1.49†	11 (29%)	155 (24%)	1.18	6 (18%)	160 (25%)	0.73	5 (16%)	161 (26%)	0.62
Acute alcohol	25 (25%)	119 (21%)	1.21	11 (29%)	133 (21%)	1.38	10 (30%)	134 (21%)	1.34	7 (22%)	137 (22%)	1.02

Dose, quantity of paracetamol; NAC, N-acetylcysteine; NSAID, nonsteroid anti-inflammatory drug.
For numerical variables are given median [1st quartile–3rd quartile]; ⋆$P<0.05$ (Mann–Whitney's test).
For frequencies are given relative risk (RR); † $P<0.05$ (chi-square test).

Table 3 Relative effect of concomitant overdose of the most frequently taken drug groups on the outcome of paracetamol intoxication.

	Benzodiazepines				*Opioid analgesics*				*Acetylsalicylic acid*				*NSAID*			
	Cases (n = *99*)	*Controls* (n = *572*)	*RR*	*OR*	*Cases* (n = *38*)	*Controls* (n = *633*)	*RR*	*OR*	*Cases* (n = *33*)	*Controls* (n = *638*)	*RR*	*OR*	*Cases* (n = *32*)	*Controls* (n = *639*)	*RR*	*OR*
HE	26 (26%)	82 (14%)	1.83⋆	1.91†	6 (16%)	102 (16%)	0.98	0.26†	8 (24%)	100 (16%)	1.55	4.87†	1 (3%)	107 (17%)	0.19⋆	0.14
Death/OLT	12 (12%)	41 (7%)	1.69	1.44	5 (13%)	48 (8%)	1.74	0.64	6 (18%)	47 (7%)	2.47⋆	6.04†	1 (3%)	52 (8%)	0.38	0.42
pp < 0.20	49 (49%)	239 (42%)	1.18	1.31	19 (50%)	269 (42%)	1.18	0.81	12 (36%)	276 (43%)	0.84	0.97	8 (25%)	280 (44%)	0.57⋆	0.58
ALT > 1000	66 (67%)	342 (60%)	1.12	1.75	20 (53%)	388 (61%)	0.86	0.53	13 (39%)	395 (62%)	0.64⋆	0.35	16 (50%)	392 (61%)	0.82	1.20
Creatinine > 200	31 (31%)	113 (20%)	1.59⋆	1.79†	10 (26%)	134 (21%)	1.24	0.81	8 (24%)	136 (21%)	1.14	1.70	4 (13%)	140 (22%)	0.57	0.60

HE, hepatic encephalopathy; OLT, liver transplant; pp, prothrombin index; ALT, alanine transaminase; NSAID, nonsteroid anti-inflammatory drug.
RR, relative risk; ⋆ $P<0.05$ (chi-square test).
OR, odds ratio from a logistic regression analysis (see text); † $P<0.05$.

Concomitant NSAID overdose showed a tendency towards a less severe outcome and was marginally significant as a protective factor in the development of HE (OR 0.14 (0.01, 1.36); $P=0.08$). In particular, no sign of increased risk of renal failure was observed.

Discussion

In the present study, 31% of the patients admitted with paracetamol poisoning had concomitantly overdosed one or more other drugs. Sedatives, analgesics, and drugs for psychiatric disorders predominated. Concomitant benzodiazepine or ASA overdose was associated with a more severe outcome, while concomitant overdosing of opioid analgesics or NSAID was associated with an improved outcome.

Availability is important in the choice of method in suicidal behaviour, which also applies to the drugs used for intended self-poisoning [33, 34]. Consequently, drugs used in self-poisoning will reflect national and regional prescribing practices [34–36]. 'Over-the-counter' (OTC) substances are easily available and are frequently involved in self-poisoning [2]. Drugs contained together in popular drug combinations are more likely to be ingested concomitantly, for therapeutic use as well as in overdose [2]. In the UK, 35% of all paracetamol is sold as drug combinations with opiates and 29% of paracetamol poisonings result from such drug combinations [2]. In 1990, half of all paracetamol related mortality in the UK resulted from a drug combination with dextropropoxyphene and was mainly attributed to the independent toxic properties of the latter [7]. In Denmark, a prescription drug combination containing paracetamol and codeine has only recently been introduced and was only used in two cases in the present study. In contrast, 86% of ASA in Denmark is sold as OTC drug combinations with codeine or caffeine, which explains the high rates of concomitant ASA and codeine overdose in the study [37]. Dextropropoxyphene is rarely prescribed in Denmark and was registered only once in the present study. On the other hand, benzodiazepines are widely prescribed, which explains the high rate of concomitant benzodiazepine overdose.

Interactions between benzodiazepines and paracetamol are not well described and not generally expected. In a recent study of paracetamol poisoning in rabbits, coadministration of diazepam (7 mg kg^{-1}) delayed morbidity and mortality, which was ascribed to a reduced gastrointestinal motility and delayed paracetamol absorption [13]. It was suggested that diazepam might be useful in the treatment of paracetamol poisoning. However, human studies with therapeutic doses of diazepam (0.2 mg kg^{-1}) or oxazepam have not shown any changes in the rate of absorption of paracetamol [10, 25, 26]. In the present study, concomitant benzodiazepine overdose resulted in an increased morbidity that may reflect additional benzodiazepine toxicity. In general, benzodiazepines have low toxicity unless taken with other CNS depressants, and deaths from benzodiazepine intoxication alone are extremely rare [38]. However, toxic doses of benzodiazepines may cause coma, respiratory depression, and hypotension, and thereby enhance the toxicity of paracetamol. Endogenous benzodiazepine-like substances are involved in the pathogenesis of liver failure and encephalopathy, and exogenous benzodiazepines are well known to provoke episodes of encephalopathy in patients with hepatic insufficiency [39, 40]. Our data do not support routine use of benzodiazepines as adjuvant treatment in patients with paracetamol poisoning. On the contrary, treating patients with concomitant paracetamol and benzodiazepine intoxication aggressively with flumazenil in order to prevent encephalopathy may be considered.

Opiates may affect the course of paracetamol intoxication by different mechanisms. Therapeutic doses of morphine and supratherapeutic doses of codeine cause a marked delay in gastric emptying and paracetamol absorption, which is likely to lead to a protective effect [10, 14, 28]. In addition, hypothermia induced by an opiate overdose may be beneficial in severe paracetamol poisoning [17]. However, independent opiate toxicity may contribute to mortality as previously described [7]. In mice, regular use of morphine may enhance paracetamol toxicity by reducing hepatic glutathione content [23].

Increased hepatic prostaglandin synthesis has been suggested as a mediator of paracetamol hepatotoxicity at a stage subsequent to toxic metabolite formation [12, 20]. Consequently, the inhibition of cyclooxygenase by ASA and NSAID may protect against paracetamol-induced hepatotoxicity [20]. In addition, NSAIDs have potentially beneficial effects on the regional blood flow of the liver, kidneys, and the brain [41–43]. Indomethacin has been suggested as a treatment of refractory intracranial hypertension in patients with HE, stroke, or traumatic brain injury [43–45]. In the present study, there was a tendency towards an improved outcome in patients with concomitant NSAID overdose. Only one of 15 patients with severe hepatotoxicity who concomitantly overdosed paracetamol and NSAID developed HE, suggesting a possible cerebral protective effect of NSAID.

Concomitant ASA overdose was associated with a marked increase in the risk of coma and death that did not involve increased hepatotoxicity. Instead, the excess mortality seemed to derive from severe ASA toxicity, and the mortality rate in this group corresponds well to that of selected patients with ASA intoxication [46,47]. In addition, ASA intoxication may result in the development of severe acidosis, which in itself is a poor prognostic

feature of paracetamol poisoning [32]. Despite the fact that the patients with concomitant ASA overdose in this study frequently presented with relatively less severe paracetamol intoxication, the main focus of the clinicians was in treating the paracetamol overdose. Our data suggest that in case of concomitant ASA and paracetamol overdose, the ASA intoxication should receive adequate attention and certainly not be overlooked. Since a discrepancy was noticed between the clinical appearance of the patient and the serum concentration of ASA, a lower treatment threshold for ASA intoxication might be considered in this category of patients.

The present study also illustrates some of the difficulties associated with obtaining reliable information on the effect of concomitant drug intake on toxicity. Even in such a large and selected population resulting in a relatively high incidence of the studied outcome variables, the strength of a study is limited and the results are open to interpretation. On the other hand, it is probably the best available source of such information. Results from animal studies cannot necessarily be extrapolated to humans, as demonstrated by the opposite effects of benzodiazepines in rabbits and humans. Human interaction studies with therapeutic drug doses cannot predict toxic effects, and studies using toxic doses are obviously not an option.

The partly retrospective design of our study may be considered a weakness. However, with the Danish registration system, patients and charts can be identified with great accuracy. At the department of hepatology, paracetamol poisoning is diagnosed routinely and a detailed account of medication is mandatory. This probably explains the high consistency and comprehensiveness of the data.

In conclusion, we found that patients admitted with paracetamol poisoning in Denmark had frequently taken concomitant overdoses of benzodiazepines or analgesics. Concomitant benzodiazepine or ASA overdose was associated with a more severe outcome that may result from the additional toxicity of these drugs. Possibly, benzodiazepine and ASA intoxication should be treated more aggressively in patients who are also paracetamol intoxicated. Concomitant overdosing of opioid analgesics or NSAID was associated with a less severe outcome.

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