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https://doi.org/10.15017/7239395

出版情報：福岡醫學雜誌. 88 (11), pp.352-357, 1997-11-25. 福岡医学会
バージョン：
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The Risk Factors of Death from the Acetaminophen Poisoning with Antipyretic-Analgesic Drugs in Japan

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Abstract Since adverse effects rarely occur with the therapeutic doses of acetaminophen, it is commonly used as a mild antipyletic and analgesic. However, overdosage of acetaminophen causes fatal hepatic failure and acute renal failure. Therefore, we evaluated the risk factors for death among the reported cases of acetaminophen poisoning in Japan, which were obtained from Japan Science and Technology Corporation, Information Center for Science and Technology (JICST) on-line service in the Kyushu University Library. In a univariate analysis, the death rate of patients with hepatic failure (23.3% vs 0%, p=0.04), disseminated intravascular coagulation syndrome (DIC) (38.1% vs 5.3%, p=0.001) or plasma exchange treatment (33.3% vs 7.9%, p=0.01) was significantly greater than those without it while a multivariate analysis revealed that DIC (with vs without; odds ratio=23.04, 95% confidence interval=2.80-189.75) and the treatment with plasma exhange (with vs without; odds ratio=14.77, 95% confidence interval=1.44-151.52) were independent risk factors. These results suggest that DIC and hepatic failure, especially requiring plasma exchange, were poor prognostic factors. In addition, about seventeen percent of the cases with less than 5 g of acetaminophen ingestion were death cases although the acute lethal adult dose is shown 13-25 g in western countries. This suggests that its acute lethal dose may be low in Japan, which may be partly due to the additional adverse effect of other drugs used in the mixed compounds while acetaminophen alone is used in western countries. An intensive treatment should be recommended for the acetaminophen poisoning patients regardless of the ingested dose.

Key words; acetaminophen, antipyletic and analgesic, overdosage, death, Japan.

Introduction

Acetaminophen (paracetamol, N-acetyl-para-aminophenol) is commonly used as mild antipyletics and analgesics. In Japan, acetaminophen is used in combination with other drugs in more than seventeen hundreds antipyletics/analgesics for symptomatic relief of pain, cough, and cold[4] because adverse effects rarely occur with the therapeutic doses of acetaminophen[1)4)5)8)9)10)]. Indeed it is considered as much safer than aspirin[4)6)8)9)10)]. However, overdosage of the drug have been associated with fatal hepatic failure and acute renal failure[1)2)4)5)8)9)10)]. Prescott[3] reported that the twenty eight patients (7.8%) had severe liver damage and the three patients (0.8%) had died from hepatic failure and the three patients (0.8%) had required hemodialysis because of renal failure among the 360 patients with acetaminophen overdosage who were transferred to the Regional Poisoning Treatment Center in Edinburgh in the United Kingdom from 1969 to 1972. In Japan, more than 20 death cases of acetaminophen poisoning were reported[3]. Therefore, we evaluated the risk factors for

death following acetaminophen poisoning in Japan.

Subjects and Methods

The author (MW) previously reviewed the 75 cases of acetaminophen poisoning in Japan[10], which were obtained from Japan Science and Technology Corporation, Information Center for Science and Technology (JICST) on-line service in the Kyushu University Library. Among them, 59 reported cases provided the dose of ingested acetaminophen, complications such as hepatic failure, renal failure and DIC, contents of treatment such as N-acetylcysteine, glutathione, hemodialysis, direct hemoperfusion and plasma exchange. The average (±SD) of age was 30.5±12.2 years old and the median of age was 27 years old ranging from 16 to 81 years old. Sixteen patients were males while 43 patients were females. The dose of ingested acetaminophen (mean±SD) was 8.4±12.1 g with the median dose of 4.8 g ranging from 1.3 to 85.0 g. The twenty nine case were reported as the death cases among these 59 cases of acetoaminophen poisoning.

In order to evaluate the various factors which may influence the death among the reported cases of acetaminophen poisoning, a case control study was carried out. Some factors which may influence the death were investigated, which were the age and gender of patients, dose of acetaminophen, complications such as hepatic failure, renal failure and disseminated intravascular coagulation syndrome (DIC), contents of treatment such as N-acetylcysteine, glutathione, hemodialysis, direct hemoperfusion and plasma exchange. The death cases were used as cases while the recovery cases were used as controls.

Statistical analysis was performed using the Statistical Analysis System package (SAS institute)[7]. Significance was determined by one way analysis of variance and the chi-square test. A multiple logistic regression analysis was used to control confounding factors. The odds ratio (OR) and their 95% conficence interval (95% CI) were then calculated for each factors on the basis of logistic regression coefficient and its standard error.

Results

As shown in Table 1, the death rate of older cases (30 years old years and older) was twice greater than those of younger cases (29 years old and younger) (24.8% vs 11.8%) but the difference failed to show the significance ($p=0.22$). In contrast, gender or dose of ingested acetaminophen did not affect the death rate of acetaminophen poisoning. Hepatic failure (with vs without; 23.3% vs 0%, $p=0.04$) and DIC (with vs without; 38.1%vs 5.3%, $p=0.001$) significantly increased the risk of death. The death rate of the patients with renal failure was twice greater than the rate of those without it (27.8% vs 12.2%) but the difference failed to show the significance ($p=0.15$). The patients treated with plasma exchange had the significantly higher death rate than those without (33.3% vs 7.9%, $p=0.01$). The death rate of the patients treated with direct hemoperfusion was twice greater than those without it (26.1% vs 11.1%) but the difference failed to show the significance ($p=0.14$). In contrast, the treatment with N-acetylcysteine, glutathione, or hemodialysis did not affect the death rate. The recently reported cases (1986 and later) had the half times smaller death rate than those reported until 1985 (12.5% vs 26.3%) but the difference failed to show the significance ($p=0.19$).

Table 2 showed the result of multiple logistic regression analysis in relation to the death

Table 1 Risk factors for the death among the reported cases of acetaminophen poisoning in Japan

		No. of reported cases	No. of death cases (%)	p-value
Age	-29 yo	34	4(11.8%)	0.22
	30+yo	25	6(24.0%)	
Gender	Female	43	8(18.6%)	0.58
	Male	16	2(12.5%)	
Dose of ACET	-4.9 g	30	5(16.7%)	0.95
	5.0 g+	29	5(17.2%)	
Complications				
Hepatic failure	without	16	0(0%)	0.04
	with	43	10(23.3%)	
Renal failure	without	41	5(12.2%)	0.15
	with	18	5(27.8%)	
DIC	without	38	2(5.3%)	0.001
	with	21	8(38.1%)	
Treatments				
NAC	without	31	6(19.4%)	0.61
	with	28	4(14.3%)	
GT	without	41	8(19.5%)	0.43
	with	18	2(11.1%)	
HD	without	36	5(13.9%)	0.44
	with	23	5(21.7%)	
DHP	without	36	4(11.1%)	0.14
	with	23	6(26.1%)	
PE	without	38	3(7.9%)	0.01
	with	21	7(33.3%)	
Calender year	-1985	19	5(26.3%)	0.19
	1986+	40	5(12.5%)	

No.: number, ACET: acetaminophen,
DIC: disseminated intravasucular coagulation syndrome,
NAC: N-acetylcysteine, GT: glutathione, HD: hemodialysis,
DHP: direct hemoperfusion, PE: plasma exchange.

Table 2 The multiple logistic regression analysis in relation to the death among the reported cases of acetaminophen poisoning in Japan.

Factors		Odds ratio	95% CI
Age (years old)	30+vs-29	2.71	0.42-17.56
Gender	male vs female	0.07	0.00-1.16
Dose of ACET (g)	5+vs-4.9	5.02	0.53-47.66
PE	with vs without	14.77	1.44-151.52
DIC	with vs without	23.04	2.80-189.75

OR; odds ratio, 95% CI; 95% confidence interval,
ACET: acetaminophen, PE: plasma exchange,
DIC: disseminated intravasucular coagulation syndrome

among the reported cases of acetaminophen poisoning. The treatment with plasma exchange (with vs without; odds ratio=14.77, 95% confidence interval=1.44-151.52) and the complication with DIC (with vs without; odds ratio=23.04, 95% confidence interval=2.80-189.75) remained the risk factor for the death.

Discussion

Since adverse effects rarely occur with the therapeutic doses of acetaminophen[1)4)5)8)9)10)], it is commonly used as a mild antipyletic and analgesic. However, overdosage of acetaminophen causes fatal hepatic failure[1)2)4)8)9)10)] and acute renal failure[1)2)4)5)8)9)10)]. Ellenhorn and Barceloux[2)] described that the minimum acute toxic dose in adults is 5-15 g and the acute lethal adult dose ranges from 13 to 25 g. In the present study, five patients (16.7%) were death cases among the 30 cases who ingested less than 5.0 g of acetaminophen. Washio et al.[9)] reported a death case of acetaminophen poisoning and reviewed the six death cases of its poisoning, which showed that the minimum dose of acetaminophen ingestion was 2.4 g. The acute lethal dose of acetaminophen seems to be lower in Japan than in western countries[8)9)10)]. This may be partly due to the additional adverse effects of other drugs such as etenzamide, bromides and caffeine because in Japan acetaminophen is used as mixed compounds in combination with other drugs while acetaminophen alone is used in western countries[8)9)10)]. Kuroki et al.[5)] showed that among the patients with acetaminophen, 92% of them ingested mixed compounds in Japan while 80% of them did acetaminophen alone in the United States.

Acetaminophen is rapidly absorbed from gastrointestinal tracts and metabolized in the liver and its metabolites is responsible for central liver necrosis after overdosage[2)]. Therefore, the prevention of its absorption is important. Unless contraindication such as coma, gastric irrigation should be done for all patients who present within 4-6 hours. In the present study, the death rate did not differ between those with smaller dose (4.9 g and less) and larger dose (5.0 g and more) of ingested acetaminophen (16.7% vs 17.2%) while the death rate was greater in those with hepatic failure (with vs without, 23.3% vs 0%, p=0.04) and with DIC (with vs without. 38.1% vs 5.3%, p=0.001). The results suggest that the dose of acetaminophen taken and the dose of actually absorbed acetaminophen seems to differ. Some patients might vomit the drug and/or receive gastric irrigation. Ingested acetaminophen might be partly removed in these patients. However, we must tell the limitation of this study. Clinicians have a tendency to report not a death case but a saved case in spite of a large dose of acetaminophem ingestion following the sucessful treatment (publication bias)[3)]. This may explain the failure to show the difference in the death rate between smaller dose and larger dose of acetaminophen ingestion.

Acetaminophen is rapidly absorbed from gastrointestinal tracts and metabolized in the liver and its metabolites is responsible for central liver necrosis after overdosage[2)]. Following administration of therapeutic dose of acetaminophen, it is extensively metabolized glucuronide and sulfate conjugates while a small fraction of a dose of acetaminophen is converted to a toxic metabolite by cytochrome p-450-dependent mixed function oxidase, which is normally trapped and made harmless by conjugation[2)]. However, the rate of formation of the toxic metabolite exceeds the maximal rate of hepatic gultathione synthesis following administration of a large dose of acetaminoph-

en[2]. Glutathione is then depleted and the excess metabolite cause liver cell damage and death[2]. Since glutathione itself does not enter cells rapidly, its precursors such as N-acetylcysteine is used to prevent liver damage following acetaminophen overdosage[2)3)]. N-acetylcysteine prevent liver damage and death following acetaminophen overdosage if given within 8 to 10 hours[3]. In the present study, however, the treatment with N-acetylcysteine (the death rate, with vs without; 14.3% vs 19.4%, $p=0.61$) or glutathione (the death rate, with vs without; 11.1% vs 19.5%, $p=0.43$) failed to show the significant preventive effect. The result may be partly explained by the limitation of this study. In the present study, we did not adjust the duration between ingestion and the start of treatment because we could not get them in all of the cases used in the study.

Ellenhorn and Barceloux[2] described that hemodialyis and peritoneal dialysis have little effect on the clinical course. In Japan, however, acetaminophen is used in combination with other drugs, hemodialysis may be effective to reduce the additional adverse effect of other drug in the mixed compounds. In the present study, the death rate was relative higher among the patients with hemodialysis treatment than those without it but failed to show the significant difference (21.7% vs 13.9%, $p=0.44$). In contrast, the patients with plasma exchage had higher death rate than those without it (33.3% vs 7.9%, $p=0.01$). The patients with severe hepatic failure should need the treatment with plasma exchage, which may explain the result.

In the multiple logistic regression analysis, the treatment with plasma exchange and the complication with DIC were independent risk factors for death. The result suggests that the patients with severe hepatic failure who need the treatment with plasma exchange and those with DIC have a poor prognosis.

In summary, the death rate of patients with hepatic failure, DIC or plasma exchange treatment was significantly greater than those without it in a univariate analysis while a multivariate analysis revealed that DIC and treatment with plasma exchange were independent risk facotrs. These results suggest that DIC and hepatic failure, especially requiring plasma exchange, were poor prognostic factors. In the present study, about seventeen percent of the cases with less than 5 g of acetaminophen ingestion were death cases although the acute lethal adult dose is shown 13-25 g in western countries[2]. This suggests that its acute lethal dose may be low in Japan, which may be partly due to the additional adverse effect of other drugs used in the mixed compounds. An intensive treatment should be recommended for the acetaminophen poisoning patients regardless of the ingested dose.

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(Received for publication October 2, 1997)

(和文抄録)

本邦における解熱鎮痛剤によるアセトアミノフェン中毒の死亡とその危険因子に関する研究

九州大学医学部公衆衛生学講座[1] 衛生学講座[2]

鷲尾昌一[1]・井上尚英[2]

常用量では副作用が少なく，安全なアセトアミノフェンは，わが国では市販の解熱鎮痛剤の主成分として広く使用されている．しかし，大量に服用すると肝不全，腎不全，播種性血管内凝固症候群(DIC)を引き起こすことが知られている．我々は九州大学医学部図書館で文献検索システム（JICST on-line service）を用い，服薬量，肝不全，腎不全，DICなどの合併症，Nアセチルシステイン(NAC)，グルタチオン，血液透析，血液吸着，血漿交換などの治療の内容が完備した59例を用いて，本邦における解熱鎮痛剤によるアセトアミノフェン中毒の死亡の危険因子を求める目的で解析をおこなった．各要因毎の解析では肝不全，血漿交換，DICが，多変量解析では血漿交換，DICが，死亡の危険因子であった．このことより，血漿交換を必要とするような肝不全やDICが，死亡の危険因子と考えられた．一方，服用量は有意の危険因子とはならなかった．その一因として嘔吐や胃洗滌のために服用量はかならずしも吸収量とは一致していないことが考えられた．欧米ではアセトアミノフェンの致死量は13-25ｇといわれているが，今回の研究では5ｇ未満の服用者の16.7%が死亡していた．このことより，日本人の致死量は欧米で言われているよりも少ないと考えられた．その一因として欧米ではアセトアミノフェン単剤の中毒であるのに対し，我が国のアセトアミノフェン中毒は配合剤による中毒であり，他の薬剤の相乗効果が存在すると考えられた．