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The analgesic effect of rescue administration of intravenous acetaminophen in cancer patients may be associated with sex and opioid dose, and the effect would appear to patients administered under 45 mg/day opioid (oral morphine equivalents)

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There have been no investigations examining the analgesic effect of rescue administration of intravenous acetaminophen (IV APAP) for pain in cancer patients. Fifty cancer patients who received IV APAP for pain at Ashiya Municipal Hospital (Hyogo, Japan) between January 2014 and July 2016 were retrospectively evaluated. The degree of pain was evaluated using a 4-point verbal rating scale. Pain intensity differences ≥ 1 defined the IV APAP effective group, and the patient' characteristics were compared by a medical chart review. Variables were extracted from medical records for logistic regression analyses of factors associated with analgesic effect. The cut-off value of opioid dose (oral morphine equivalent) was determined using receiver operator characteristic (ROC) curve analysis. Thirty eight (76%) patients experienced an analgesic effect of rescue administration of IV APAP. Sex (odds ratio [OR] 5.4014; p = 0.0397) and opioid dose used for pain control (OR 0.9901; p = 0.0147) were found to be associated with the efficacy of rescue administration of IV APAP. The cut-off value of opioid dose (oral morphine equivalent), which may be difficult to match the analgesic effect of IV APAP, was calculated to be more than 45 mg/day. This study demonstrated the efficacy of a rescue administration of IV APAP for pain in cancer patients, and revealed that sex and opioid dose may be associated with the analgesic effect. Furthermore, this study also proposes a criterion for the analgesic effect.

1. Introduction

Acetaminophen (N-acetyl-p-aminophenol [APAP]) is an aniline-based antipyretic analgesic used worldwide, and is the first step on the analgesic ladder of the World Health Organization (WHO) in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs) as a non-opioid analgesic for cancer pain treatment. APAP is available in three dosage forms (oral, suppository, intravenous [IV]); the oral and IV formulations are usually used in adults. A previous study investigating the utility of IV APAP for cancer pain reported that IV APAP reduced opioid dose, side effects and medical costs, and improved pain, patient satisfaction, and facilitated rehabilitation (Pasero and Stannard 2012). Among the three APAP dosage forms, IV administration has the advantage of immediately higher blood levels of the drug compared with oral and rectal administration (maximum concentration time [t_{max}] = 15 min) (OFIRMEV®: RxList.com.). This t_{max} is shorter than for other popular rescue opioids, namely, oral morphine sulfate (solution, t_{max} = 45 min) (Hoskin et al. 1989), oral oxycodone hydrochloride hydrate (tablet, t_{max} = 84 min) (ROXICODONE®: RxList.com.), fentanyl citrate (sublingual, t_{max} = 30 min) (ABSTRAL®: RxList.com.), and fentanyl citrate (buccal, t_{max} = 60 min) (ONSOLIS®: RxList.com.).

However, there have been no investigations examining the analgesic effect of rescue administration of IV APAP, although many previous studies involving cancer patients have reported the effect of daily administration of IV APAP over a period of several days (Stambaugh 1982; Stockler et al. 2004).

Accordingly, the present study investigated the analgesic effect of rescue administration of IV APAP for pain in cancer patients, and factors associated with the effect; we also aimed to propose a criterion for the analgesic effect.

2. Investigations and results

There were 38 (76%) patients in the IV APAP effective group. Patient demographic information and clinical backgrounds are summarized and compared in Table 1. There were significantly more men (p = 0.02) and significantly fewer opioid users in the effective group (p = 0.03). The opioid dose (oral morphine equivalent) was significantly higher in the non-effective group (p < 0.01). Furthermore, the effective group demonstrated significantly higher BUN levels (p = 0.02). The effective group tended to exhibit higher AST levels (p = 0.07). There were no significant differences in IV APAP administration rate or the number of patients between the groups. In addition, there were also no significant differences in age, pain score before IV APAP administration, IV APAP dose, the number of patients who used each opioid, NSAIDs and oral APAP, and laboratory values, except BUN.

Results of the univariate logistic-regression analysis suggested that sex (p = 0.0280) and opioid dose (oral morphine equivalent) (p = 0.0088) were factors associated with the analgesic effect of IV APAP (Table 2A), with odds ratios (ORs) of 5.1429 and 0.9904, respectively. The subsequent multivariate logistic regression analysis confirmed that sex (p = 0.0397) and opioid dose (oral morphine equivalent) (p = 0.0147) were factors significantly associated with the analgesic effect of IV APAP (Table 2B), with ORs of 5.4014 and 0.9901, respectively.

In addition, the cut-off value of opioid dose (oral morphine equivalent), which may be difficult to achieve the analgesic effect of IV APAP, was calculated to be more than 45 mg/day (Fig. 1). The area under the ROC curve was 0.7664 (95% confidence interval 0.6102 to 0.9227).

Table 1: Patient demographic information and clinical background

Characteristic	IV APAP effective group	IV APAP non-effective group	p
Age, years, mean ± SD	67.3 ± 15.9 (n = 38)	71.2 ± 7.8 (n = 12)	0.27[a]
Male / female, n	14 / 24	9 / 3	0.02[b]
Weight (kg), mean ± SD	51.2 ± 12.9 (n = 32)	48.4 ± 10.5 (n = 10)	0.53[c]
BMI (kg/m^2), median (IQR)	19.6 (17.3 - 22.6) (n = 30)	18.8 (16.2 - 20.0) (n = 10)	0.31[d]
Pain score before IV APAP administration, median (IQR)	2.0 (2.0 - 2.0) (n = 38)	2.0 (2.0 - 2.3) (n = 12)	0.47[d]
Pain score before IV APAP administration, n (%)			
3	7 (18.4)	3 (25.0)	0.76[e]
2	25 (65.8)	8 (66.7)	
1	6 (15.8)	1 (8.3)	
Opioid medication, n (%)	22 (57.9) (n = 38)	11 (91.7) (n = 12)	0.03[b]
NSAIDs medication, n (%)	18 (47.4) (n = 38)	8 (66.7) (n = 12)	0.20[b]
Oral APAP medication, n (%)	3 (7.9) (n = 38)	3 (25.0) (n = 12)	0.14[b]
Oral APAP dose (mg/day), mean ± SD	1200 ± 520 (n = 3)	1967 ± 451 (n = 3)	0.13[c]
Opioid dose, oral morphine equivalents (mg/day), median (IQR)	10.0 (0.0 - 60.0) (n = 38)	102.5 (43.8 - 247.5) (n = 12)	< 0.01[d]
IV APAP dose (mg), median (IQR)	500 (500 - 1000) (n = 38)	800 (500 - 1000) (n = 12)	0.27[d]
IV APAP dose (mg, 1000 / < 1000), n	11 / 27	6 / 6	0.16[b]
IV APAP administration rate (mL/h), median (IQR)	200 (200 - 240) (n = 38)	270 (200 - 400) (n = 12)	0.11[d]
IV APAP administration rate (mL/h, 400 / < 400), n	7 / 31	5 / 7	0.98[b]
Laboratory values before IV APAP administration			
AST (U/L), median (IQR)	29.5 (22.8 - 55.5) (n = 28)	22.5 (15.3 - 27.3) (n = 10)	0.07[d]
ALT (U/L), median (IQR)	22.0 (10.5 - 41.5) (n = 27)	27.0 (14.0 - 29.0) (n = 9)	0.87[d]
γGTP (U/L), median (IQR)	66.5 (21.5 - 194.5) (n = 26)	53.0 (35.5 - 75.3) (n = 10)	0.65[d]
Scr (mg/dL), mean ± SD	0.8 ± 0.3 (n = 28)	0.6 ± 0.2 (n = 10)	0.26[c]
BUN (mg/dL), mean ± SD	25.7 ± 13.4 (n = 28)	17.6 ± 6.4 (n = 10)	0.02[a]

[a] Welch's t test; [b] Fisher's extra test; [c] Student's t-test; [d] Mann-Whitney U test; [e] Chi-squared test. ALT, alanine aminotransferase; IV APAP, intravenous N-acetyl-p-aminophenol; AST, aspartate aminotransferase; BMI, body mass index; γGTP, gamma glutamyltransferase; Scr, serum creatinine; BUN, blood urea nitrogen; NSAIDs, non-steroidal anti-inflammatory drugs. SD indicates standard deviation. IQR indicates interquartile range.

3. Discussion

We demonstrated the efficacy of rescue administration of IV APAP for pain in cancer patients, and revealed that sex and opioid dose used for pain control may be associated with the analgesic effect. Furthermore, we also propose a cut-off value of opioid dose (oral morphine equivalent) associated with the effect (45 mg/day). To our knowledge, this is the first study to report the efficacy IV APAP, and associated factors and a criterion for the analgesic effect of rescue administration of IV APAP.

In this study, the IV APAP effective group required a significantly lower opioid dose (oral morphine equivalent); consequently, opioid dose was extracted as a factor associated with the analgesic effect of IV APAP. Because there were no significant differences in VRS between the groups before IV APAP administration, IV APAP was not able to demonstrate a clear analgesic effect for pain, when relatively high-dose opioids are required for relief.

Although the effect of concomitant use of strong opioids with APAP is currently a contentious issue. Stockler et al. (2004) reported that the concomitant use of strong opioids and APAP reinforces the analgesic effect. In contrast, Israel et al. (2010) reported that concomitant use demonstrated no such effect. We cannot directly compare our results with these studies because our study methods were different, including the pain evaluation scale and subject enrolment criteria. However, our study and previous reports agree that APAP may not clearly demonstrate an analgesic effect for pain, which usually requires relatively high opioid doses for relief. Israel et al. (2010) reported that the concomitant use of strong opioids and APAP could relieve pain in patients in whom fewer opioids were administered. Additionally, we propose a cut-off value to predict the efficacy of rescue administration of IV APAP in cancer patients based on opioid dose. If an objective criterion, such as a cut-off value, is established by accumulation of further evidence, it will significantly contribute to medical care, including aspects of risk management and cost. For example, it may facilitate the formulation of treatment plans and/or avoid unnecessary administration of IV APAP.

There were more women in the IV APAP effective group in this study, and sex was considered to be a factor associated with analgesic effect. This suggests that women can achieve an analgesic effect from IV APAP. This may be due to sex-related differences in the metabolism of APAP. Previous studies have reported that men have higher activity levels of glucuronyl transferase, which is the primary enzyme in glucuronic acid conjugation in the APAP metabolic pathway. Moreover, the clearance of APAP in males has been reported to be higher than in females (Divoll et al. 1982; Mucklow et al. 1980; Wojcicki et al. 1979). Therefore, given the differences in APAP clearance, women were more likely to experience the analgesic effect of IV APAP because the blood concentration of the drug may be higher than in men. This result provides new information about APAP, which has been a very popular drug worldwide for many years, and may require the consideration of sex differences for use in pain relief in cancer patients.

Furthermore, the IV APAP effective group demonstrated significantly higher BUN levels and tended to exhibit higher AST levels in this study. We assume that this caused an increase in the blood concentration of APAP and that the analgesic effect would appear. The main enzyme involved is cytochrome P450 (CYP) 2E1, which metabolizes 30-80% of the APAP dose. Up to approximately 25% is metabolized by CYP3A4 and CYP2D6 (Kalsi et al. 2011).

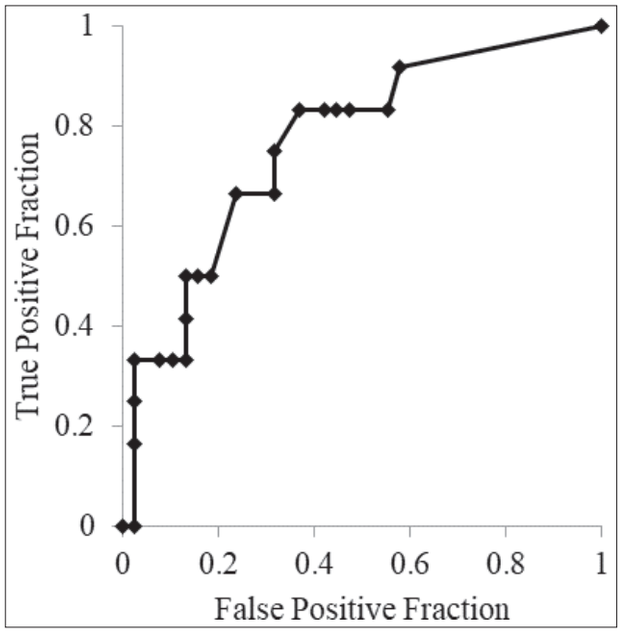

Fig. 1: Receiver operating characteristic curve for detecting the threshold of intravenous N-actyl-p-aminophenol (IV APAP) analgesic effect. IV APAP effective or non-effective were defined as dependent variables, and opioid dose was the independent variable. The square shows opioid dose (oral morphine equivalents).

Table 2: Univariate and multivariate logistic regression analyses

A: Univariate analysis

			CI of Odds ratio	
Independent variable	**p**	**Odds ratio**	**Lower 95%**	**Upper 95%**
Sex	0.0280	5.1429	1.1902	22.2221
Opioid dose, oral morphine equivalents	0.0088	0.9904	0.9833	0.9976
Blood urea nitrogen	0.0710	1.0707	0.9942	1.1531

B: Multivariate analysis

			CI of Odds ratio	
Independent variable	**p**	**Odds ratio**	**Lower 95%**	**Upper 95%**
Sex	0.0397	5.4014	1.0827	26.947
Opioid dose, oral morphine equivalents	0.0147	0.9901	0.9823	0.9981

In cases of liver function decline, the decreased activity of CYP2E and CYP3A causes an increase in the blood concentration of APAP (Frye et al. 2006). In addition, the urinary unchanged drug excretion rate of APAP was low (3-5%) after metabolization in the liver, although it exhibits exceptional pharmacokinetics when it is administered to patients with end-stage renal failure. Meanwhile, the serum APAP level increases to approximately three times that of healthy individuals and the half-life is extended to more than double (Martin et al. 1991). Despite the rescue use of IV APAP in this study, the blood concentration of APAP may become higher in patients with decreased renal function due to poor urinary excretion of glucuronic- and sulfuric acid-conjugated compounds.

In contrast, the analgesic effect of rescue administration of IV APAP did not appear to be dependent on the administration rate. It is currently appropriate for IV APAP to be administered over a period of 15 min because the blood concentration becomes almost equivalent to oral APAP if it is administered in this time interval (Mucklow et al. 1980). However, from our results, even if the administration intervals are modified according to patient situation, the analgesic effect of rescue administration of IV APAP would remain.

This study had several limitations, so that it was retrospective, single-center designed and had a small sample size. Additionally, we suspect that we were not able to capture potential changes in pain that are detected using an 11-phase scale because we evaluated pain using only a four-phase scale. A 1-point change in the pain scale has clinical importance (Jaeschke et al. 1989; Wells et al. 1993), and Hui et al. (2016) reported that even if pain scores vary by more than 1 point on an 11-phase scale, patients feel their change in symptoms. Therefore, detailed evaluations using finer-phase pain scales and additional measurements, including quality of life, will be necessary in future studies. Because we did not measure blood concentrations of APAP, we remain largely speculative about the conclusion that women experienced the analgesic effect of rescue administration of IV APAP. Measurements of blood levels of the drug will be necessary in future studies to identify the factors influencing the analgesic effect.

Nevertheless, we demonstrated the efficacy of rescue administration of IV APAP for pain in cancer patients, and reveal that sex and opioid dose used for pain control may be associated with analgesic effect; moreover, we also propose an objective criterion (i.e., a cut-off value) for its analgesic effect. In the future, enhanced pain treatment for cancer patients, including an increase in treatment options, is anticipated from additional prospective cohort studies verifying our results using different evaluation methods.

4. Experimental

4.1. Setting and patients

A total of 50 cancer patients who were administered IV APAP for pain palliation purposes between January 2014 and July 2016 at Ashiya Municipal Hospital (Hyogo, Japan) were retrospectively evaluated. From medical records, we investigated age, sex, weight, body mass index (BMI), pain score before IV APAP administration, number of individuals who were administered opioids, NSAIDs and oral APAP, opioid dose (oral morphine equivalent), IV APAP dose and number of patients according to dose, IV APAP administration rate and number of patients according to administration rate, and the levels of five laboratory parameters before IV APAP administration: blood aspartate aminotransferase (AST); blood alanine aminotransferase (ALT); blood gamma-glutamyl transpeptidase (gGTP); serum creatinine (Scr); and blood urea nitrogen (BUN). In addition, patients were classified according to whether the single IV APAP dose was > 1000 mg or ≤ 1000 mg, and also classified according to IV APAP administration rate (above or below 400 mL/h) because the full dose (100 mL) is usually administered over a period of 15 min.

4.2. Analgesic evaluation

The degree of analgesic effect before and after IV APAP administration was evaluated using a 4-point verbal rating scale (VRS), scored from 0 to 3 as follows: none = 0; weak = 1; strong = 2; and severe = 3 (Stambaugh 1982). The pain intensity difference (PID) before and after IV APAP administration was calculated and patients were divided according to PID ≥ 1 (IV APAP effective group), and PID = 0 (IV APAP non-effective group).

4.3. Factor analysis of the analgesic effect of IV APAP

Factors associated with the analgesic effect of IV APAP were identified using univariate and multivariate logistic regression analyses. In the univariate analysis, sex, opioid dose (oral morphine equivalent), and BUN level before IV APAP administration were defined as independent variables and, based on the significant differences reported in Table 1, were divided and defined as IV APAP effective or non-effective as the dependent variables in each. According to the results of the univariate analysis, items with a statistically significant difference (i.e., $p < 0.05$) to independent variables were carried into the multivariate analysis with IV APAP effective or non-effective as the dependent variables.

4.4. Cut-off value determination of opioid dose (oral morphine equivalent) to assess analgesic effect

The cut-off value of opioid dose (oral morphine equivalent) was determined by plotting a receiver operator characteristic (ROC) curve. IV APAP effective or non-effective were defined as dependent variables, and opioid dose (oral morphine equivalent) was the independent variable.

4.5. Statistical analysis

Comparisons of age and BUN level at IV APAP administration were evaluated using Welch's *t* test. The ratio of men to women, the number of patients who used each opioid, NSAIDs and oral APAP, the number of patients according to IV APAP dose, and the number of patients according to IV APAP administration rate were evaluated using the Fisher's exact probability test. Additionally, the Student's *t*-test was used to compare weight, oral APAP dose and Scr level. BMI, pain score before IV APAP administration, opioid dose (oral morphine equivalent), IV APAP dose, IV

APAP administration rate, and AST, ALT, and gGTP levels were compared using the Mann-Whitney U-test. The chi-squared test was used to compare the number of patients defined by pain score before IV APAP administration. Statistical analysis was performed using Bell Curve (Social Survey Research Information Co., Ltd., Tokyo, Japan) for Excel (Microsoft Corporation, Redmond, WA, USA); the level of significance was set at 5%.

4.6. Ethical approval

All patients provided written informed consent to participate in the study, which was conducted with the approval of the Ethics Review Board of Ashiya Municipal Hospital (approval number, 34).

Conflicts of interest: The authors declare no that there is no conflict of interest.

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