SINGLE DOSE PHARMACOKINETIC COMPARATIVE STUDIES BETWEEN INTRAMUSCULAR ACETAMINOPHEN FORMULATION WITH AND WITHOUT LIDOCAINE IN HEALTHY THAI VOLUNTEERS

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ABSTRACT

The pharmacokinetics of two commercial brands of intramuscular acetaminophen formulation, with and without lidocaine, were studied and compared in nine healthy Thai male volunteers after a single intramuscular dose. No significant differences ($P > 0.05$) in the volume of distribution (V_d), plasma drug clearance(Cl_p) and area under the concentration-time curve (AUC) between the two formulations were observed, however, there were significant differences ($P < 0.05$) in the absorption rate constant (K_a), absorption half-life [$t_{½}$ (abs)], and peak plasma concentration (C_{max}) between the two intramuscular acetaminophen formulations ($3.79 \pm 1.32\ h^{-1}$, 0.20 ± 0.07 h, and $4.08 \pm 0.52 \mu g.ml^{-1}$ for acetaminophen 300 mg VS $2.55 \pm 0.66\ h^{-1}$, 0.29 ± 0.07 h, and $3.68 \pm 0.45\ \mu g.ml^{-1}$ for acetaminophen 300 mg plus lidocaine 20 mg, respectively) used in this study. These data indicate that the absorption rate of acetaminophen in the formulation with lidocaine was significantly reduced . The C_{max} acetaminophen in the presence of lidocaine was also reduced($P < 0.05$). However, the C_{max} of these two formulations were lower than the lower limit of plasma acetaminophen effective concentrations (10 - 20 $\mu g.ml^{-1}$). Therefore, it is doubtful whether these two intramuscular acetaminophen formulations are useful for their analgesic antipyretic actions.

Keywords: acetaminophen, pharmacokinetic, lidocaine, intramuscular.

INTRODUCTION

Acetaminophen, usually called paracetamol in some regions of the world , was first introduced in medical treatment by Von Mering in 1893[1]. It has antipyretic and analgesic properties similar to aspirin [2] but it is well tolerated and produces fewer side effects than aspirin[3].Unlike aspirin, acetaminophen has only weak anti-inflammatory activity. At therapeutic doses acetaminophen is a very safe analgesic drug. It may produce acute centrilobular hepatic necrosis when taken in overdose[4].The incidence of acetaminophen overdose steadily increase as its use (instead of aspirin) as an antipyretic and analgesic increase[3,5].

Currently, several acetaminophen dosage forms are commercially available in the market as elixir, syrup, tablet, rectal suppository and formulation for intramuscular injection. Pharmacokinetic data of acetaminophen were reported after intravenous and oral administration[6]. However, comparative pharmacokinetic studies among the intramuscular acetaminophen formulations in healthy Thai male subjects have not been performed. In Thailand, the intramuscular acetaminophen dosage form is often prescribed by some physicians when rapid antipyretic and analgesic actions are desired. The acetaminophen formulations for intramuscular injection in Thailand are quite different among the pharmaceutical manufactures. However, it differs only the lidocaine hydrochloride containing in the formulations. The widely used intramuscular formulations are those which contain only acetaminophen 300 mg or formulation containing acetaminophen 300 mg plus lidocaine hydrochloride 20 mg dissolved in 2 ml steriled vehicle for injection. Lidocaine remains one of the most frequently used antiarrhythmic drugs for the treatment of acute ventricular arrhythmias following myocardial infarction, including digitalis toxicity[7,8]. The other widely use of lidocaine is as local anesthetic for infiltration to reduce pain [9].The purpose of adding lidocaine in the formulation is to reduce pain at the injection site because it has a local anesthetic activity. At present, comparative studies on pharmacokinetic among acetaminophen intramuscular formulations have not been investigated in healthy Thai male subjects. Thus, this study was designed to compare the kinetics of the two brands of intramuscular acetaminophen formulations obtained from the same pharmaceutical manufacturer in healthy volunteers and also to investigate the effect of lidocaine which was added into the intramuscular acetaminophen formulation on the pharmacokinetic of acetaminophen as well.

MATERIALS AND METHODS

Subjects

Nine adult healthy Thai male volunteers aged 17-32 years and weighing 54-69 kg. They gave written informed consent to the study which was approved by the Ethics Committee for Human Experimentation, Faculty of Science, Prince of Songkla University, Hat Yai, Thailand. The subjects were considered to be healthy on the basis of medical history, physical examination and routine laboratory tests (CBC, renal and liver function tests). They were all non-smokers but some took coffee or alcohol occasionally. Subjects were asked to abstain from any medications, alcohol or coffee 2 weeks prior to the study and during the study.

Drugs

The standard acetaminophen was obtained from Sigma Chemical Co. (St. Louis, Mo, U.S.A.). Two commercial brands of acetaminophen formulation for intramuscular injection which were manufactured and marketed in Thailand by the same Pharmaceutical manufacturer were selected for this study. One contains only acetaminophen 300 mg, the other comprises of acetaminophen 300 mg and lidocaine hydrochloride 20 mg. All ingredients were dissolved in 2 ml of steriled vehicle for intramuscular use only.

Drug administration

The present series of investigation comprised of two separated phase-randomized crossover studies, performing at 3 weeks apart. The experimental design was identical in each phase. A single intramuscular dose of each commercial brand of acetaminophen formulation was given to each subject. They were administered in a 2 ml volume by intramuscular injection into the deltoid muscle. An intravenous catheter cannula NO. 20G (Nipro Safelet Cath ®, Nipro Medical Industries Ltd., Japan) was inserted into a forearm vein and kept patent with heparinized saline (heparin 5 $IU.ml^{-1}$). Venous blood samples (5 ml) were collected in heparinized tubes (heparin 1 $IU.ml^{-1}$ blood) before and at 10,20,30,45 minutes, 1,1.5,2,3,4,6 and 8 h after drug administration. The venous blood samples were immediately centrifuged at 3000 rpm for 10 minutes, then plasma was separated and frozen at -20°C until analyzed.

Acetaminophen analysis

Plasma acetaminophen was determined by high performance liquid chromatography (HPLC) with ultraviolet detection as described previously. [10] The HPLC system consisted of a Jasco PU-980 pump, a Rheodyne injector with a 20 µl sample loop and a Jasco UV 975 detector. Detection was made with the variable wave length UV detector set at 254 nm and peak area was measured with a Jasco 807-IT integrator. A Jasco recorder attenuation was set at 32 and chart speed was 2 mm per minute. Separation was achieved on reversed-phase µ-Bondapak C18 column (30 cm × 3.9 mm I.D., Particle size 10 µm). A guard-pack precolumn module was used to obviate the effect of rapid column degeneration. The mobile phase was 5% acetonitrile in 95% 20 mM orthophosphoric acid and adjusted to pH 3.0 with 20% potassium hydroxide. The flow rate was 2 ml per minute. The calibration curve for acetaminophen peak area was linear in the concentration range of 1 - 20 $\mu g.ml^{-1}$ ($r = 0.999$). Coefficient of variations of mean normalised peak area at the calculated concentration in this study were less than 5%. An average recovery of acetaminophen from plasma was above 95%.

Pharmacokinetic analysis

The kinetic behavior of acetaminophen was described by mathematical functions derived from a one-compartment model in which the distribution of the drug between blood and tissues is instantaneous and the elimination of the drug is a first-order process. [11] The maximum plasma acetaminophen concentration (C_{max}) and the time at which these were reached (t_{max}) were obtained by inspection of plasma concentration versus time profiles. The elimination rate constant (K_e) was estimated and determined by linear least-square regression analysis of the linear

segment of the log plasma drug concentration-time profile. The half life ($t_{½}$) of drug were calculated simply by dividing K_e into 0.693. Area under the concentration-time curve (AUC) for each acetaminophen formulation were calculated by the linear trapezoidal method. Plasma drug clearance (Cl_p) were determined by Dose/AUC. The volume of distribution (V_d) were estimated from Cl_p / K_e . The absorption rate constant (K_a) were determined by the method of residuals and the absorption half-life, $t_{½}$ (abs) was calculated by dividing K_a by 0.693.

Statistical analysis

Pharmacokinetic parameters of acetaminophen after administration of each commercial brand formulation were compared by the Student's paired, two-tailed t-test with differences considered significant at $P< 0.05$. Data were presented as the mean ± SD. (n = 9). In addition, the 95% confidence interval for the difference between mean values was calculated.

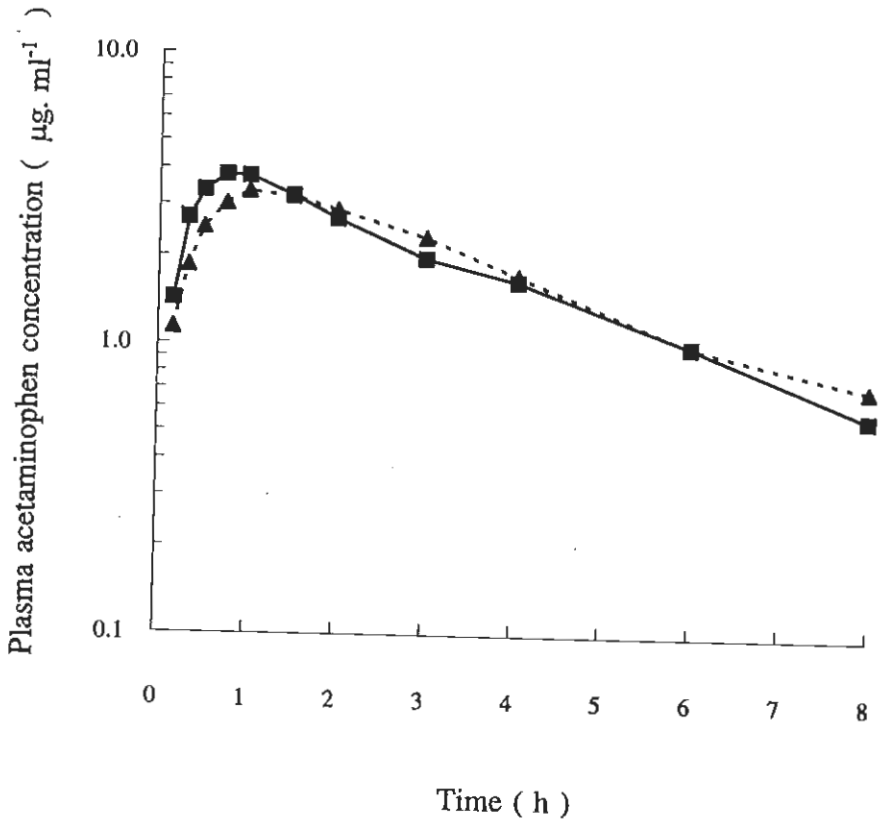

Figure 1. Mean plasma acetaminophen concentrations of two commercial brands of intramuscular acetaminophen formulations after single intramuscular dose in nine healthy subjects (Acetaminophen 300 mg: ■—■; Acetaminophen 300 mg plus lidocaine 20 mg: ▲- -▲).

RESULTS

Nine adult male healthy Thai volunteers enrolled and completed this study. There were no reported medical events in all phases of the study. The mean plasma concentrations versus time profiles and pharmacokinetic parameters (mean ± SD) for each commercial brand of intramuscular acetaminophen formulation, with and without lidocaine, are illustrated in Fig. 1 and shown in Table 1, respectively. There were significant difference ($P < 0.05$) in C_{max}, $t_{½}$ (abs) and K_a between the two intramuscular acetaminophen formulations used in this study. Comparison on the basis of C_{max}, $t_{½}$ (abs) and K_a of these two formulations, it suggested that lidocaine reduced the absorption rate of acetaminophen and its peak plasma concentration after intramuscular administration. However, It was noted that C_{max} of both intramuscular acetaminophen formulations were 4.08 ± 0.52 and 3.68 ± 0.45 $\mu g.ml^{-1}$, respectively.

Table 1 Pharmacokinetic parameters of acetaminophen after a single intramuscular dose of two drug formulations in nine healthy subjects. Values are presented as mean ± s.d.(n = 9).

Pharmacokinetic parameters	*Acetaminophen formulations*[a]				
	Acetaminophen 300 mg	*Acetaminophen 300 mg plus lidocaine HCl 20 mg*	*P value*	*Mean difference*	*95% confidence interval of the difference*
C_{max} ($\mu g.ml^{-1}$)	4.08 ± 0.52	3.68 ± 0.45	S (P = 0.0326)	-0.3989	-0.7553 to -0.0425
t_{max} (h)	0.86 ± 0.18	1.14 ± 0.44	NS (P = 0.1175)	0.2778	-0.0874 to 0.6430
$t_{1/2}$ (abs) (h)	0.20 ± 0.07	0.29 ± 0.07	S (P = 0.0216)	0.0856	0.0163 to 0.1549
$t_{1/2}$ (h)	2.50 ± 0.72	2.60 ± 0.63	NS (P = 0.6516)	0.1011	-0.3961 to 0.5984
V_d ($L.kg^{-1}$)	1.01 ± 0.17	1.10 ± 0.29	NS (P = 0.3201)	0.0878	-0.1032 to 0.2787
K_a (h^{-1})	3.79 ± 1.32	2.55 ± 0.66	S (P = 0.0230)	-1.2389	-2.2573 to -0.2205
K_e (h^{-1})	0.31 ± 0.13	0.28 ± 0.08	NS (P = 0.5339)	-0.0222	-0.1011 to 0.0566
AUC ($\mu g.ml^{-1}.h$)	14.64 ± 2.42	14.27 ± 2.79	NS (P = 0.4031)	-0.3700	-1.3365 to 0.5965
Cl_p ($ml.min^{-1}.kg^{-1}$)	5.02 ± 1.74	5.07 ± 1.52	NS (P = 0.8342)	0.0478	-0.4618 to 0.5574

[a] Commercial brands of intramuscular formulation and produced by the same pharmaceutical manufacturer

S : Significant difference ($P < 0.05$)

NS : Not significant difference ($P > 0.05$)

DISCUSSION AND CONCLUSION

Acetaminophen is an over-the-counter analgesic and antipyretic widely used either alone or in fixed combination. Commercial brands of intramuscular acetaminophen formulations are often prescribed by some physicians both in private clinics and hospitals. At present, we still do not have any information of the comparative studies on pharmacokinetic data of various intramuscular acetaminophen formulations in healthy subjects. However, disposition and absorption of several acetaminophen dosage forms have been demonstrated both in normal and diseased human subjects. Acetaminophen is poorly absorbed from the stomach but its absorption occurs mainly in the small intestine by passive diffusion with first-order kinetics, therefore, the rate of absorption depends on the gastric emptying rate [1,11]. In healthy subjects, acetaminophen is well absorbed from the gastrointestinal tract after oral administration. It has a volume of distribution of approximately 0.9 litre.kg $^{-1}$ (V_d). The plasma half-life ($t_{\frac{1}{2}}$) ranges from 1.9 to 2.5 h and the total body clearance from 4.5 to 5.5 ml.kg $^{-1}$. min $^{-1}$[1]. In addition, acetaminophen is also well absorbed from the rectum, even though the rate of absorption is slower than following oral administration[12,13]. Mean peak plasma acetaminophen concentrations in fasting healthy subjects occur within 15-30 min following an oral solution administration[14] ;and at 20 min[15] , 60 min[16] and 1.4 h[17] after ingestion of acetaminophen tablets. In the present study , mean peak plasma acetaminophen concentrations of the formulation with and without lidocaine occurred at 1.14 ± 0.44 and 0.86 ± 0.18 h ($P > 0.05$), respectively after intramuscular administration. We also found that C_{max}, $t_{\frac{1}{2}}$ (abs) and K_a of these two intramuscular acetaminophen formulations, with and without lidocaine, were significantly different ($P < 0.05$). Therefore, we suggested that lidocaine, added into the formulation altered the acetaminophen pharmacokinetics by reducing the rate of acetaminophen absorption after intramuscular administration. Mean peak plasma acetaminophen concentration(C_{max}) was also decreased in the lidocaine-added formulation. However, all pharmacokinetic parameter values except C_{max} of the two commercial brands of intramuscular acetaminophen formulation in healthy volunteers were similar to the previously reported by many investigators. It must be noted that C_{max} of the two intramuscular acetaminophen formulations, with and without lidocaine, used in this study were 3.86 ± 0.45 and 4.08 ± 0.52 μg.ml $^{-1}$) respectively, which were lower than the lower limit of the plasma acetaminophen effective concentrations for analgesic and antipyresis (10-20 μg. ml^{-1})[1,6]. According to these data, we suggested that a physician should carefully consider before prescribing these two intramuscular acetaminophen formulations to the patients for their analgesic and antipyretic actions. The doses of intramuscular acetaminophen injection given to patients should be increased to achieve the plasma therapeutic level.

In summary, our study has demonstrated that the intramuscular acetaminophen formulation with lidocaine compared to that without lidocaine was only significantly different in C_{max} , $t_{\frac{1}{2}}$ (abs) and K_a . Therefore, we can imply that lidocaine added into the intramuscular formulation alters the C_{max} , $t_{\frac{1}{2}}$ (abs) and K_a of acetaminophen, which reflect to the decrease in acetaminophen absorption rate after intramuscular administration. Its peak plasma concentration of the formulation with lidocaine was also reduced by

lidocaine as evidence shown by decreasing C_{max} . However, the results in this study presented here also showed that C_{max} of these two intramuscular acetaminophen formulations are much lower than the lower limit of plasma acetaminophen effective concentrations. For more information, our next study will compare the pharmacokinetic parameters among different brand names of intramuscular acetaminophen formulation produced by several pharmaceutical manufacturers in Thailand in normal subjects. These studies would provide more information to a physician for decision making for drug selection which intramuscular acetaminophen formulation should be prescribed or avoided in medical practice.

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