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SHORT COMMUNICATION

PHARMACOKINETICS OF ACETAMINOPHEN AFTER INTRAMUSCULAR ADMINISTRATION

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INTRODUCTION

Acetaminophen is extensively used as an over-the-counter mild analgesic and antipyretic. Data on the pharmacokinetics of acetaminophen are exclusively based on its intravenous and oral administration in humans.[1–3]

Recently, an intramuscular injection was developed to provide a more convenient route of administration when the patient's disease precludes oral dosing. Since the rate and extent of absorption of intramuscularly injected drugs are unpredictable,[4–7] a study was undertaken to examine acetaminophen kinetics following intramuscular administration to human volunteers.

MATERIALS AND METHODS

Subjects

Six healthy male volunteers aged 27 to 38 years and weighing 55 to 78 kg enrolled in and completed participation in the study. The volunteers were informed of the nature and the aim of the study and made themselves acquainted with the protocol. No other medications were taken during the period beginning at least 2 weeks prior to, and during, the study.

Study protocol

Subjects received on separate occasions (at least 1 week apart) 300 and 600 mg acetaminophen as intramuscular injections (Apotel®) in the buttock. Thus, each

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volunteer received intramuscularly one 2 ml or two 2 ml injections of a solution containing 300 mg of acetaminophen in a mixture of water and organic solvents.

Venous blood samples (~ 3 ml) were withdrawn through an indwelling cannula into heparinized tubes at frequent time intervals. The blood was centrifuged and the plasma was harvested into plastic tubes, immediately frozen, and kept at -20° until the analysis.

Drug assay

Plasma samples were analysed by a high performance liquid chromatographic method[8] slightly modified in that 13 per cent (v/v) of methanol, 0·75 per cent (v/v) of acetic acid in 0·02M sodium acetate was used as the mobile phase.

RESULTS AND DISCUSSION

The plasma concentration of acetaminophen versus time plots after intramuscular doses of 300 and 600 mg of the drug are shown in Figures 1 and 2, respectively. As depicted in Figure 1, the data obtained after intramuscular administration of 300 mg doses fell into two distinct groups. In the first group, the volunteers (Figure 1(B)) showed fast absorption while volunteers in the second group absorbed the drug relatively slowly, (Figure 1 (A)). The most plausible explanation for these findings is that the injections into three of the volunteers were actually delivered into fat in spite of the fact that all injections were intended to be intramuscular. Although little is known about the differences in availability of drugs after intramuscular of intra-adipose

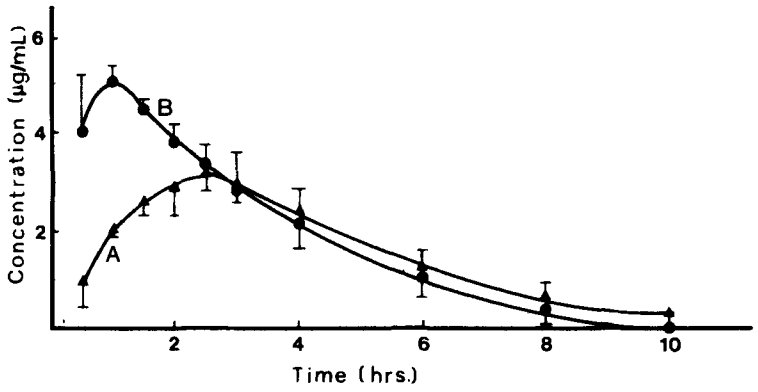

Figure 1. Plasma concentrations of acetaminophen ± SD after the intramuscular administration of 300 mg to six volunteers. The data have been divided into two groups (n=3); one exhibiting relatively slow absorption (A) and the other faster absorption (B)

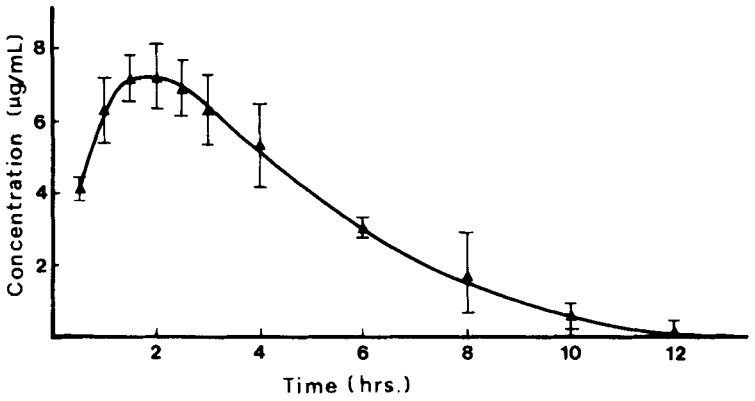

Figure 2. Plasma concentrations of acetaminophen ± SD after the intramuscular administration of 600 mg to six volunteers

injections, there are some reports[9-11] in the literature which support this explanation. Thus, sex differences in absorption of cephadrine and dapsone[10] after intramuscular administration have been observed and attributed to the greater thickness of gluteal fat in females than in men. It seems likely, therefore, that the higher levels and more rapid absorption occurred when the drug was injected into the muscle (Figure 1 (B)), and the lower plasma concentration profile was obtained after injection into the fat (Figure 1(A)). It is interesting to note that the three volunteers exhibiting relatively slow absorption (Figure 1(A)) were all heavier (average weight 75 kg) than the three faster-absorbing volunteers (average weight 64 kg, (Figure 1(B)). The weight difference will certainly be associated with a corresponding difference in the thickness of gluteal fat.

In contrast to the 300 mg dose data, the administration of 600 mg acetaminophen resulted in consistent absorption in all subjects (Figure 2). The differences in the rates of absorption at the two dose levels are probably linked with the different volumes of the solution administered.[12] It is likely that the absorption of drug from the lower dose was relatively slow because the drug remained in a very localized depot of 2 ml volume. Further, the rate of absorption of drug from the lower dose was variable and dependent upon the actual site (muscle or fat) to which the 2 ml of solution was delivered. The higher dose (600 mg), administered as 4 ml of solution, would no doubt diffuse to a larger area of tissue thus enhancing the rate of absorption and avoiding the localization in fat.

The graphically estimated pharmacokinetic parameters (C_{max}, t_{max}, and AUC) for the two treatments are presented in Table 1. Differences in the extent of bioavailability as measured by AUC_{0-10h} for the slow and fast absorbing

Table 1. Summary of the pharmacokinetic parameters, mean ± SD, obtained after intramuscular administration of 600 and 300 mg of acetaminophen to six healthy volunteers

Parameters	600 mg	300 mg		
		Group A*	Group B†	Levels of significance‡
C_{max}(μg ml^{-1})	7·52 ± 0·51	3·36 ± 0·58	5·18 ± 0·24	$p<0·01$
t_{max} (h)	1·7 ± 0·4	2·5 ± 0·0	0·8 ± 0·3	$p<0·01$
AUC (μg.h.ml^{-1})	37·46 ± 7·71§	16·28 ± 4·70[11]	18·23 ± 3·17[11]	N.S

* Corresponds to the data of Figure 1 (A).
† Corresponds to the data of Figure 1 (B).
‡ Probability of equivalence between the values of the parameters of Groups A and B as determined by t-test; N.S. at $p \square 0·05$ levels.
§ AUC to 12 h
[11] AUC to 10 h.

volunteers groups, administered 300 mg acetaminophen doses, were not statistically significant at the p=0·05 level. However, the differences in bioavailability rate parameters, C_{max} and t_{max}, were statistically significant.

In conclusion, the results of the present study indicate that the absorption of acetaminophen after intramuscular administration of 600 mg dose in 4 ml of solution, is consistent; the resulting plasma levels are comparable to those obtained after oral administration of an equivalent dose.[8,13] The erratic absorption of acetaminophen observed when the lower dose was administered in 2 ml of solution, revealed that the gluteal injections intended to be intramuscular, but which were in fact delivered to fatty tissues, were slowly absorbed. In general, the rate of acetaminophen absorption following intramuscular injection is slower than that after oral administration of the same dose.[8,13] Nevertheless, the slower absorption results in plasma levels which are above that level needed for therapeutic effectiveness. This is exemplified by the data in Figure 2 where plasma levels higher than 5 μg ml^{-1} are maintained for more than 3 h. Thus, when oral dosing is precluded, the use of 600 mg intrasmuscular doses in 4 ml of solution may be appropriate since the absorption of drug is consistent and therapeutic levels would be achieved. Moreover, the intramuscular route avoids the loss of 20 per cent of drug due to the first-pass effect associated with oral dosing.[14]

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