Ibopamine (SK&F 100168) pharmacokinetics in relation to the timing of meals

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The effect of the timing of a standard meal relative to a single oral dose of 200 mg ibopamine, on the appearance of its pharmacologically active metabolite, epinine, in plasma was investigated in a randomised crossover study in 12 healthy volunteers. After a 12 h fast, ibopamine was administered either in the fasting state (no meal), or 1 h before, 0.5 h before, immediately after, 2 h after or 3 h after a standardised meal. Blood samples taken immediately before and at intervals for 3 h after dosing were analysed for free epinine. Maximum concentration ($C_{\max}$), time to $C_{\max}$ ($t_{\max}$), and area under the concentration-time curve (AUC) for free epinine in plasma were calculated. When compared with the fasting state, $C_{\max}$ and AUC_{0-3h} were significantly reduced when ibopamine was given immediately after or 2 h after a meal. AUC was also reduced for ibopamine given 0.5 h before a meal. $t_{\max}$ was significantly delayed when ibopamine was given immediately after, or 2 or 3 h after a meal. Thus, administration of ibopamine with or shortly after a meal reduced the rate and extent of appearance of free epinine in plasma. The clinical significance of reduced epinine levels on acute dosing in the presence of food is unknown.

Keywords ibopamine epinine food effects pharmacokinetics healthy volunteers

Introduction

Ibopamine, SK&F 100168 (*N*-methyldopamine *O*, *O'* diisobutyryl ester hydrochloride) is an orally administered analogue of dopamine possessing inotropic and vasodilator activity which is currently being developed for the treatment of congestive heart failure. Following oral administration ibopamine is hydrolysed to epinine (*N*-methyldopamine), which is thought to be responsible for the pharmacological effects (Leier *et al.*, 1986). Studies *in vitro* have demonstrated that the hydrolysis of ibopamine is accomplished very rapidly by plasma esterases (Pocchiari *et al.*, 1986) but the site of hydrolysis of ibopamine *in vivo* is not yet known. In man, epinine undergoes extensive 'first-pass' metabolism, being rapidly conjugated with sulphate by phenol-sulphotransferase, an enzyme widely distributed in gut mucosa, liver, platelets and brain (Anderson & Weinshilboum, 1980).

Since both food and fluid intake influence drug absorption and metabolism, particularly

where the drug undergoes extensive first pass metabolism (Welling, 1977), the present study was designed to assess the effects of the timing of a standard meal in relation to a single oral dose of 200 mg ibopamine on the levels of free epinine in the plasma of healthy volunteers.

Methods

Twelve healthy subjects (six male, six female, mean age 25.4 years, mean weight 68.2 kg) gave written informed consent to participate in the study, the protocol for which had been approved by a local independent Ethics Review Committee. After an overnight fast, each subject received a single oral dose of 200 mg ibopamine either in the fasting state (no meal), or 1 h before, 0.5 h before, immediately after, 2 h after or 3 h after a standardised meal on six separate occasions in a balanced, randomised order. Consecutive study days for each subject were at least 6 days apart.

The 483 kcal standardised meal comprised milk, cheese, bread, marmalade and orange juice and consisted of 19% protein, 35.5% fat and 45.5% carbohydrate. Blood samples (8ml) were collected before the dose of ibopamine and at 10, 20, 30, 40, 60, 80, 100, 120, 150 and 180 min after dosing for estimation of plasma free epinine.

Maximum concentrations of epinine ($C_{\max}$), time to maximum concentration ($t_{\max}$), and area under the plasma concentration-time curve (AUC_{0-3}) over the sampling period were calculated. Analysis of variance was performed on these three parameters, using the residual mean square to estimate 95% confidence intervals (C.I.) for the difference in response between the five fed states and the fasted state.

Results

Figure 1 shows the mean plasma free epinine concentrations for the 12 subjects over the 3 h sampling period for each treatment. Table 1 shows mean values for $C_{\max}$, $t_{\max}$ and AUC_{0-3} for the six treatments.

$C_{\max}$ was significantly reduced when ibopamine was taken immediately after (-10.6 ng ml $^{-1}$, 95% CI -17.7 , -3.5) and 2 h after the meal (-5.9 ng ml $^{-1}$, 95% CI -12.9 , 1.2), compared with the fasting state.

$t_{\max}$ was significantly delayed when compared with the fasting state, when ibopamine was taken immediately after ($+31.2$ min, 95% CI 0.7 , 61.7), 2 h after ($+65.1$ min, 95% CI 34.6 , 95.6) and 3 h after the meal ($+35.0$ min, 95% CI 4.5 , 65.5).

There was statistical evidence that AUC_{0-3} differed from the fasting state in three situations, being reduced when ibopamine was given 0.5 h before (-248 ng ml $^{-1}$ min, 95% CI -499 , -3), immediately after (-499 ng ml $^{-1}$ min, 95% CI -750 , -248) and 2 h after the meal (-275 ng ml $^{-1}$ min, 95% CI -526 , -24).

Ibopamine was well tolerated. Two subjects experienced headache on one occasion each, although on different dosing sequences. These events were considered to be possibly drug-related.

Discussion

When compared with plasma levels of free epinine in the fasting state, $C_{\max}$ and AUC_{0-3} were significantly reduced when 200 mg ibopamine was given immediately after or 2 h after a standardised meal. AUC_{0-3} was also significantly reduced when ibopamine was given 0.5 h before the meal. In addition, $t_{\max}$ was significantly delayed when ibopamine was given immediately after, 2 h after or 3 h after the meal when compared with the fasted state. Thus, administration of ibopamine with or shortly after a meal reduced the rate and extent of appearance of free epinine, the pharmacologically active metabolite, in the plasma.

There are two possible explanations for this. Firstly, since most drugs are absorbed from the small intestine and it is known that meals delay gastric emptying (Welling, 1977), this would result in a delay in absorption and hence in the

Figure 1 Mean plasma free epinine concentration after ibopamine 200 mg given at different time intervals in relation to a meal ($n = 12$). ■ no meal, □ 1 h before meal, ● 0.5 h before meal, ○ end of meal, ▲ 2 h after meal and △ 3 h after meal.

Table 1 Mean values with standard error of difference for $C_{\max}$, $t_{\max}$ and AUC_{0-3} for each of the treatments

	$C_{\max}$ ($ng\ ml^{-1}$)	$t_{\max}$ (min)	AUC_{0-3} ($ng\ ml^{-1}\ min$)
No meal	17.31	41.7	904
1 h before meal	20.96	32.0	922
0.5 h before meal	16.76	35.5	656
End of meal	6.72	72.9	405
2 h after meal	11.43	106.8	629
3 h after meal	17.35	76.7	850
SED	2.608	11.27	92.6

appearance of epinine in the plasma. The change in gastric emptying would also result in retention of ibopamine in the acidic environment of the stomach for longer, and under these conditions ibopamine may be more easily hydrolysed to epinine. Epinine has a lower relative bioavailability than a molar equivalent amount of ibopamine (Boyce *et al.*, 1985), hence a reduced gastric emptying rate could also account for the reduced plasma free epinine levels found when ibopamine was given shortly after food.

Secondly, saturation of liver enzymes by epinine could result in higher plasma levels of free epinine under fasting conditions. Under such conditions, absorption of ibopamine and its hydrolysis to epinine may occur more rapidly, effectively presenting phenolsulphotransferase in the liver with a bolus dose of epinine. If the enzyme is rapidly saturable by epinine, sulphoconjugation may be reduced and the proportion of free epinine remaining in the plasma higher. Conversely, the reduced gastric emptying caused by meals may result in smaller amounts of epinine being presented to phenolsulphotransferase over

a longer time period. Under these conditions the enzyme would not become saturated, resulting in higher levels of sulphate conjugates and lower bioavailability of free epinine in the plasma. Plasma levels of epinine sulphate were not measured in this study, so this hypothesis could not be tested.

These results broadly support the findings of a similar study carried out by Smith Kline & French in Germany (de Mey *et al.*, 1986). Since reduced bioavailability of free epinine may affect the pharmacodynamic response to ibopamine, work is being undertaken to establish the relationship between epinine pharmacokinetics and the pharmacodynamic effects of ibopamine. However, ibopamine has previously been given to many patients with congestive heart failure in trials worldwide with no specific advice regarding food intake.

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