EFFECTS OF FOOD AND EXERCISE ON THE ABSORPTION OF EFFERVESCENT ASPIRIN

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- 1 The absorption of effervescent aspirin was studied in normal volunteers of both sexes under varied conditions of activity in both fasting and non-fasting states.
- 2 Moderate activity resulted in no significant changes in absorption compared with that at rest.
- 3 In non-fasting subjects the absorption was reduced but this reduction was attenuated with time until after 60 min the plasma levels were similar.
- 4 There was no interaction between the resting/non-resting and fasting/non-fasting absorption.

Introduction

During investigations into the absorption of drugs in patients suffering from migraine, it was found necessary to undertake studies in non-migrainous subjects to determine the effects upon absorption of factors other than the migraine attack. Since migraine is a paroxysmal disorder for which there is no universally effective provocative test, the patients must normally be studied as acute 'emergencies' under conditions which cannot be fully controlled. This paper reports the results of absorption studies using effervescent aspirin in non-migrainous subjects of both sexes when food intake and exercise levels were varied.

Methods

Subjects

Eight volunteer subjects (four male and four female) were chosen from hospital medical, nursing, research and administrative staff. All gave negative histories for headaches and gastrointestinal disease except for one subject who underwent appendicectomy two years previously. The male subjects were aged 28-50 years (mean weight 73.5 kg) and the female subjects 19-24 years (mean weight 53.1 kg).

Materials

Aspirin was given as a single dose of three tablets containing a total of 900 mg acetylsalicylic acid in

an effervescent base equivalent to 1,800 mg sodium bicarbonate and 1,200 mg anhydrous citric acid dissolved in 150 ml of water (Tabs Claradin, Aspro-Nicholas).

Procedures

Each subject was tested on four separate days when conditions of exercise and food intake were controlled as in Table 1. Treatment orders were allocated using a latin square design to remove any possible sequence effect. Fasting subjects were allowed no oral intake from midnight on the day before the test other than tea or coffee without milk or sugar taken at least 2 h before the test. Non-fasting subjects were given a standard meal of cereal, milk, coffee and sugar 15 min before the test. Resting subjects maintained a supine position on the couch throughout the test whilst active subjects continued with their normal work in the laboratory, clinic or office. An interval of at least one week was allowed between tests.

Analysis

Blood was collected into heparinized tubes via an indwelling venous catheter at 15 min intervals from the start of the test to 75 minutes. Plasma samples were deep frozen and stored for up to two weeks before analysis. After thawing, plasma salicylic acid levels were estimated by the method of Saltzman (1948), using an Aminco-Bowman spectrophotofluorimeter.

Results

Between conditions comparison

A three-way analysis of variance was performed on the data obtained across the eight subjects (Table 2). This may be summarized as follows:

(a) As may be expected from the time course of the study, the plasma salicylate levels showed a large variation with time (line 1, Table 2).

(b) Changes in level of activity had no significant effect upon absorption (line 3, Table 2). The lack of difference in absorption between the two activity conditions was reasonably constant over time (line 6, Table 2).

(c) Food ingested 15 min before the aspirin resulted in reduced plasma salicylate levels (line 2, Table 2). There was an interaction between food ingestion and the variation in plasma salicylate level over time (line 5, Table 2). This is illustrated in Fig. 1, where it can be seen that the differential effects of fasting v. non-fasting were attenuated with increasing time.

(d) Changes in activity level did not modify the effects of food upon absorption (line 4, Table 2).

Fig. 1 Mean plasma salicylate levels in fasting (○) and non-fasting (●) subjects after ingestion of 900 mg aspirin from an effervescent formulation (n = 8).

Table 1 Absorption of effervescent aspirin—test conditions

Treatment	Conditions
A ₁	Fasting and resting
A ₂	Fasting and active
B ₁	Non-fasting and resting
B ₂	Non-fasting and active

Between groups comparison

The male and female groups differed significantly in body weight (Table 3) and, as would be predicted from this, the peak salicylate levels in females were higher than in males (Table 4). However, the total amount of salicylate measured in the samples (averaged over the four conditions) were not significantly different for males and

Table 2 Three-way analysis of variance for effects of activity and food on salicylate levels over time

Source of variance	Degrees of freedom	Sum of squares	Variance estimate	F ratio	P
(a) Main effects					
Time	4	177.2795	44.3199	13.755	<0.001
Fasting/non-fasting	1	53.4534	53.4534	16.590	<0.001
Resting/non-resting	1	3.9752	3.9752	1.234	N.S.
(b) Interactions					
Fasting/non-fasting x resting/non-resting	1	0.2146	0.2146		N.S.
Fasting/non-fasting x time	4	42.9885	10.7471	3.3362	<0.05
Resting/non-resting x time	4	8.2660	2.0590	0.6391	N.S.
Time x fasting/non-fasting x resting/non-resting	4	0.7181	0.1795		N.S.
Residual	140	450.9859	3.2213		
Total	159	731.6521			

females ($F = 3.544$, $P < 0.125$) which implies that there is comparatively little difference between the sexes in the area under the absorption curve up to 75 minutes.

Discussion

The absorption of a drug from the gastro-intestinal tract is primarily related to its physico-chemical characteristics (Brodie, 1964). For a given drug the rate of absorption is modified by a number of factors including particle size; alimentary motility; mucosal blood flow; digestive secretions and intestinal contents (Smythe, 1964). Although particle size and other factors in the formulation of a drug may have a profound effect upon its absorption and bio-availability (Wagner, 1964; Levy & Guntow, 1963), these factors are not relevant in the present experiment where the drug was administered in solution. Measurement of mucosal blood flow is not yet possible in man (Bynum & Jacobson, 1971) and there are no published studies of digestive secretions during drug absorption studies.

The intestinal contents can be controlled by dietary measures and in so far as alimentary motility is affected by exercise (Holdstock, Misiewicz, Smith & Rowlands, 1970) this factor can be standardized. Most clinical pharmacological studies allow for the effects of food and exercise upon drug absorption by controlling the experimental conditions to the extent that subjects are

tested either fasting, or after a standard meal, and at rest, or under 'normal activity'. There appears to be few studies where food intake has been varied and there are none in which their interaction is recorded although Barr, Adir & Garrettson (1971) report an uncontrolled case where bed rest was thought to further impair absorption of tetracycline which had already been reduced by sodium bicarbonate.

Whilst it would seem likely that pharmaceutical companies study the effects of food upon the absorption of most new products, surprisingly few reports are found in the literature. Perhaps the best known example in the impairment of absorption of tetracyclines by milk and milk products (Price, Zolli, Atkinson & Luther, 1957) whilst recent cases where the relationship of drug ingestion to meals are considered to be important include the use of slow-release potassium (Benishay & Engelman, 1973) and L-dopa (Morgan, Bianchine, Spiegel, Butley, Rivera-Calimlim & Hersey, 1971; Gillespie, Mena, Cotzias & Bell, 1973). It is of note that for the latter two drugs these effects were fully appreciated only after they had been in use for some time and, certainly in the case of L-dopa, the therapeutic implications are of some importance.

The influence of dosage formulation and physiological factors upon the absorption of aspirin were recently reviewed by Martin (1971). He criticized many studies for failing to take account of one or more of these factors and for attempting comparisons using 'standard prepara-

Table 3 One-way analysis of variance for male/female weight differences

<i>Source of variance</i>	<i>Degrees of freedom</i>	<i>Sum of squares</i>	<i>Variance estimate</i>	<i>F ratio</i>	<i>P</i>
Between groups	1	840.8	840.8	52.16	<0.001
Within groups	6	96.7	16.2		
Total	7	937.5			

Mean body weight for males = 73.5 kg; mean body weight for females = 53.1 kg.

Table 4 One-way analysis of variance for male/female differences in peak plasma salicylate levels averaged over all treatment conditions

<i>Source of variance</i>	<i>Degrees of freedom</i>	<i>Sum of squares</i>	<i>Variance estimate</i>	<i>F ratio</i>	<i>P</i>
Between groups	1	4.3734	4.3734	13.888	<0.005
Within groups	6	1.8896	0.3149		
Total	7	6.2630			

Mean peak plasma salicylate level for males = 7.21 mg %

Mean peak plasma salicylate level for females = 8.71 mg %

tions' which differed greatly in formulation and bioavailability. The present investigation took particular account of the volume of fluid administered; the quantity of food consumed and the position of the resting subject.

Martin (1971) demonstrated the influence of the volume of fluid upon absorption of aspirin in an experiment where it was shown that the initial absorption was doubled when the volume of water was increased from 75 to 150 ml. In the present study the same volume of water was given to all subjects in order to minimize variance. The volume 150 ml was chosen since it ensures a stable solution and is representative of the volume which is used clinically.

When aspirin is administered in solution, it is theoretically possible that some of the drug will be precipitated at the low pH of the resting gastric juice. Effervescent formulations are thought to avoid precipitation by the neutralizing action of the sodium bicarbonate which, in the doses used, effects a substantial increase in gastric pH (Lolli & Smith, 1946). Although the rise in pH will reduce the concentration of unionized aspirin it is also thought to increase the rate of gastric emptying and thus to allow earlier onset of rapid intestinal absorption (Lolli & Smith, 1946; Hunt, 1963).

Impairment of the rate of absorption of aspirin by food may be expected to result from a reduced rate of gastric emptying and from adsorption of the drug to food particles. Wood (1967) reported that food increased the half-life of absorption from commercial aspirin tablets. Using five different preparations in normal volunteers the half-life of absorption was more than doubled by the non-fasting condition and even in the fastest case, the half-life exceeded 1 hour. The present experiment demonstrated a statistically significant reduction in the rate of absorption of an effervescent aspirin preparation in the non-fasting condition. As this effect is attenuated with time (to the extent that little difference remained after 1 h), it could be suggested that the difference is clinically unimportant. The difference, however, could become important if it were shown that absorption was already impaired as part of a disease process or if it were found that certain foods have more pronounced effects than others, as they do in the case of paracetamol absorption (Jaffe, Colaizzi & Barry, 1971).

Reduced absorption of aspirin has been reported when subjects were resting in the left-supine position compared with an upright seated position (Martin, 1971, Truitt & Morgan, 1964). In this experiment lateral positions were avoided and the resting subjects remained in the true supine position with the head of the couch elevated 20-30 degrees.

Physical activity has been shown to increase motor activity in the gastro-intestinal tract with increased segmentation and mass movements in the colon (Holdstock *et al.*, 1970). It was, therefore, expected that the increased gastro-intestinal activity in the active subjects would increase the rate of aspirin absorption, but, in fact, no significant difference was found. These findings cannot be extrapolated to strenuous activity where the changes in gastro-intestinal activity can be presumed to be more pronounced as a result of the rise in body temperature (Misiewicz, Waller, Fox, Goldsmith & Hunt, 1968). The lack of effect, however, from moderate activity combined with the lack of interaction between activity and food is of interest in relation to the many studies where absorption in bed-fast 'patients' is compared with the active 'controls'.

Although the female group had higher peak salicylate levels and were much lighter than the male group, the small difference between the sexes in total amount of salicylate absorbed suggests that, in fact, the overall mg/kg salicylate levels may be lower in females than males. This is of interest in view of the hypothesis that there may be a sex-linked difference in aspirin metabolism (Menguy, Desbaillets, Masters & Okabe, 1972). The observations of Cummings & Martin (1964), that blood salicylate levels showed a good inverse relationship to body weight was made in healthy male subjects on a repeated dosage and they do not, therefore, contrast with the present findings. Further studies are being made using male and female subjects matched for age and weight.

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