No interference with the drug or its metabolites from normal plasma constitutes was observed (Fig. 2A). The retention times of several drugs that might be prescribed simultaneously with amoxapine were determined (Table II). Little interference would be expected under the experimental conditions.

The method has been applied to the analysis of many samples obtained from patients receiving amoxapine orally. The drug and its 8-hydroxy metabolite are present in relatively high concentrations (Fig. 2B). However, the 7-hydroxy metabolite is found in low concentration. This may be due to its short half-life (8).

Major advantages of the method are the small sample volume required, the simplicity and high recovery using a single extraction step with no derivatization, and the use of an isocratic mobile phase. The sensitivity is sufficient for routine analysis of patient samples and for pharmacokinetic studies.

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ACKNOWLEDGMENTS

The authors thank Robert I. Biberdorf for his valuable help. Also, the authors acknowledge Lederle Laboratories and Ives Laboratories for providing free authentic samples of the drugs and metabolites.

Isosorbide Dinitrate Plasma Concentrations and Bioavailability in Human Subjects after Administration of Standard Oral and Sublingual Formulations

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Received September 13, 1982, from the *Department of Metabolism and Pharmacokinetics, Huntingdon Research Centre, Huntingdon, PE18 6ES England and the Institute of Clinical Pharmacology, Dublin, Ireland.* Accepted for publication December 23, 1982.

Abstract □ The bioavailability of isosorbide dinitrate from formulations containing 5, 10, and 20 mg in tablets and 10 mg in solution for oral use and 5 mg in tablets for sublingual use, has been compared. When adjusted for dose, the peak mean plasma drug concentrations after oral administration were similar (*e.g.*, 9.2 ng/mL after a 10-mg tablet) and about one-half that obtained after sublingual administration. Drug concentrations declined monoexponentially with mean half-lives ranging from 25–36 min. The relative bioavailability of isosorbide dinitrate from the oral formulations was not significantly different ($p > 0.05$) over the dose range studied, whereas the relative bioavailability after sublingual administration was about twice as great ($p < 0.01$) as that after oral administration. The plasma drug concentration–time profile after administering the 5-mg sublingual tablet was similar to that obtained after administering orally a solution containing 10 mg, indicating that the latter should be as clinically effective as the former.

Keyphrases □ Isosorbide dinitrate—rate and extent of bioavailability from various oral formulations compared, oral and sublingual formulations compared, humans □ Bioavailability—isosorbide dinitrate, oral and sublingual formulations compared, human □ Vasodilators—isosorbide dinitrate, oral and sublingual formulations compared, humans

Isosorbide dinitrate is an anti-anginal organic nitrate vasodilator that is in extensive clinical use. Following the development of suitably sensitive GC assays (1–3) for the measurement of isosorbide dinitrate in plasma, there have been several reports of the plasma levels of isosorbide dinitrate after the administration of different formulations of the drug (4–9). Sustained-release formulations have proven to be of particular interest. However, none of these reports have compared the relative bioavailability of isosorbide dinitrate from increasing doses of standard oral formulations. Such studies are described in this paper.

EXPERIMENTAL

Drug Administration—Two studies were conducted: the first compared a 5-mg sublingual tablet formulation with a 10-mg oral solution and 10- and 20-mg standard oral tablet formulations of isosorbide dinitrate[1]. The second study compared a 5-mg standard oral tablet formulation[1] with its 10-mg counterpart investigated in the first study. In each study, separate groups of 12 male volunteers each were involved, and the experimental conditions were the same. All subjects (18–40 years old and 58–85 kg) gave their written consent. Within 7 d before and after either study, each subject was given a complete physical examination including routine laboratory screening tests. During the study, the subjects remained under medical supervision. No adverse reactions, apart from headache (4 subjects), were reported by any subject. The studies were approved by the Institutional Review Board. Each of the oral dosage formulations was administered with 100 mL of water according to a complete crossover repeated Latin-square design with an interval of 1 week between doses. The sublingual formulation was retained under the tongue until it completely disintegrated; the subjects were instructed to avoid swallowing during this period. For at least 12 h predosing and for 4 h postdose the subjects fasted, and activity and subsequent diet were standardized.

At predose and after dosing, blood samples were collected into heparinized tubes by venipuncture, immediately cooled, and centrifuged. The resultant plasma was removed and stored at −20°C under conditions in which the drug was stable throughout the assay period.

Drug Assay—Isosorbide dinitrate in plasma was measured by an electron

[1] Formulations (Risordan) were provided by Theraplix, Paris, France. The respective batch numbers were 416, 430, 6659, 6665, 6747 for Risordan 5 mg (sublingual), 5 mg (oral), 10 mg (tablet), 20 mg and 10 mg (solution), respectively.

0022-3549/84/0500-0699$01.00/0

Table I—Mean Plasma Drug Concentrations [a] after Administration of Oral and Sublingual Formulations of Isosorbide Dinitrate

Time, Min	Oral 10-mg Solution	Oral 10-mg Tablet	Oral 20-mg Tablet	Sublingual 5 mg Tablet
10	8.2 ± 6.6	3.2 ± 3.3	3.2 ± 4.0	7.7 ± 6.7
20	9.4 ± 3.9	7.6 ± 3.7	14.0 ± 11.6	8.6 ± 4.4
30	9.2 ± 3.4	9.2 ± 2.9	17.5 ± 10.6	7.6 ± 2.8
40	7.3 ± 2.6	9.1 ± 2.6	16.9 ± 7.7	6.4 ± 2.7
50	5.6 ± 1.9	7.1 ± 2.7	13.6 ± 4.7	4.2 ± 1.7
60	4.3 ± 1.6	5.3 ± 2.1	12.0 ± 4.2	3.2 ± 1.0
75	2.7 ± 1.1	3.6 ± 1.9	9.2 ± 3.6	2.0 ± 0.7
90	1.7 ± 0.7	2.4 ± 1.8	7.2 ± 3.5	1.5 ± 0.9
120	0.8 ± 0.5	1.2 ± 1.1	3.9 ± 1.9	0.7 ± 0.5
150	ND[b]	ND[b]	2.2 ± 1.2	ND[b]

[a] Nanograms per milliliter ± *SD*. [b] ND = not detected (<0.5 ng/mL).

Table II—Mean Plasma Drug Concentrations [a] after Administration of Two Oral Formulations of Isosorbide Dinitrate

Time, Min	5-mg Tablet[b]	10-mg Tablet
10	1.8 ± 1.7	5.7 ± 3.7
20	10.4 ± 6.3	12.6 ± 3.5
30	11.2 ± 4.5	10.9 ± 2.9
40	10.3 ± 5.5	9.0 ± 3.7
50	7.8 ± 3.2	6.6 ± 2.3
60	6.5 ± 3.0	5.1 ± 2.4
75	4.5 ± 2.2	3.4 ± 1.1
90	3.0 ± 1.4	2.2 ± 0.7
120	1.5 ± 0.9	1.2 ± 0.4
150	0.7 ± 0.7	ND[c]

[a] Nanograms per milliliter ± *SD*. [b] Two tablets (10 mg) administered. [c] ND = not detected (<0.5 ng/mL).

capture GC assay (3) with glyceryl trinitrate as the internal standard. Plasma isosorbide dinitrate levels were calculated by reference to standard curves constructed by adding known amounts of the drug to control human plasma. During this procedure and the subsequent assay, isosorbide dinitrate was completely stable at 4° or 20°C. The recovery of isosorbide dinitrate from plasma over the concentration range 1–15 ng/mL was 91 ± 10% *SD*. The precision of the method for the measurement of isosorbide dinitrate in plasma (n = 5) was 18, 9, and 11% at 1, 5, and 10 ng/mL, respectively.

Data Processing—Apparent half-lives for the decline of plasma drug concentrations were calculated by least-squares regression analysis of log concentration against time from measurements during the terminal linear phase of the plasma drug concentration–time curves. As isosorbide dinitrate kinetics appear to follow a "flip-flop" model (10), these half-lives relate to drug absorption, not to elimination. Areas under the plasma concentration–time curves, scaled to equal doses, were calculated by the trapezoidal rule or by using spline functions, and adjusted to infinite time. Whether the infinite time adjustment was carried out at a concentration of ~2 ng/mL (where assay precision was ~≤10%) or at a lower concentration (where assay precision was poorer), the difference in the resultant calculated mean areas was <~3% (mean 1.4% range 0.3–3.3%).

Areas, peak plasma concentrations and their times of occurrence, and apparent "absorption" half-lives were subjected to an ANOVA for crossover designs (11). Formulation means were compared with the reference mean by Dunnett's test (12, 13) and compared pairwise by the Newman-Keuls procedure (14, 15). The total variance was separated into that due to subjects, day of administration, formulations, and residual.

RESULTS AND DISCUSSION

Plasma Drug Concentrations—Mean concentrations of isosorbide dinitrate in plasma after administration of the various formulations are shown in Tables I and II. Drug levels were detected in the plasma of at least eight subjects at the first sampling time after administration of the tablet formulations and in all subjects after administration of the solution. Drug was not detected (<0.5 ng/mL) in at least five subjects at 150 min after administration of all formulations except the 20-mg dose. Drug was even undetected in the plasma of some subjects at 120 min after administration. Mean plasma drug levels obtained after equivalent oral doses as a solution and as a tablet were generally similar, but as expected, peak mean levels were reached sooner after administration of the solution.

Inspection of the data shows that the peak mean plasma drug levels obtained after administration of 5-, 10-, and 20-mg tablet formulations were linearly related to dose.

The mean plasma drug levels obtained after administration of the 10-mg tablet to two separate groups of subjects in different studies were remarkably similar (*cf.* Tables I and II).

Mean plasma drug levels obtained after the 5-mg sublingual dose were similar to those after a 10-mg oral dose and in the same range as previously reported (4, 9, 16).

With respect to the type of isosorbide dinitrate formulation administered, the plasma drug levels shown in Tables I and II are similar to those reported in the literature (4–7).

Bioavailability Parameters—Peak plasma levels of isosorbide dinitrate and the times of occurrence are shown in Table III. Although the peak levels of the 10-mg tablet and 10-mg solution were similar, the times at which they were reached were significantly different. With due allowance for dose, mean peak levels from the 20-, 10-, and 5-mg tablets (the latter given as 2 × 5 mg) were similar as were their times of occurrence. The former result suggests that over this dose range, at least, a similar proportion of isosorbide dinitrate was probably absorbed unchanged into the peripheral circulation. It should be noted that an oral dose of [^{14}C]isosorbide dinitrate was almost completely absorbed with respect to radioactivity (17), whereas the systemic availability of isosorbide dinitrate orally is ~25% (18) due to considerable first-pass metabolism in the liver and perhaps even during absorption from the GI tract. It has also been reported that a similar proportion of isosorbide dinitrate was absorbed from a 20-mg sustained-release formulation over the 20–100-mg dose range in healthy subjects (19), and from an apparently standard formulation over the 15–120-mg dose range in patients (20).

Although relatively greater with respect to the administered dose, the mean peak level of isosorbide dinitrate following a sublingual dose was reached hardly any sooner than from a 10-mg solution. This result, and the similarity between the respective plasma drug concentration–time curves, implies that a dose of 10 mg of isosorbide dinitrate as an oral solution should produce about the same onset and duration of clinical effect as a 5-mg sublingual dose.

Measured areas under the plasma drug concentration–time curves are shown in Table III. The mean AUC ratios, when adjusted for dose/body weight, after administration of 5-, 10-, and 20-mg tablet formulations were

Table III—Mean (± *SD*) Bioavailability Parameters of Isosorbide Dinitrate for the Various Formulations [a]

Parameter	Oral 5-mg Tablet[b]	Oral 10-mg Tablet	Oral 20-mg Tablet	Oral 10-mg Solution	Sublingual 5-mg Tablet
Peak concentration in individuals (ng/mL)	(14.0 ± 6.1)	10.6 ± 2.3 (14.0 ± 2.8)	22.4 ± 9.9[c,f,g]	11.7 ± 6.2[d]	10.9 ± 5.3
Time of peak concentration (min)	(34.2 ± 13.8)	35.0 ± 9.0[e] (22.5 ± 8.7)	39.1 ± 13.1[c]	24.4 ± 9.0	21.7 ± 11.1[d,f]
Area (ng min/ml)	(711 ± 229)	600 ± 185 (668 ± 152)	1370 ± 361[c,f,g]	583 ± 158	497 ± 168[h]
Half-life (min)	(30.2 ± 5.5)	26.9 ± 9.4 (28.2 ± 5.2)	36.3 ± 8.2[c,f,g]	25.3 ± 9.4	28.7 ± 7.4

[a] Data in parentheses have been obtained from a different group of subjects. [b] This formulation (given as 2 × 5 mg) was compared statistically ($p > 0.05$) with the 10-mg tablet only. [c] Significantly different ($p < 0.01$) from 10-mg solution (Dunnett's test). [d] Significantly different ($p < 0.01$) from 20-mg tablet (Newman-Keuls pairwise comparison). [e] Significantly different ($p < 0.05$) from 10-mg solution (Dunnett's test). [f] Significantly different ($p < 0.01$) from 10-mg tablet (Newman-Keuls pairwise comparison). [g] Significantly different ($p < 0.01$ or <0.05) from 5-mg sublingual tablet (Newman-Keuls pairwise comparison). [h] Significant differences occur (*c,d,f*) with this parameter when data were adjusted for dose/body weight.

similar to that after a 10-mg solution indicating that there were no dosage form or dose level effects on the extent of bioavailability of isosorbide dinitrate over the 5–20 mg dose range (*i.e.*, a similar relative fraction of the dose of isosorbide dinitrate reached the peripheral circulation unchanged after administration of each formulation). The mean adjusted AUC after administration of the sublingual 5-mg dose was significantly different from those after the oral tablet formulations, as might be expected. Indeed, previous studies have shown that the extent of bioavailability of isosorbide dinitrate from a sublingual formulation was at least twice that from the same formulation given orally (4), since some but not all of a sublingual dose avoids first-pass elimination. A large proportion of a sublingual dose is usually swallowed (18).

The conventional 95% confidence limits (21, 22) of mean areas expressed as a percent of the mean from the 10-mg solution formulation taken as a reference were −19 to +29%, −6 to +50%, and +32 to +109% from the 10-mg oral tablet, 20-mg oral tablet, and 5-mg sublingual tablet, respectively. These limits were −11 to +24% for the 5-mg oral tablet when the 10-mg oral tablet was taken as the reference (Table III). These confidence limits are fairly narrow even though plasma concentrations of isosorbide dinitrate can vary by several-fold between subjects, and the group of subjects studied was not particularly large.

Drug Half-Life—Isosorbide dinitrate kinetics appear to follow a "flip-flop" model (10, 18) and, therefore, the monoexponential decline of the concentrations in plasma can be regarded as reflecting the rate of drug absorption.

Among the orally administered formulations, the drug absorption half-life was shortest after the 10-mg solution dose, but only the drug half-life observed after the 20-mg tablet was significantly longer ($p < 0.01$) than that after the 10-mg solution. A shorter half-life after the sublingual dose would not be expected because the 5-mg tablet was retained in the mouth during disintegration before a notable proportion was swallowed. The half-lives measured in these studies are in close agreement with those reported in the literature (4, 9, 10, 18).

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ACKNOWLEDGMENTS

The authors are grateful to Theraplix, Paris, for financial support.

Disintegrating Force as a New Formulation Parameter

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Abstract □ Some coated aspirin tablet formulations were evaluated by relating their properties to disintegrating force development patterns. The treatment of disintegrating force–time curves was effected using the Weibull distribution as proposed for dissolution. Such parameters as the maximum disintegrating force developed, the time needed to reach 63.2% maximum disintegrating force (τ_d) the shape parameter, the lag time, and the input value were used for evaluating the formulas examined. It was concluded that the input values, the integrating force development rate at time τ_d, can be employed as a new formulation parameter since, when correlated with the crushing strength, it allows an overall evaluation of the formula examined.

Keyphrases □ Disintegrating force—new formulation parameter, Weibull distribution, coated aspirin tablets □ Formulations—disintegrating force as a new parameter, Weibull distribution, coated aspirin tablets □ Weibull distribution—disintegrating force as a new formulation parameter, coated aspirin tablets

In a previous paper (1), the disintegrating force of tablets was defined as the force developed inside a tablet depending on the liquid–solid contact. It was shown that curves obtained by plotting disintegrating force *versus* liquid contact time had patterns following saturation kinetics dependent on the liquid penetration into voids. Since compact structure (defined by voids distribution and interparticle bonding) and disintegration–dissolution performance are strictly related, the investigations of the disintegration behavior of a tablet should provide a means for the evaluation of the structure obtained.

It is well known that disintegration time as measured by official apparatuses does not satisfactorily describe the disintegration properties of tablets, as demonstrated by the methods proposed to evaluate disintegration (2–5). Because disintegrating force–time curves could be related to the structure of tablets (6), these deserved a deeper investigation in view of their employment not only for studying the bioavailability-related properties of tablets, but also to assess the structure–technological parameter relationships.

The aim of the present work was to employ the disintegrating force parameters for studying coated aspirin tablet

0022-3549/84/0500-0701$01.00/0