Lack of bioequivalence between disulfiram formulations

Exemplified by a tablet/effervescent tablet study

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Abstract — A comparison of the bioavailability of disulfiram (DSF) after administration of non-effervescent Antabuse® tablets (CP Pharmaceuticals, UK) and Antabuse® effervescent tablets Antabus® (A/S Dumex, DK) has been made in two cross-over studies.

The first study included 6 volunteers who were given 400 mg DSF after an overnight fast. The bioavailability of DSF after administration of non-effervescent was found to be only 27 % of that achieved with effervescent tablets.

The second study included 24 volunteers who were given 800 mg DSF after a light standardized meal. The relative bioavailability of DSF after administration of non-effervescent compared with effervescent tablets was found to be only 34 %.

In addition to the difference in bioavailability of DSF after administration of the two preparations, a considerable difference was seen between the two studies. A light meal seems both to increase the bioavailability of DSF and to reduce the interindividual variation. A two to threefold increase in the bioavailability of DSF was found.

Thus, the bioavailability of DSF appears to depend on both the formulation (preparation) and the mode of administration. A lack of bioequivalence between the two investigated DSF preparations was found.

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Introduction

Although Disulfiram (DSF) has been used in the treatment of alcoholism for many years [1], its pharmacokinetics, including bioavailability and metabolism, are not very well known.

Recent years have seen the introduction of better analytical equipment and some light has been shed on the metabolism of DSF, but new metabolites are still being discovered.

The bioavailability of DSF is, however, difficult to measure, partly because DSF cannot be administered intravenously owing to its insolubility in aqueous media, and partly because, after absorption it almost immediately cleaves to its monomer, diethyldithiocarbamate (DDC) [2, 3, 4], which is again further metabolised. Thus, DSF is not detectable in plasma after a single administration, only after repeated administrations [5].

The bioavailability of DSF in humans has been studied with radioactive labelled DSF (^{14}C or ^{35}S) [1, 6, 7, 8]. Faeces were collected for at least 72 hours after administration and the radioactivity was measured. Bioavailability was found to be 80—90 %, i.e. almost complete. This method has the disadvantage that measurement of the radioactivity is non-selective, and decomposition of DSF before absorption is not taken into account.

For comparison of the bioavailability of a particular drug substance in various preparations, measurement of a metabolite in plasma is often a useful indicator of the relative bioavailability. DSF cleaves to its monomer DDC, which is further metabolised to methyl diethyldithiocarbamate (Me-DDC) [2, 9, 10, 11]. Me-DDC is stable in plasma, it is produced in measurable amounts, and it has a "suitable" plasma half-life ($t_{1/2}$ = 6.3 hours) [10]. The serum concentration of Me-DDC is thus considered a usable measurement of the relative bioavailability of DSF in the comparison of different preparations.

The aim of this study was to compare the bioavailability of DSF after oral administration of Antabuse® tablets (produced by CP Pharmaceuticals, UK) and Antabus® effervescent tablets (produced by A/S Dumex, DK).

Materials and methods

A pilot study was performed before the main study. Both studies were carried out in a randomised cross-

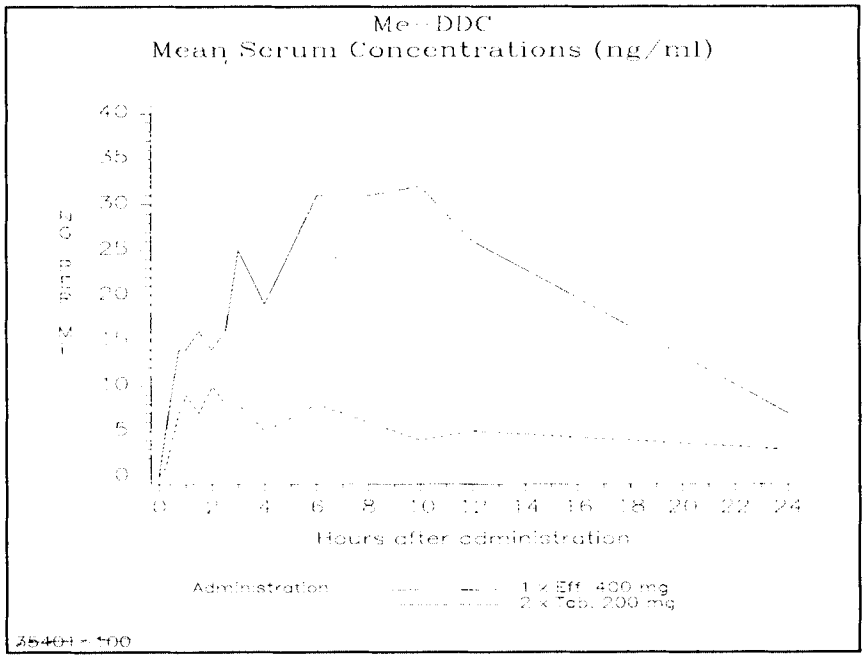

Figure 1: Mean serum concentrations of the DSF metabolite Me-DDC as a function of time after oral administration of Antabus® effervescent tablets and Antabuse® tablets 2×200 mg. (n = 6)

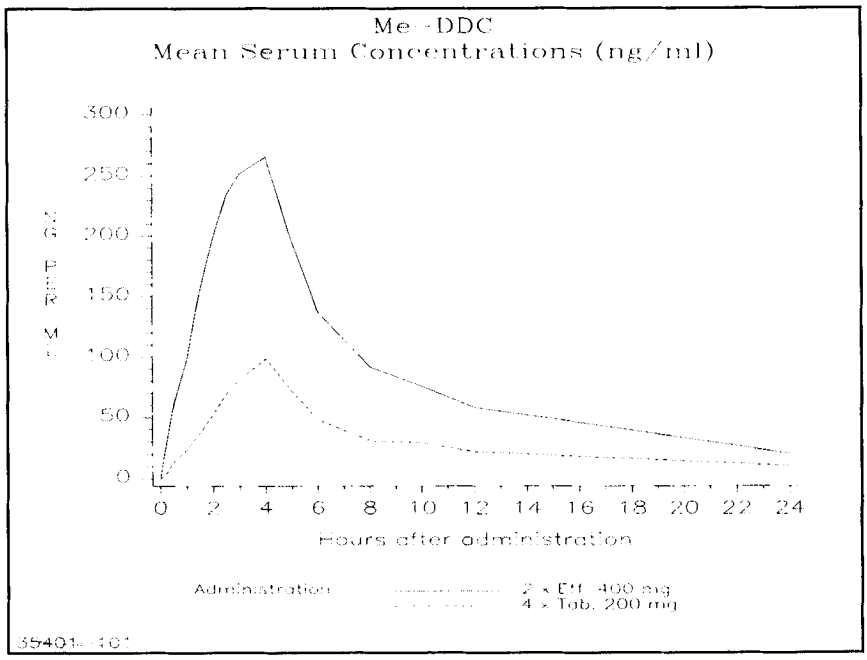

Figure 2. Mean serum concentrations of the DSF metabolite Me-DDC as a function of time, after administration of 2×400 mg DSF as Antabus® effervescent tablets and 4×200 mg DSF as Antabuse® tablets. (n = 24)

over design with volunteers. The two trial days were separated by a one-week wash-out period.

Blood samples were taken from the volunteers according to the following schedule: Before administration, at 15, 30, 45, 60, 90, 120, and 150 minutes, and at 3, 4, 6, 8, 10, 12, and 24 hours.

Serum samples were assayed for Me-DDC by a specific liquid chromatographic method [12]. The limit of quantitation was 5 ng/ml.

Pilot study

Six healthy volunteers (3 men, 3 women; mean age 26 ± 6 years) were given 400 mg of DSF, administered as 1 effervescent tablet (dispersed in 200 ml of water) or 2 tablets (swallowed with 200 ml of water). All subjects fasted for at least eight hours before and four hours after drug administration.

Results of the pilot study

The mean serum concentrations of Me-DDC as a function of time are shown in Fig. 1. The t_{max}, C_{max} and AUC_0^{24} are given in Table I. C_{max} is the maximum Me-DDC serum concentration, and t_{max} is the time at which it occurs. AUC_0^{24} is the area under the serum concentration time curve calculated by the trapezoidal rule. The half-life ($t_{1/2}$) of Me-DDC was not calculated, as the results showed no clear elimination phase.

The relative bioavailability of Me-DDC

$$F_{rel} = \frac{AUC_0^{24}\ (tabl)}{AUC_0^{24}\ (eff.tabl)} \cdot 100\,\%$$

after administration of the two preparations is given in Table I.

The results showed large variations, and not the classical serum concentration time profile of Me-DDC as previously shown by Johansson [10, 12]. The serum concentrations of Me-DDC after administration of the Antabuse® tablet were only just above the quantitation limit of the assay.

Main study

The results of the pilot study necessitated some changes in the design of the main study.

The dose was increased from 400 mg to 800 mg, administered as 2 effervescent tablets (dispersed in 200 ml of water) or 4 tablets (swallowed with 200 ml of water).

To minimize the variation in the results, the volunteers were given a standardized light meal 15 minutes before administration of DSF. The purpose of the light meal was to ensure that the stomach emptied at a more even rate. The volunteers fasted for at least 8 hours before and, apart from the light meal, until 4 hours after administration.

Twenty-four volunteers were entered in the study (14 men and 10 women; mean age 24 ± 4 years).

Results of the main study

Mean serum concentrations of Me-DDC as a function of time are shown in Fig. 2. The t_{max}, C_{max}, AUC_0^{24}, and AUC_0^{∞} are given in Table I. C_{max} is the maximum Me-DDC serum concentration, and t_{max} is the time at which it occurs. The half-life ($t_{1/2}$) of Me-DDC in serum is calculated on the serum concentrations of Me-DDC in the elimination phase (8—24 hours) by single logarithmic regression. AUC_0^{24} is the area under the serum concentration time curve calculated by the trapezoidal rule. AUC_0^{∞} is found by adding AUC_0^{24} and AUC_{24}^{∞}, where AUC_{24}^{∞} is calculated on the $t_{1/2}$ and the serum concentration of Me-DDC at 24 hours as estimated by linear regression.

The relative bioavailability of Me-DDC

$$F_{rel} = \frac{AUC_0^{\infty}\ (tabl)}{AUC_0^{\infty}\ (eff.tabl)} \cdot 100\,\%$$

after administration of the two preparations is shown in Table I.

An analysis of variance on C_{max}, t_{max} and AUC_0^{∞} was done with the main effects, *SUBJECT within SEQUENCE* (order of treatments), *SEQUENCE, PERIOD* and *TREATMENT*. The results are listed in Table II. No statistically significant difference was found in the t_{max} ($p = 0.96$), whereas there was a statistically significant difference in the C_{max} ($p < 0.0001$) and the AUC_0^{∞} ($p < 0.0001$).

Discussion

Table I summarizes all the pharmacokinetic parameters calculated in the two studies. Considerable differences are seen, both between studies and between preparations.

The pilot study showed a large difference in the bioavailabilities of the two preparations studied, but it also showed large interindividual differences. A long absorption phase was seen, and it was not possible to define a clear elimination phase within 12 hours of administration of DSF. Consequently, the half-life of Me-DDC could not be calculated.

Owing to the results of the pilot study, showing low serum concentrations of Me-DDC, the DSF dose given in the main study was doubled. The scheduled fasting conditions were also changed, as the volunteers were given a light meal before administration of DSF, in order to achieve a more even emptying of the stomach and thereby a well-defined absorption phase [13, 14].

Table 1. Pharmacokinetics of Me-DDC after administration of DSF (mean + SD)

PRODUCT	n	dose (mg)	t_{max} (h)	C_{max} (ng/ml)	$t_{1/2}$ (h)	AUC_0^{24} (ng/ml x h)	AUC_0^{∞} (ng/ml x h)	F_{rel} %
Antabuse® tablets CP Pharmaceuticals, UK	6	400*	2.2 ± 1.4	14 ± 8	—	124 ± 104	—	27 ± 22
Antabus® eff. tablets A/S Dumex, DK	6	400*	6.7 ± 4.2	39 ± 23	—	497 ± 282	—	
Antabuse® tablets CP Pharmaceuticals, UK	24	800**	3.7 ± 1.0	124 ± 63	13.4 ± 5.4	736 ± 477	855 ± 559	34 ± 9
Antabus® eff. tablets A/S Dumex, DK	24	800**	3.8 ± 1.4	324 ± 168	8.0 ± 2.1	2096 ± 1162	2337 ± 1294	

* The volunteers fasted at least 8 hours before and until 4 hours after administration of DSF.
** Fasting as above, except for a standardized light meal given 15 minutes before administration of DSF.

Table II.

Estimated relative value in per cent = $\frac{\text{4 tablets of 200 mg}}{\text{2 efferv.tabs. of 400 mg}} \times 100\%$

Parameter	Per cent	90 % conf. interval
C_{max}	38	33, 44
t_{max}	100	83, 120
AUC_0^{∞}	35	31, 38

The serum concentration time profiles in the pilot study indicate that a rather large fraction of DSF is absorbed later than 4 hours after administration, i.e. after the end of the fast.

The changes brought about a classic Me-DDC serum concentration time profile, with a much lower interindividual variation in the results. Furthermore, the doubled dose of DSF produced serum concentrations of Me-DDC that were higher than expected.

The difference in the bioavailabilities of DSF from the two preparations was found to be almost the same in the two studies. In both studies, the relative bioavailability of the non-effervescent Antabuse® tablet compared with the Antabus® effervescent tablet was found to be about 30 %. This is probably attributable to the difference in the mode of administration and the characteristics of the DSF raw material. The Antabus® effervescent tablet is dispersed in water and the raw material has a hydrophilic surface (easy to wet). The Antabuse® tablet is swallowed whole with water and contains a raw material with a hydrophobic surface (hard to wet). The particle size of the raw material is the same in both preparations. In vitro, the difference is expressed by the rates of dissolution, with that from the effervescent tablet being the faster.

Even if the results of the main study are corrected for the given double dose of DSF, the bioavailability is still 2—3 times greater than that found in the pilot study. Moreover, the interindividual variation was smaller in the main study, and the classic serum concentration time profile of Me-DDC also emerged. A possible explanation is the light meal given immediately before drug administration. It is well known that food intake or a drug vehicle can affect the bioavailability of drug substances [13]. Solubilisation by bile, transport via micelles and absorption via chylomicrons to the lymphatic system appear to play important roles in the absorption of highly lipophilic drug substances, like griseofulvin and tetracycline [13,15,16]. DSF is a highly lipophilic drug and probably acts in a similar manner. Food stimulates the secretion of bile, brings about the formation of micelles, and increases the lymph flow in the thoracic duct by as much as a factor of 5—10, all of which provides better conditions for the absorption of highly lipophilic drug substances.

Our observation, that the bioavailability of DSF depends on the preparation and the mode of administration, does not agree with findings in earlier studies with radioactive-labelled DSF. If, as these studies report, the bioavailability of DSF is 80—90 %, it would not be possible to show the differences in the serum concentrations of Me-DDC as demonstrated in the present two studies. The implication is that extensive decomposition of DSF must occur before absorption (first pass metabolism). Owing to the lability of DSF, and especially DDC, in an aqueous acidic environment ($pH < 7$) [2] it is possible that DSF is hydrolysed in the stomach to its monomer, DDC, which in turn breaks down to diethylamine (DEA) and carbon disulphide (CS_2). DEA and CS_2 are readily absorbed. Another possibility is further breakdown of DSF by microorganisms in the colon and absorption of the breakdown products from the colon. Decomposition of DSF before absorption and absorption of the breakdown products could explain the high bioavailability previously found.

Conclusion

The bioavailability of DSF appears to depend on both the formulation (preparation) and the mode of administration.

In the present studies, the relative bioavailability of DSF after administration of Antabuse® tablets (CP Pharmaceutical, UK) compared with that after administration of Antabus® effervescent tablets (A/S Dumex, DK) was found to be about 30 %.

A light meal taken immediately before administration of the drug produced a two to threefold increase in the bioavailability of DSF.

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Discussion

The participants agreed that over the years the bioavailability issue has lacked good comparative studies. The present study clearly shows that both the actual pharmaceutical preparation and the conditions under which it is administered are of utmost importance for achieving the desired clinical response if the alcoholic ingests alcohol. A factor of three in the bioavailability of two preparations is a dramatic difference. This may explain why doctors in the UK have often found it necessary to exceed the daily recommended doses, which are mostly based on Scandinavian experience with the more readily available preparation.

At the same time this makes it difficult to compare the results of clinical studies performed in various countries, particularly as the name Antabuse does not guarantee that the quality of the product is the same from one country to another. For instance, the Antabuse product marketed in the USA, the UK and Scandinavia are all different.

It was agreed that the bioavailability of disulfiram in any preparation would be higher, and probably more reproducible, if the tablets were taken with some food in the stomach. The reasons for the higher bioavailability should be the subject of further studies.