AVAILABILITY OF METHAQUALONE FROM COMMERCIAL PREPARATIONS: *in vitro* AND *in vivo* STUDIES IN MAN

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- 1 The plasma profiles of methaqualone obtained from different commercially available preparations have been compared. Tablets were absorbed more efficiently than capsules. Mandrax preparations achieved much higher plasma levels than Melsedin tablets or the Melsed or Sedaquin capsules. These differences appear to be due to formulation factors.
- 2 The efficacy of the different drugs as hypnotics corresponded well with the blood levels achieved.
- 3 There was a significant correlation between the *in vitro* $1/t_{50\%}$ and the *in vivo* peak plasma levels. Thus *in vitro* dissolution studies can be used to predict the efficiency of absorption of different formulations in man.

Introduction

The hypnotic methaqualone was first introduced in Britain by Boots in 1960 and was marketed as the tablet Melsedin which contains 150 mg methaqualone hydrochloride. This preparation was never widely prescribed. In 1965, Roussel introduced a combination tablet, Mandrax, which contains 250 mg, methaqualone base and 25 mg diphenhydramine hydrochloride. Mandrax rapidly achieved a considerable popularity and a survey in 1968 showed that it was the most commonly used hypnotic, accounting for 30% of all hypnotic prescriptions (Wade, 1970; Matthew, 1973). Other preparations have been marketed but none has been so popular.

It is surprising that Mandrax, a methaqualone preparation marketed five years after the first methaqualone containing product should have become so much more widely used. Mandrax has achieved this and it is claimed that this is because methaqualone together with diphenhydramine is a more efficient hypnotic (Beaubhen, Kristof, Lehmann & Ban, 1968; Hoffmeister & Koller, 1970). We therefore decided to investigate the plasma methaqualone concentrations produced by Mandrax and other commercially available preparations and to attempt to correlate these with formulation factors.

Methods

Materials

The following commercially available preparations as supplied by the respective manufacturers were investigated in the present study: Mandrax Tablet A (marketed prior to 1970); Mandrax Tablet B (marketed since 1970, Roussel Laboratories Ltd); Mandrax Capsule; Melsedin Tablet and Melsed Capsule (The Boots Company Ltd); Sedaquin Compound Capsule and Sedaquin Forte Capsule (Therapharm Ltd).

Studies in vivo

The investigation was carried out in two parts; in the first Mandrax capsules and tablets were compared with the Melsed capsule and Melsedin tablet, in the second the Mandrax preparations were compared with Sedaquin compound and Sedaquin forte capsules. Five subjects participated in each study. They were all informed healthy volunteers aged 20-40 years and three were female.

Studies were carried out at weekly intervals. The subjects were fasted for 12 h and an intravenous cannula was inserted into a large forearm vein from which blood samples were taken. Each study lasted 6 hours. A high fluid intake was

Fig. 1 Mean plasma profiles of Mandrax, Melsed and Melsedin preparations. Five subjects took Mandrax tablet B (●), Mandrax capsule (×), Melsed capsule (□) and Melsedin tablet (■). Three subjects took Mandrax tablet A (○).

maintained either by giving 500 ml 5% dextrose hourly through the cannula or by drinking a similar quantity of water. Subjects fasted during the study.

A sample of blood (10 ml) was collected into lithium heparin tubes before the drug was ingested. A blood sample was taken at 30 min after, then at 15 min intervals for 1.5 h, at 30 min

intervals for the next hour and at hourly intervals for the last 3 h of the study. The plasma was separated immediately by centrifuging for 5 min at 3,000 g, stored where necessary at 0–4°C and then analysed within 12 h by a gas-liquid chromatographic method of Mitchard & Williams (1972).

During these investigations the clinical efficacy was judged by noting when patients felt sleepy, when they went to sleep and the time spent asleep. The studies were controlled as far as possible in that they were performed in the same room, under the same conditions, at the same time of day and with every effort made to reduce disturbing influences. The assessment of hypnotic effect was based on the conclusions of two independent observers together with the impressions of the subjects and was made before the blood samples were analysed.

Studies in vitro

The release of methaqualone from methaqualone containing preparations was followed using an *in vitro* dissolution test based on the rotating basket method of Searl & Pernarowski (1967). Two samples of each preparation were examined. Two litres of dissolution medium—pH 2.0 buffer solution (0.1 M potassium chloride made up to pH 2.0 with 0.1 N hydrochloric acid) was placed in a two-necked 2 litre capacity round bottomed flask and maintained at $37^{\circ} \pm 0.5^{\circ}\text{C}$ in a constant temperature water bath. The methaqualone preparations were placed in a basket (Hanson-65-212-40 mesh screen) attached to a high torque stirring motor and rotated at 100 r.p.m. in the pH 2.0 buffer solution. The height of the basket from the bottom of the flask was constant throughout the dissolution profile studies. Samples were removed from the dissolution medium via the side-arm by a long sampling pipe attachment set at a constant height and angle. Samples (5 ml) were removed at 2, 5, 10, 15 and 20 min, and then at 10 min intervals for 1 hour. The volume was maintained constant by adding 5 ml dissolution medium after each sample had been taken. Methaqualone (in the presence of diphenhydramine) was assayed spectrophotometrically at 281 nm, path length of 1 cm and the extinction related to a previously constructed calibration graph.

Results

In vivo studies

Figure 1 shows the mean plasma methaqualone concentrations achieved by the first group of five subjects who took the new Mandrax tablet B, the

Fig. 2 Mean plasma profiles of Mandrax and Sedaquin preparations in five subjects. (●), Mandrax tablet B; (x), Mandrax capsule; (Δ), Sedaquin forte capsule; (▲), Sedaquin compound capsule.

Mandrax capsule and the Melsed and Melsedin preparations, and the three subjects who took the earlier Mandrax tablet A. This shows a striking difference between the two Mandrax tablets, the higher peak values of the Mandrax preparations and the more rapid rates of absorption achieved by the tablet dose forms compared with the capsules.

Figure 2 shows the mean values obtained by the five volunteers in the second study who took Mandrax B tablets, Mandrax capsules and the Sedaquin preparations. Once again the Mandrax tablet and capsule produced the higher peak values. As might be expected, the differences in the profiles are only noticed during the absorptive phase. A striking similarity exists between the profiles obtained for the different preparations during the drug elimination phase.

A more detailed analysis of the data from both studies is set out in Table 1.

Correlations between the peak plasma levels and the hypnotic effects of the different preparations are shown in Table 2.

In vitro studies

Typical dissolution rate profiles of the seven preparations examined are shown in Fig. 3; the within batch variation in dissolution rate was found to be small. The dissolution time curves conformed approximately to a first order process. This type of behaviour can be obtained for two

Fig. 3 Dissolution profiles of methaqualone preparations at 37°C in pH 2.0 buffer. (x), Mandrax capsule; (○), Mandrax tablet A; (●), Mandrax tablet B; (Δ), Sedaquin forte capsule; (▲) Sedaquin compound capsule; (□), Melsed capsule; (■), Melsedin tablet.

cases of *in vitro* dissolution under sink conditions (Wagner, 1969).

The first case assumes that during some part of the dissolution process the surface area changes exponentially with time.

$$S_t = S_0 e^{-k(t-t_0)} \quad (\text{Equation 1})$$

Where S_0 is the surface area available for dissolution when the first order dissolution phase began at time t_0 and k is the first order rate constant. Substitution into the classical Noyes-Whitney equation yields

$$dw/dt = KC_s S_0 e^{-k(t-t_0)} \quad (\text{Equation 2})$$

Where C_s is the saturation solubility of the drug, K is the dissolution constant and dw/dt is the dissolution rate.

Integration of equation 2 yields an expression of the form

$$\log (W^\infty - W) = \log M - \frac{k(t-t_0)}{2.303} \quad (\text{Equation 3})$$

Where $W^\infty - W$ is the amount of drug undissolved at time t and $M = k/k \cdot C_s \cdot S_0$. Thus a plot of

$\log (W^\infty - W)$ versus $(t - t_o)$ will be linear with slope $-K/2.303$.

In the second case (Wagner, 1971; Gibaldi & Feldman, 1967) it is assumed that the effective surface area available for dissolution at time t is proportional to the quantity of drug remaining undissolved

$$S_t = k'(W^\infty - W) \quad (\text{Equation 4})$$

substituting once again into the Noyes-Whitney equation

$$dw/dt = KC_s k'(W^\infty - W) \quad (\text{Equation 5})$$

and an integration

$$\log (W^\infty - W) = \log W^\infty - \frac{k''t}{2.303} \quad (\text{Equation 6})$$

where $k'' = KC_s k'$.

Plots of $\log$ percent $(W^\infty - W)$ vs $t(t - t_o)$ for each product are shown in Fig. 4 and demonstrate that a linear relationship obtains between $\log$ percent $(W^\infty - W)$ and time.

The dissolution characteristics of the dosage forms have been characterized by the rate constant k from the gradients and the time for half the methaqualone to dissolve ($t_{50\%}$) determined from the whole of the dissolution-time profile.

A linear relationship is demonstrated between peak plasma concentration and $1/t_{50\%}$ for six of the preparations (Figure 5).

The calculated correlation coefficient (r) of 0.992 is greater than the theoretical values of r at probability levels $P' = 0.05$ and 0.01 , thus showing a significant correlation between peak plasma concentrations for six of the preparations studied and $1/t_{50\%}$. However, the old Mandrax A preparation deviates from this relationship, having an extremely rapid dissolution rate. This maybe because it is an old preparation which had been stored for a number of years. Unfortunately, it is not possible to correlate the dissolution rates of other commercially available preparations with

Fig. 4 Plot of $\log \% (W^\infty - W)$ v. time $(t - t_o)$, where $(W^\infty - W)$ is the amount of drug undissolved at time t , for the methaqualone preparations. (x), Mandrax capsule; (o), Mandrax tablet A; (e), Mandrax tablet B; (Δ), Sedaquin forte capsule; ($\triangle$), Sedaquin compound capsule; ($\square$), Melsed capsule; ($\blacksquare$), Melsedin tablet.

plasma levels and thereby validate this relationship.

Discussion

Therapeutic non-equivalence is a problem for prescribers (Schneller, 1969; Florence, 1972) well illustrated by reference to the 14 different preparations of methaqualone commercially available in the United Kingdom as set out in Table 3. There are nine manufacturers producing two dose forms,

Table 2 Correlations between the peak plasma levels and the hypnotic effects of the methaqualone preparations

Drug preparation	Hypnotic effect	Peak plasma methaqualone level ($\mu\text{g/ml}$)
Mandrax Tablet A	+++	7.49
Mandrax Tablet B	++	2.90
Mandrax Capsule	++	2.65
Melsedin Tablet	+/++	2.35
Melsed Capsule	+	1.72
Sedaquin Forte Capsule	+	1.97
Sedaquin Compound Capsule	+	2.12

+++ More than 3 h sleep; ++ 1-3 h sleep; + less than 1 h sleep.

Fig. 5 Correlation between peak plasma methaqualone concentration and $1/t_{50\%}$ where $t_{50\%}$ is the time for half the methaqualone to dissolve, for six of the preparations studied. (x), Mandrax capsule; (●), Mandrax tablet B; (Δ), Sedaquin forte capsule; (▲), Sedaquin compound capsule; (□), Melsed capsule; (■), Melsedin tablet.

tablet and capsule and these may contain the drug as the free base or as the hydrochloride salt. There are three different doses of the base and three of the salt. In the salts, when the hydrochloride is subtracted, the methaqualone content is smaller than at first appears. The choice is further complicated by the fact that some preparations contain diphenhydramine and some do not. The doctor

who wants to prescribe methaqualone has a considerable choice as we have shown the plasma levels of the drug achieved in his patient will depend on which preparation he chooses.

Having chosen a particular preparation, the blood levels will depend on the type of patient (studies indicate that methaqualone accumulates in adipose tissues, Akagi, Oketani, Takada & Suga, 1963) and the variation between individuals is the cause of the high standard deviations recorded in Table 1. This variation was anticipated since the subjects received the unit of dosage commercially available and no allowance was made for body weight or volume of distribution which Williams, Kendall & Mitchard (1973) have recently shown markedly influence plasma methaqualone concentrations.

Dose form

A comparison of the dose forms can only be made by considering the data obtained for Mandrax. The *in vitro* dissolution studies showed only a small difference between Mandrax tablet B and the Mandrax capsule, $t_{50\%}$ of 11 and 12 min respectively. This is reflected in the *in vivo* studies which showed slightly lower, later plasma methaqualone peak after taking the capsule.

Diphenhydramine content

The apparent effect of diphenhydramine in promoting the absorption and increasing the peak plasma methaqualone concentration can be seen by comparing the Melsed and Mandrax capsule studies. It is tempting to attribute the difference

Table 3 Commercially available methaqualone containing preparations available in the United Kingdom

Preparation	Tablet or capsule	Methaqualone base (mg)	Methaqualone hydrochloride (mg)	Diphenhydramine hydrochloride (mg)
Lancesomnal	Capsule		130	50
Mandrax	Capsule and tablet	250		25
Matthoderm	Tablet	250		25
Melsed	Capsule	250		
Melsedin	Tablet		150	
Paldona	Tablet	250		25
Paxidorm	Tablet		150	
Quaalude	Tablet	300		
Revonal	Tablet	200		
Sedaquin	Tablet		150	
Sedaquin Forte	Capsule		250	
Sedaquin Compound	Capsule and tablet	250		25

There are also 14 other preparations available for the foreign market.

to the presence of diphenhydramine. Other formulation factors appear to be more important, as is apparent from a comparison of Mandrax tablets A and B. It is interesting to speculate that the success of Mandrax was due to the efficacy of the earlier formulation.

Efficacy of preparations

Assessing the hypnotic effects of drugs is difficult since other factors such as noise, boredom, and tiredness will influence the time taken to go to sleep and the time spent asleep. However, as shown in Table 2, there is a correlation between hypnotic effect and peak plasma levels of the drug. Both the observers and the participants were able to recognize that they were approaching the peak plasma level and when the plasma estimations had been performed it appeared that the subjects tended to sleep once the blood level exceeded 2.5 µg/ml.

Although equations 3 and 6 are derived from

different basic principles, both are of similar mathematical form (equations of a straight line). Our dissolution studies have demonstrated that there is a linear relationship between $\log(W^\infty - W)$ and time. However, these studies were not designed to provide information relating to the appropriateness of the principles from which the two equations were derived.

The *in vivo* studies have shown that different preparations give very different plasma levels. However, the relationship between the *in vivo* and *in vitro* studies summarized in Fig. 5 show that it is possible to predict from simple *in vitro* tests what the *in vivo* plasma levels will be.

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References

- AKAGI, M., OKETANI, Y., TAKADA, M. & SUGA, T. (1963). Studies on metabolism of 2-Methyl-3-0-tolyl-4(3H)-quinazolinone. II. Physiological disposition and metabolic fate of 2-Methyl-3-0-tolyl-4(3H)-quinazolinone. *Chem. Pharm. Bull. (Tokyo)*, **11**, 321-324.
- BEAUBHEN, J., KRISTOF, F.E., LEHMANN, H.E. & BAN, T.A. (1968). A comparison of the hypnotic properties of Mandrax and its two constituents. *Curr. ther. Res.*, **10**, 231-232.
- FLORENCE, A.T. (1972). Generic equivalence: a look at the literature. *Pharm. J.*, **208**, 456-463.
- GIBALDI, M. & FELDMAN, S. (1967). Establishment of sink conditions in dissolution rate determinations. Theoretical consideration and application to non disintegration dosage forms. *J. Pharm. Sci.*, **56**, 1238-1242.
- HOFFMEISTER VON-W. & KOLLER, S. (1970). Clinical trial of a combination of methaqualone and diphenhydramine and methaqualone in a double blind test. *Arzneim-Forsch.*, **20**, 261-264.
- MATTHEW, H. (1973). Prescribing Mandrax. *Br. med. J.*, **1**, 367.
- MITCHARD, M. & WILLIAMS, M.E. (1972). An improved quantitative gas-liquid chromatographic assay for the estimation of methaqualone in biological fluids. *J. Chromatogr.*, **72**, 29-34.
- SCHNELLER, G.H. (1969). Hazards of therapeutic non equivalency of drug products. *J. Amer. Pharm. Ass.*, **NS 9**, 455-459.
- SEARL, R.O. & PERNAROWSKI, M. (1967). The biopharmaceutical properties of solid dosage forms. *Can. Med. Ass. J.*, **96**, 1513-1520.
- WADE, O.L. (1970). *Adverse Reactions to Drugs*. London: William Heinemann Medical Books Ltd.
- WAGNER, J.G. (1969). Interpretation of percent dissolved-Time plots derived from *in vitro* testing of conventional tablets and capsules. *J. Pharm. Sci.*, **58**, 1253-1257.
- WAGNER, J.G. (1971). *Biopharmaceutics and Relevant Pharmacokinetics*. Hamilton, Illinois: Drug Intelligence Publications.
- WILLIAMS, M.E., KENDALL, M.J. & MITCHARD, M. (1974). *Br. J. clin. Pharmac.* (in press).