In vitro — in vivo evaluation of a sustained-release phenylpropanolamine oral dosage form

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ERRATA

Dowse,R,Haigh,JM, and Kanfer,I: **In vitro-in vivo** evaluation of a sustained-release phenylpropanolamine oral dosage form. **SAPJ**, 49,10,1982,485-487.

Typographical errors appeared in the text and certain figures, and should appear as follows:
Results and discussion:

Line 6 of the 3rd paragraph under the heading **Dissolution rates** on page 486, should read '40-60%' and not '40-40%'. Under **In vitro-in vivo correlations,** the second line from the top on page 487 should have read 'by iteration on ICL computer, i.e. F^{∞}, t_o, t_d and ß'. In line 6 of the same paragraph, 'Figure 5' should be deleted so that the line reads 'rotating basket method. As can be observed the fit . . .'

ABSTRACT

There is increasing interest in measuring pharmacokinetic parameters of phenylpropanolamine (PPA), a sympathomimetic amine used in over-the-counter nasal decongestants and anorectic formulations.

A high pressure liquid chromatographic (HPLC) procedure was developed to enable direct ultraviolet detection of PPA, after extraction from serum and urine, without prior derivatization of the drug. This method was used to assay samples obtained from a bioavailability study of sustained-release PPA tablets. The mean serum and urine profiles obtained are presented.

The sustained-release tablets were subjected to dissolution testing utilizing the United States Pharmacopoeia (USP XIX) rotating basket method. An internal standard was incorporated into the dissolution fluid to enable direct analysis of the samples by HPLC. A comparison of three different dissolution fluid regimens was carried out to determine if release of the drug was affected by the change in pH of the medium and to select the most convenient method for the final dissolution studies.

Some preliminary observations relating to correlations between rate of drug release from the sustained-release dosage form and percent drug absorbed are presented.

Introduction

Phenylpropanolamine (PPA), a sympathomimetic amine structurally related to ephedrine, is widely used as a component in over-the-counter nasal decongestant and anorectic medications (1). It has, however, been the focus of much controversy due to doubts concerning the efficacy of the drug in its use as an anorectic agent (2,3) and due to the side effects caused by the higher doses of PPA required for appetite suppression (4,5). Many of the preparations containing PPA are sustained-release formulations and there is increasing interest in measuring blood concentrations and evaluating pharmacokinetic parameters of PPA.

The most widely used method of determination of PPA in biological fluids has been gas-liquid chromatography (GLC), as this provides the sensitivity required to measure the levels of PPA found in biological fluids after the administration of therapeutic doses. Derivatives such as the heptafluorobutyryl derivative (6) and the pentafluorophenyloxazolidine derivative (7) have been used to determine PPA in plasma by GLC. Urine levels have been determined by nitrogen-selective GLC after extraction from alkaline urine (8).

The major problem involving the use of HPLC for determining PPA in serum and urine has been lack of sensitivity in the detection of the drug, as PPA has a relatively low molar absorptivity. Mason (9) overcame this by extracting from plasma and derivatizing PPA with *o*-phthaldehyde to form a highly fluorescent product and using fluorescence detection with which he was able to quantitate as little as 5 ng/ml PPA in plasma.

The method of extraction and subsequent determination by HPLC reported here is simple, rapid and precise. No derivatization is necessary and concentrations of PPA can be determined down to 25 ng/ml in serum. The method was applied to both urine and serum. In addition, an HPLC method was also utilized to determine the dissolution rate of PPA from a solid oral dosage form.

Experimental

(a) Dissolution rate determinations

In vitro dissolution studies were carried out on sustained-release tablets containing 150 mg phenylpropanolamine hydrochloride. Simulated intestinal fluid (pH 7.2 ± 0.05) was prepared containing the internal standard, phenylephrine hydrochloride (PEP) (0.5 mg/ml).

The USP XIX rotating basket apparatus was used, with each beaker containing 500 ml dissolution fluid which was maintained at 37°C. A single tablet was placed in each basket and rotation at 100 rpm was immediately initiated. Aliquots were withdrawn at specified times from the same point within the beaker with a 1 ml pipette. There was no replacement of dissolution medium, but the decrease in volume was compensated for in the calculation of results. Six tablets were tested to determine their dissolution characteristics.

A calibration curve was constructed using five different concentrations of PPA hydrochloride made up with the internal standard solution. Tablet purity was also tested using HPLC. ▶

(b) **Analysis of serum and urine**

Similar extraction methods were used for both serum and urine and involved chloroform extraction from a sample adjusted to pH 10 with a saturated sodium carbonate solution. The internal standard solution (ephedrine hydrochloride in water) was added to the contents of the tube prior to extraction. PPA was then back-extracted from the chloroform into 5% v/v acetic acid. Aliquots of the acetic acid extract were injected directly onto a reverse-phase C_{18} column (Waters Associates) and detected at 220 nm. Calibration curves were established using five different concentrations to cover the expected ranges and spiked samples treated in exactly the same manner as above.

A bioavailability study involving 6 normal, healthy volunteers was undertaken. Each volunteer received one sustained-release tablet containing 150 mg PPA hydrochloride following an overnight fast. Blood and urine samples were collected at specified intervals and representative samples of the urine were frozen immediately. The serum was separated by centrifugation and frozen until analysis.

Results and discussion

(a) **Dissolution rates**

The tablets were found to contain 98% of the stated amount of PPA hydrochloride.

Analyses of the dissolution samples by HPLC were rapid and precise. The incorporation of the internal standard in the dissolution fluid enabled the sample to be injected directly onto the column without any pretreatment such as extraction or derivatization of the drug. The internal standard also compensated for inaccuracies associated with failure to remove precise sample volumes.

No *in vitro* dissolution parameters are specified for sustained-release formulations of PPA (pKa 9,4) but it has been found that freely soluble drugs with a pKa value of 8 to 10 have produced satisfactory *in vivo* responses if their *in vitro* release rates approximated the following: 20 - 40 % release within the first ½ hour, 40 - 40% within 2 hours, 60 - 80% up to 4½ hours and greater than 80% in 7 hours (11). The mean profile of 6 tablets shown in Figure 1 can be seen to follow this pattern of release satisfactorily.

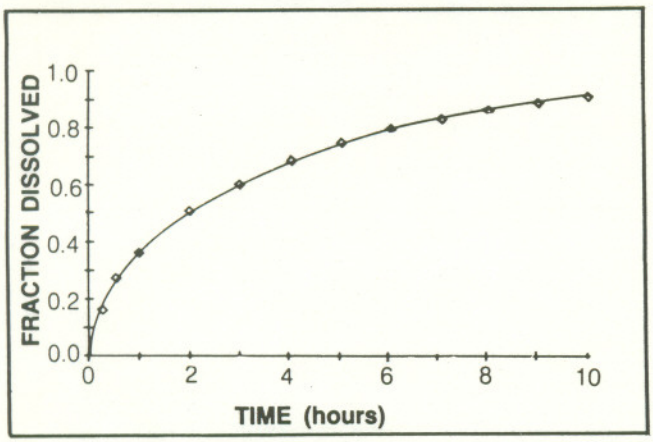

Fig. 1: The average dissolution profile of six sustained-release phenylpropanolamine tablets (150 mg).

(b) **Analysis of serum and urine**

The back-extraction avoids the lengthy procedure of evaporating large volumes of the organic extract to dryness and subsequent reconstitution, but still enables concentration of the extract. The percentage recovery of PPA from both urine and serum was approximately 80 %.

Reports have suggested that no significant metabolism of PPA occurs (12), so interference by metabolites was not a problem. No other interfering peaks in the chromatogram were encountered. Calibration curves were found to be linear over the entire concentration ranges studied.

Reverse-phase paired ion chromatography using 1-heptanesulphonate sodium as the pairing agent was utilised for all determinations. The method was sensitive enough to allow direct UV detection at a wavelength of 220 nm. Figure 2 represents the mean serum concentration-time curve. Figure 2 peak blood levels occurred 4 to 6 hours after ingestion of the tablet with maximum concentrations varying between 210 to 410 ng/ml of serum. The mean cumulative urinary excretion profile after ingestion of the PPA tablet is depicted in Figure 3. Recovery of PPA from the urine after 24 hours ranged between 67 to 70% of the unchanged drug.

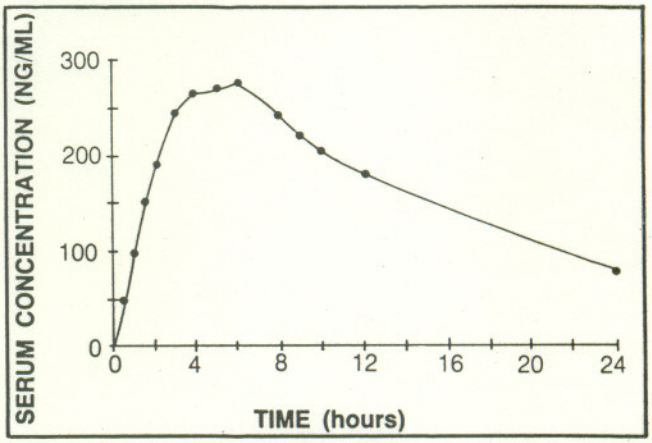

Fig. 2: The average serum levels obtained from six subjects after the ingestion of one sustained-release phenylpropanolamine tablet (150 mg).

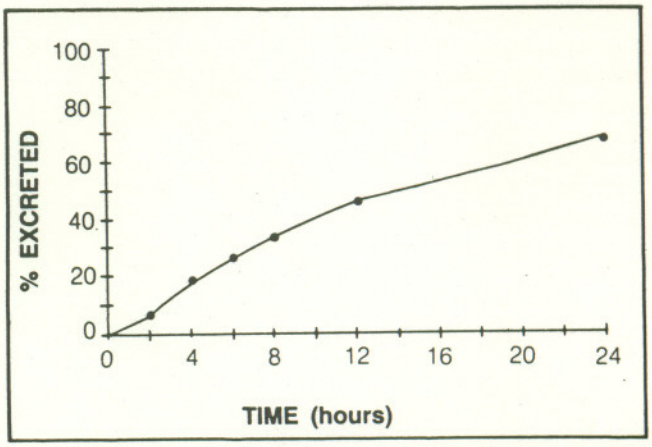

Fig. 3: The average cumulative urinary excretion profile obtained after administering one sustained-release phenylpropanolamine tablet (150 mg) to each of six subjects.

(c) *In vitro — in vivo* **correlations**

In vitro dissolution data are extremely useful as an adjunct to oral solid dosage form development. Although several *in vitro* parameters have been described and serve as useful criteria for the assessment of drug release characteristics, attempts to correlate these with *in vivo* performance leave much to be desired.

Whereas various empirical equations and statistical treatments have been reported in the literature, most of these suffer from various limitations. Langenbucher (13,14) and recently Riegelman and Upton (15) have described the utility of the Weibull function for *in vitro — in vivo* correlations.

Dissolution data were fitted to the Weibull equation

which can be seen in Figure 4 and the 4 variables estimated by iteration on an ICL computer, i.e. F^{00}, t_o, t_d and B. Figure 5 depicts the observed dissolution rate data and the predicted values as calculated from the Weibull equation obtained from the average of 6 tablets using the official rotating basket method. Figure 5 as can be observed the fit is excellent, with a correlation coefficient of 0.9990.

In vivo data from the bioavailability study described previously were evaluated using the Wagner-Nelson deconvolution which can be seen in Figure 6. Absorption rate data determined from the above equation were used to generate percentage absorbed versus time plots. These data were subsequently also fitted according to the Weibull distribution function to see if it is as useful in describing the absorption rate process as for the dissolution rate process. The fit can be seen in Figure 7. There is slightly more scatter about the predicted values as calculated from the Weibull function fit to the data, but the fit is still good, with a correlation coefficient of 0.9933.

$$F = F^{\infty}\left[1 - e^{-\left(\frac{t - t_o}{t_d}\right)^{\beta}}\right]$$

F = fraction of the dose dissolved at time t
F^{∞} = amount dissolved at infinite time
t = time
t_o = the lag time for dissolution after disintegration
t_d = mean dissolution time
β = shape parameter

Fig. 4: Weibull equation.

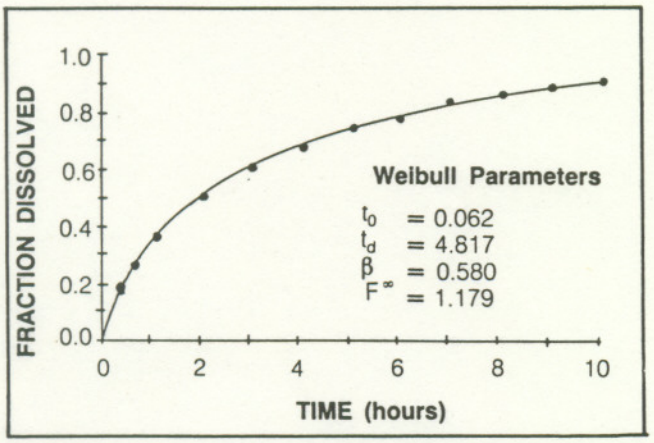

Fig. 5: The average dissolution profile and Weibull function fit for six sustained-release phenylpropanolamine tablets (150 mg). The solid curve represents the Weibull fit to the data.

$$\frac{A_T}{V} = C_T + K\int_0^T C.dt$$

A_T = amount of drug which is absorbed between time O and T
V = volume of distribution
C_T = concentration C at time T

Fig. 6: Wagner-Nelson equation

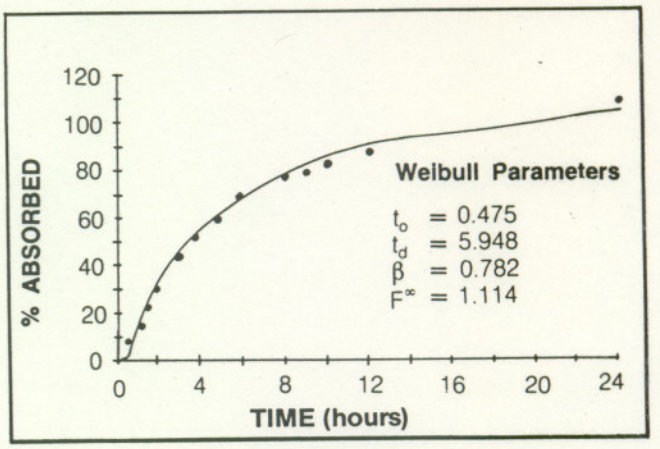

Fig. 7: Wagner-Nelson analysis of the average serum concentration-time curve after administering one sustained-release phenylpropanolamine tablet (150 mg) to each of six subjects.

It is thus seen that the *in vitro* dissolution rate process for this particular PPA sustained-release formulation is well described by the Weibull equation and that utilizing the appropriate deconvolution procedure, the resultant percent absorbed versus time plot can be successfully fitted to the same function.

Critical steps in the process of *in vivo* drug release may therefore possibly be identified by comparison of the *in vitro* and *in vivo* parameters.

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